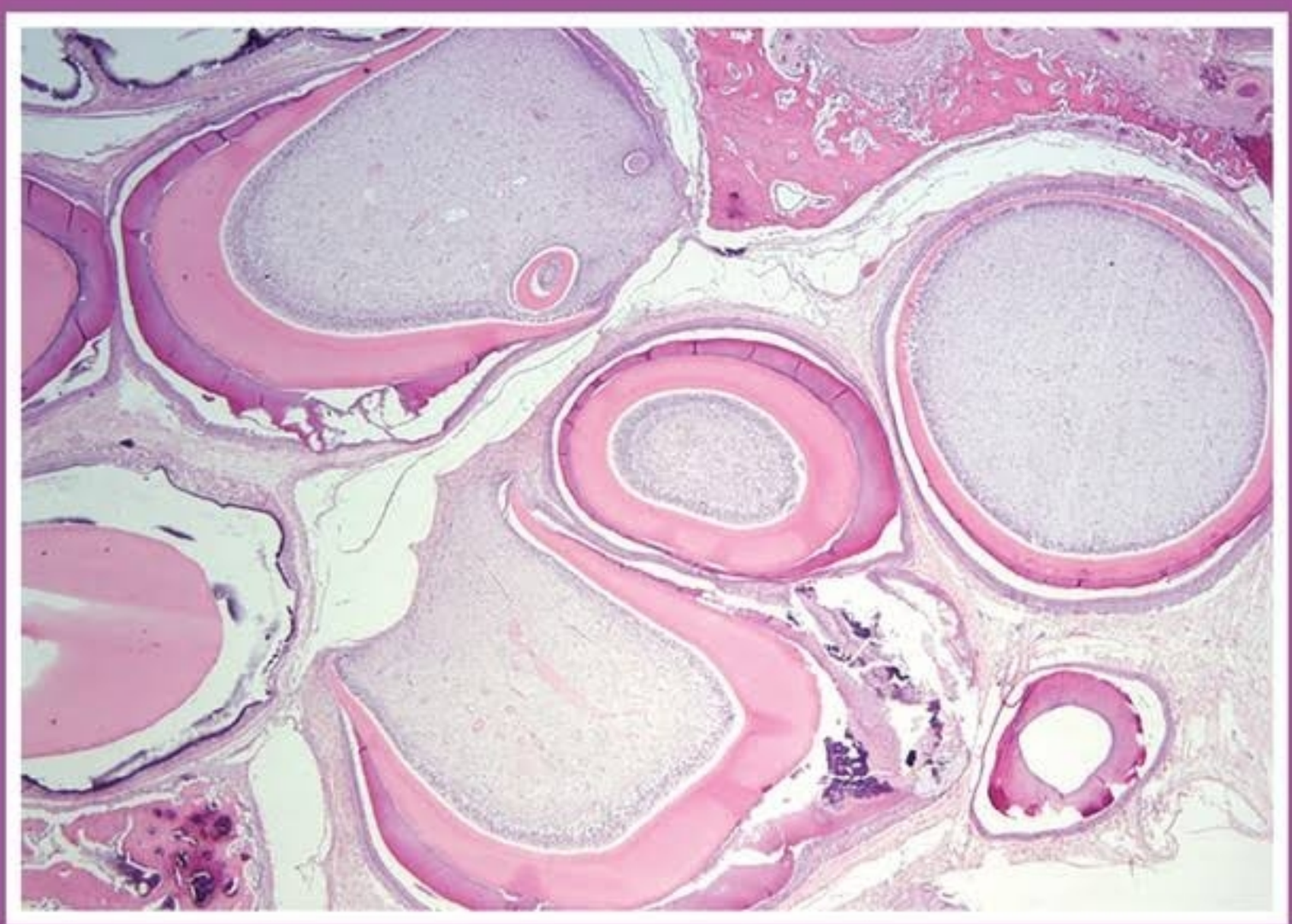
Veterinary Oral and Maxillofacial Pathology

Brian G. Murphy • Cynthia M. Bell • Jason W. Soukup



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Preface

This book is an attempt to address a perceived deficiency in the veterinary pathology literature and to provide a current and useful resource for diagnostic veterinary pathologists, veterinary dentists, oral surgeons, resident trainees and others with an interest in oral and maxillofacial pathology of veterinary species.

The text is *focused on methods for establishing a diagnosis and set of differential diagnoses*. Many oral lesions are unique (tooth-related lesions, fibrous lesions of the oral mucosa and jaws), and have their own nomenclature and embryologically informed pathogenesis. These lesions can be confusing to the non-specialist and are a central focus of this work.

Differential diagnoses for each lesion are a prominent feature of the text and expose the philosophy that lesion classification in oral pathology is ever- evolving. As much as possible, we have attempted to be up front with the reader concerning the often considerable ambiguity and morphologic overlap of oral lesion classification. The importance of a multi-modal approach to lesion classification is stressed throughout. We have attempted to directly address the controversies over lesion taxonomy and relationships between lesions, pathogenesis, and lesion nomenclature, and to not ignore or obfuscate these issues. Although examples of oral lesions are drawn from diverse species, the principal focus is on mammalian companion animals (dog, cat, horse) with less of an emphasis on ruminants, camelids and laboratory animal species (primate, rodent and rabbit).

Each chapter stresses the importance of a holistic approach in establishing a meaningful diagnosis, taking into consideration the patient signalment, lesion history, the often invaluable opinion of the submitting clinician, pre-biopsy imaging findings, and gross features of lesions, *in addition* to the histological features of the submitted specimen. In an attempt to clarify what is often perceived as an impenetrable subspecialty of veterinary pathology, the text has been richly illustrated with relevant radiographs, clinical, gross and histologic images (including special stains and IHC), as well as line drawings and diagrams. Key gross and histologic features, along with differential diagnoses to consider, have been provided for each lesion.

Although the focus of this work is on the establishment of a diagnosis and differential diagnoses, information has also been provided on lesion pathogenesis, prognosis, and treatment. It is *not the goal* of the authors to cover all of the oral and maxillofacial lesions which have been heretofore described in domestic animals, but rather to focus on complex and unique oral lesions, as well as those that a diagnostic veterinary pathologist would likely encounter in a surgical biopsy practice. It is important for the pathologist to recognize that what they see from day-to-day in their practice, even a busy specialist practice, may not represent the diversity of actual maxillofacial/oral pathology that occurs in veterinary species. Pathologists have a window on a subset of disease- those lesions that get biopsied or are present at the time of the animal's death (discovered during the necropsy examination).

Oral lesions that also occur in other systems and/or have been exhaustively described elsewhere will be less emphasized. Lesions encountered by clinical oral specialists (dentists) but rarely sampled or submitted for histological examination (palatal developmental disorders, malocclusions) will also be less emphasized. It is not the goal of this work to duplicate quality information available from other resources.

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We are grateful for the numerous clinical and gross images provided by residents, veterinary clinicians, dentists and anatomic pathologists. Images are the backbone of this work; without them, the story would be greatly diminished. Each of these specific contributions has been acknowledged where it appears throughout the textbook.

We would also like to thank our families for their support, love and tolerance.

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About the Companion Website

Don't forget to visit the companion website for this book:

www.wiley.com/go/murphy/pathology



We have created a companion website featuring a series of guided histological tours showcasing select oral pathology lesions (oral malignancies, odontogenic tumors, proliferative fibro-osseous lesions, oral inflammation, etc.). Microscopic images have been digitally captured using a slide scanner and appended to an annotated voice file (BGM and CMB) strategically walking the viewer through the lesions' salient diagnostic features. It is the authors' hope that the reader will find these annotated digital files to be useful.

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1

A Philosophical Approach to Establishing a Diagnosis

Lesions in the oral cavity of veterinary species are common, and the pathologist's correct diagnosis can play an important role in the well-being of animals and owners alike. Unfortunately, multiple factors can conspire to make the diagnosis of oral and maxillofacial lesions difficult: some oral lesions can be rare and one-of-a-kind, lesions may require extensive decalcification, the existing literature is arguably less comprehensive for oral diseases than for other body systems, and perhaps most importantly, oral lesions with markedly different outcomes can demonstrate coalescing morphologic features. It is the authors' opinion that the factors that make these lesions challenging to diagnose can also make them intellectually attractive, and the pursuit of the most appropriate diagnosis a rewarding one. This book was written with this concept ever in mind.

While lesions in the oral cavity can share multiple morphologic features with lesions in other body systems, some oral lesions are absolutely unique and may be found nowhere else. In addition, pathologic lesions arising from the jaw can also be unique, as maxillary and mandibular bone tissue is embryologically and physiologically unlike bone of the appendicular skeleton. Perhaps most importantly, the oral cavity and jaws of higher vertebrates include teeth, the sole anatomic structures that bridge the skeletal and digestive systems.

One of the most important goals for a diagnostic pathologist is to establish the correct diagnosis – *to put the right lesion into the right categorical box*. To accomplish this, veterinary pathologists have long utilized the framework of human oral disease as a template for organizing the oral lesions of veterinary species. While humans and veterinary species share certain features of oral pathophysiology, it is the authors' opinion that oral lesions that occur in human beings do not fully capture the great diversity of pathology that occurs in veterinary species. Likewise, many clinicopathological entities in humans are defined or subclassified by specific demographic, behavioral, and/or environmental factors that are unlikely to be significant in animals.

Diagnosis is a form of *categorization,* and the process of categorization is a human construct. We created *categorization* as a means of dividing up the natural world. Making sense of veterinary oral pathology through categorization is a process that has been going on for more than a century, and many individuals have made important contributions to this effort. Unfortunately (or perhaps fortunately), nature is highly complex. Because this effort to diagnose and categorize is a difficult one, it is essentially an iterative process, and such attempts will always remain works in progress.

In order to establish a diagnosis, many pathologists adhere to a heuristic process of morphologic pattern recognition. For the experienced pathologist, this cognitive process may even occur at a level beyond conscious recognition. The diagnosis *just feels right*. Although the end goal of establishing a correct diagnosis may be met, a dependency on the process of pattern recognition alone remains an imperfect one, as oral lesions can and frequently do share overlapping morphologic features.

Bell curves can be constructed as simple, two-dimensional metaphors representing the diversity of morphologic types found within a particular type of lesion (Figure 1.1). For such curves, the diversity of a particular morphologic feature or collection of features within a lesion can be represented along the x-axis, while the frequency of occurrence of those features in a population of lesions is mapped along the y-axis. In such a system, a steep and narrow bell curve suggests that relatively little morphologic diversity exists within the lesion type, while a broad-based bell curve suggests the opposite. Superimposition of these curves graphically demonstrates this concept of overlapping morphologic features (Figure 1.2). Structural overlap between lesions presents a diagnostic challenge for the pathologist and is a concept that will be returned to throughout this book.

It is the opinion of the authors that the examination of histologic features frequently allows the designation of a principal diagnosis along with one or more differential diagnoses. These differential diagnoses are important

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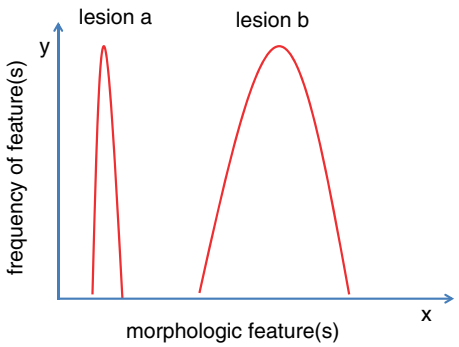


Figure 1.1 Bell curves representing lesion diversity and frequency. For a given lesion, the *x*-axis can represent a single morphologic feature or set of morphologic features that collectively comprise the lesion in question. The *y*-axis represents how common the particular morphologic feature(s) is/are within a group of similar lesions; lesions with a broad curve are morphologically diverse and therefore more difficult to diagnose.

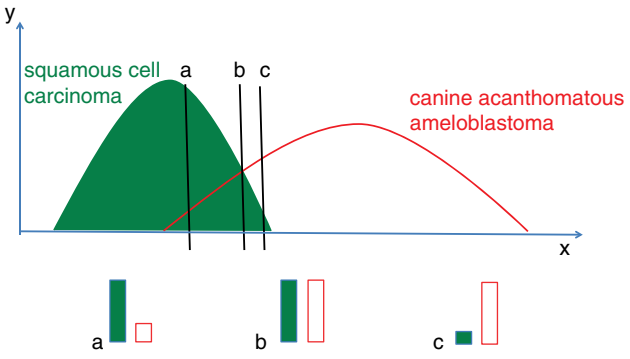


Figure 1.2 Superimposed bell curves are a metaphor for the morphologic overlap between related lesions. Some lesions, like squamous cell carcinoma (SCC) and canine acanthomatous ameloblastoma (CAA) can either be morphologically distinct lesions (extreme right and left edges of the two bell curves) or share multiple features (within the region of curve overlap). Sections a, b, and c represent lesions that are most likely to be SCC, equally likely to be SCC or CAA, or more likely to be CAA, respectively.

and should be included in the report sent to the submitting clinician. Assigning a principal diagnosis and accompanying set of differential diagnoses effectively conveys a measure of ambiguity, which may have great value for the clinician. For these reasons, histologically related lesions (differential diagnoses) have been included for each lesion type described in this book.

To assist in this difficult but ultimately rewarding endeavor, the judicious use of appropriate immunohistochemical assays and/or special stains can be invaluable to inform the final diagnosis. Perhaps even more importantly, clinical data, most typically available through the submitting clinician, should be sought out. Patient signalment, anatomic location, and lesion natural history can be invaluable facets of the final diagnosis. Radiographic imaging studies and/or three-dimensional imaging studies like computed tomography may be available. The opinion of the clinician/ radiologist regarding such studies, or better yet, the diagnostic images themselves, should be reviewed by the pathologist in conjunction with the gross and histological features of the submitted sample.

If not openly offered, the opinion of the submitting clinician should be sought out, as an astute clinician will often have made a preliminary clinical diagnosis prior to submission. This *clinical diagnosis* may be correct, based upon the clinician's experience, the anatomic location, results of diagnostic imaging studies, signalment of patient, clinical signs, and prior biopsy results. The diagnosis of relatively common oral lesions such as odontogenic cysts and equine cementomas (nodular hypercementosis) are highly dependent upon their anatomic relationship with teeth, jawbones, and/or the paranasal sinuses. Some clinicians have a curious policy of withholding such information from the pathologist in a dubious attempt to "not influence the diagnostic process." It is likely that these same clinicians would be at a loss if their own clients withheld important clinical information for the same reason.

There is also value in seeking out the opinions of colleagues or even trainees. At academic institutions, such opinions are typically readily available, and such advice may even be offered without asking for it! Useful discussions can also occur in the setting of private diagnostic labs, even in those laboratories staffed by a single pathologist. The common use of digital images facilitates rapid communication, and networks of colleagues around the world are often willing to lend a hand. Finally, following a challenging lesion *down the road* can be a valuable learning experience in itself. Does the eventual clinical outcome fit the diagnosis, and most importantly, can one learn from it?

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2

Histological Features of Normal Oral Tissues

Histopathological evaluation of oral tissues requires a solid understanding and familiarity with the normal microscopic anatomy. Several tissues, such as teeth, are anatomically unique to the oral cavity. The authors hope that this brief chapter will assist readers with acquiring this basic understanding and enable them to interpret tissue changes accurately and meaningfully. We highly recommend Ten Cate's *Oral Histology* [1] as a highly detailed and authoritative resource for learning more about the unique histology, development, and physiology of oral tissues.

2.1 Oral Mucosa

Oral mucosa covers the entire surface of the oral cavity with the exception of the gingiva, which is a specialized form of mucoperiosteum (discussed below). The mucosa consists of surface epithelium and lamina propria. In most areas, there is also a distinct submucosa of fibrous connective tissues that is looser (usually) and supports other structures such as glands, muscle, and larger vessels and nerves. Depending on the location within the oral cavity, the mucosa varies in thickness and extent of keratinization. For example, particularly delicate buccal mucosa (also called vestibular mucosa) and sublingual mucosa line the inner surface of the cheeks and the floor of the mouth, respectively. In contrast, the palatal mucosa lining the hard palate is more durable, with thicker epithelium, occasional keratinization, and compact collagen within the lamina propria (Figure 2.1).

The non-keratinized epithelium (e.g. buccal and sublingual mucosa) has four layers that are distinguished by morphological differences – from deep to superficial: basal cell layer, prickle cell layer, intermediate cell layer, and superficial layer. Identification of layers is slightly different with keratinized epithelium (e.g. hard palate and dorsal tongue): basal cell layer, prickle cell layer, granular cell layer, and keratinized (usually parakeratinized) layer. In the oral cavity, unlike the epidermis, parakeratinization can be a normal pattern of squamous cell maturation/ differentiation. The lamina propria (also called mucosa propria) is divided into two layers – papillary and reticular. The papillary layer *interdigitates* with epithelial pegs and has capillary loops in close proximity to the epithelial basement membrane. With small vessels and bundles of collagen, the deeper reticular layer blends into the underlying submucosa (Figure 2.1).

The submucosa also varies in density and amount of collagen matrix. Minor salivary glands and their associated ducts are widely distributed throughout the oral submucosa (Figure 2.2). Occasionally, organized lymphoid tissue is present within the submucosa, particularly in the soft palate of young animals. As in the dermis, inflammation is often superficial, and cellular infiltrates are densely distributed within the lamina propria (see Figure 2.3).

Specialized mucosa of the tongue includes various types of papillae (filiform, fungiform, vellate). Some species, especially cats, also have filiform keratin projections on the hard palate mucosa. The rostral hard palate has an *incisive papilla* composed of cartilage that should not be mistaken for pathology.

2.2 Gingiva

The gingiva is a unique and distinct tissue that is characterized by surface epithelium and its underlying fibrous stroma which, together, comprise a mucoperiosteum. In the gingiva, there is no distinct lamina propria or submucosa, since the fibrous stroma extends from the epithelial basement membrane to the periosteal surface of the underlying alveolar bone of the jaw. The fibrous stroma is poorly cellular and overwhelmingly composed of densely organized, intersecting robust bundles of fibrillar collagen. Gingival stroma has an indistinct transition to periosteum – these two tissues are firmly connected by abundant extracellular fibers.

Like the oral mucosa, the gingiva has variation among specific anatomical sites. This variation is not as much a function of location along the dental arcades as it is

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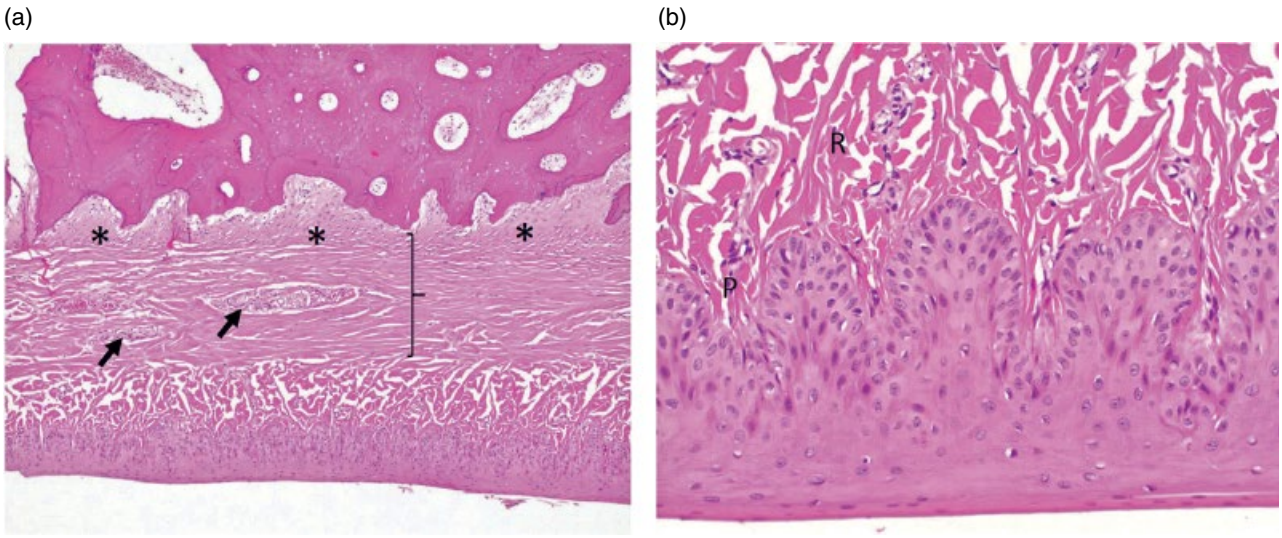


Figure 2.1 Histologic images of the hard palate of a five-month-old male boxer dog. (a) There is a compact fibrous submucosa (bracket) between the palatal mucosa and the periosteum (asterisks) of the palatine bone. Neurovascular bundles (arrows) course within this layer. (b) The mucosal epithelium of the hard palate is thick relative to many other area of the oral cavity, and the surface layers may be parakeratinized. The papillary (P) layer of the lamina propria interdigitates with the epithelium, and the reticular (R) layer contains more prominent vasculature.

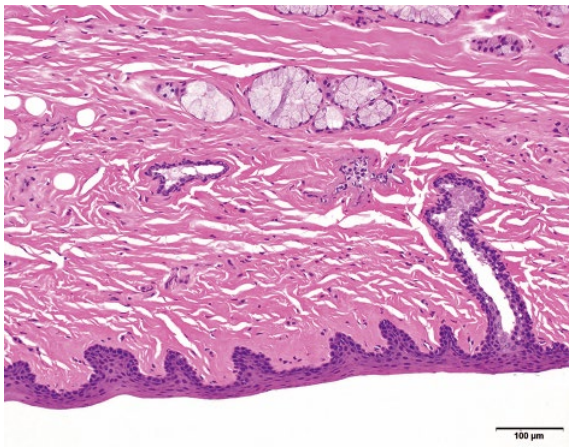


Figure 2.2 Histologic image of the soft palate mucosa from a seven year old, spayed female domestic short-haired (DSH) cat. Minor salivary glands are abundant throughout the oral mucosa. These glands open directly onto the mucosal surface via small ducts.

location with respect to individual teeth. The *attached gingiva* is a more or less flat layer that covers alveolar bone; it is mucoperiosteum and organized as described above. The *free gingiva* represents the unattached margin of this mucoperiosteum as it meets and transitions to tissues that line the sulcus, then attaches near the cementoenamel junction of the tooth (Figure 2.4).

The free gingiva is comprised of tissue from two different embryological sources, and this difference is readily appreciated in the mature animal. The outer surface is derived from gingiva, whereas the lining of the sulcus is derived from odontogenic origin, specifically the reduced enamel epithelium and dental follicle that once surrounded

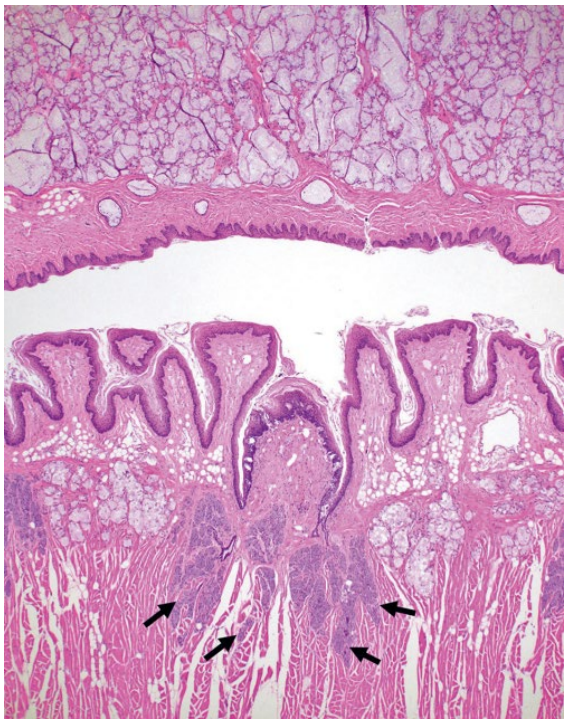


Figure 2.3 Histologic image of the tongue and soft palate of a seven-year-old, spayed female, DSH cat. At the level of the soft palate, the caudal oral soft tissues in the cat are very rich in salivary tissue. Mucous salivary glands are abundant dorsal to the palatal mucosa, and within the submucosa and superficial skeletal muscle of the tongue. The tongue has both pale-staining mucous salivary glands and more basophilic serous salivary glands (arrows). In the center of the image, the lingual mucosa forms a fungiform papilla. The lingual mucosa is otherwise undulant, which correlates with mucosal ridges that can be seen grossly on the caudal dorsal surface of cat tongues.

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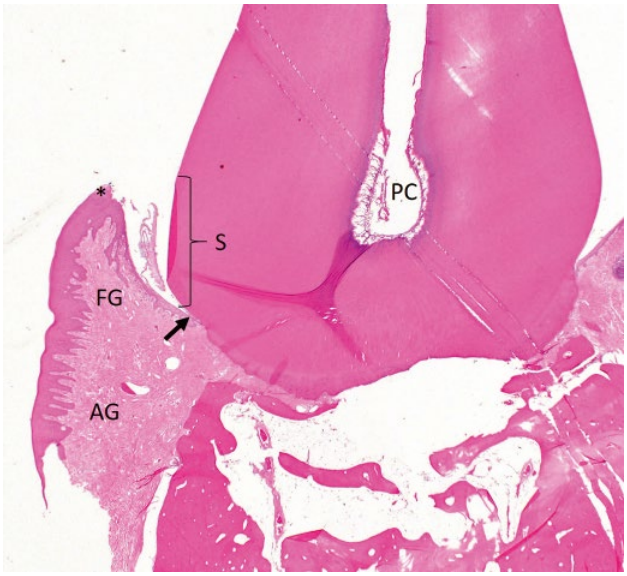


Figure 2.4 Histologic image of a normal premolar tooth from a seven year old dog. The free gingiva (FG) surrounds the base of the tooth crown, forming a sulcus (S). The depth of the sulcus (bracket) is from the gingival margin (asterisk) to the point where the sulcular epithelium attaches to the tooth (arrow). The attached gingiva (AG) covers alveolar bone. Tissues within the pulp canal (PC) are distorted due to artifact.

the crown of the tooth prior to eruption. As such, the free gingiva does not exist prior to tooth eruption. The sulcular epithelium has features of odontogenic epithelium, and the fibrovascular connective tissue under the sulcular epithelium is more similar to periodontal ligament than it is to fibrous gingival stroma. At the base of the sulcus, the site of attachment is particularly rich in fibers, similar to the attachment interface between gingival stroma and periosteum. The epithelium of the sulcus also attaches to the tooth at the base of the crown – this attachment is less obvious histologically, but some sections will show a thin epithelium reflecting onto the tooth surface (Figure 2.5). Loss of this epithelial attachment is an important step in the development of periodontal disease. To clarify, the attached gingiva is not the same as the attached epithelium. Attached gingiva covers alveolar bone and contrasts with the free gingiva. Attached epithelium is toward the base of the gingival sulcus where the gingiva anchors at the base of a tooth crown.

Gingival fiber bundles are abundant and unequally distributed within the tissues, tending to be most abundant where a ligamentous attachment is necessary between gingiva and bone, as well as between gingiva and the cervical portion of the tooth. Collagen fibers are by far most abundant (Figure 2.6). In addition to collagen

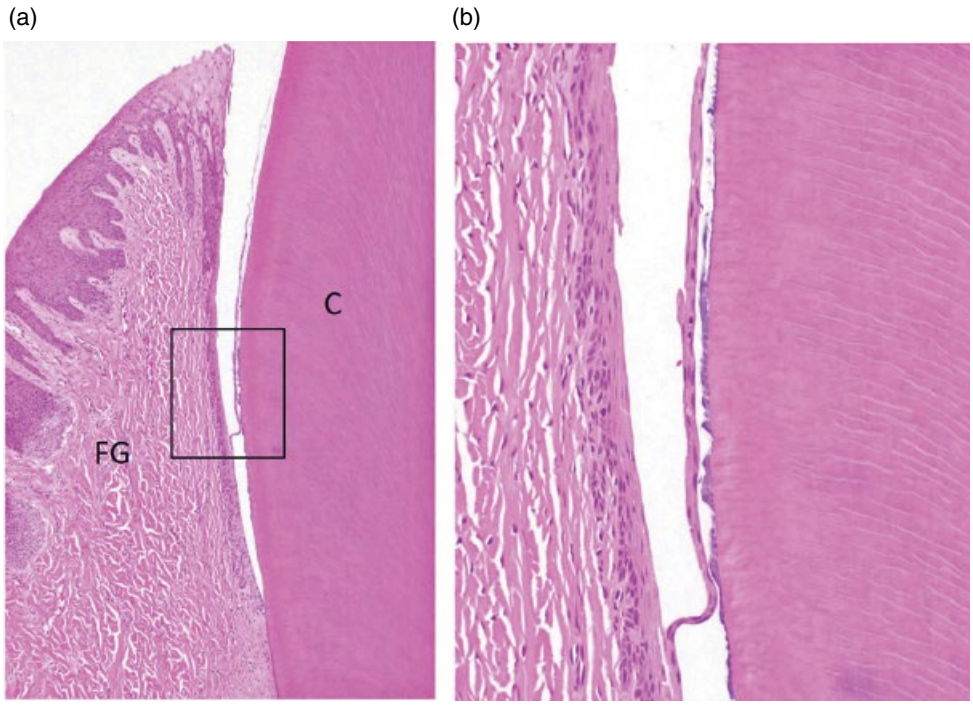


Figure 2.5 Histologic images of a normal tooth from a five-month-old, male Boxer dog. (a) A narrow cleft of clear space separates the free gingiva (FG) from the tooth crown (C), which is an artifact of processing. (b) Higher-magnification (area within the box of a) shows continuity between the sulcular epithelium and epithelium that attaches broadly and directly to the tooth surface. The broad zone of attachment is exaggerated in this case because the tooth is not fully erupted, but histological evidence of attachment is rarely seen in decalcified sections because, in the natural state, the epithelium adheres to enamel.

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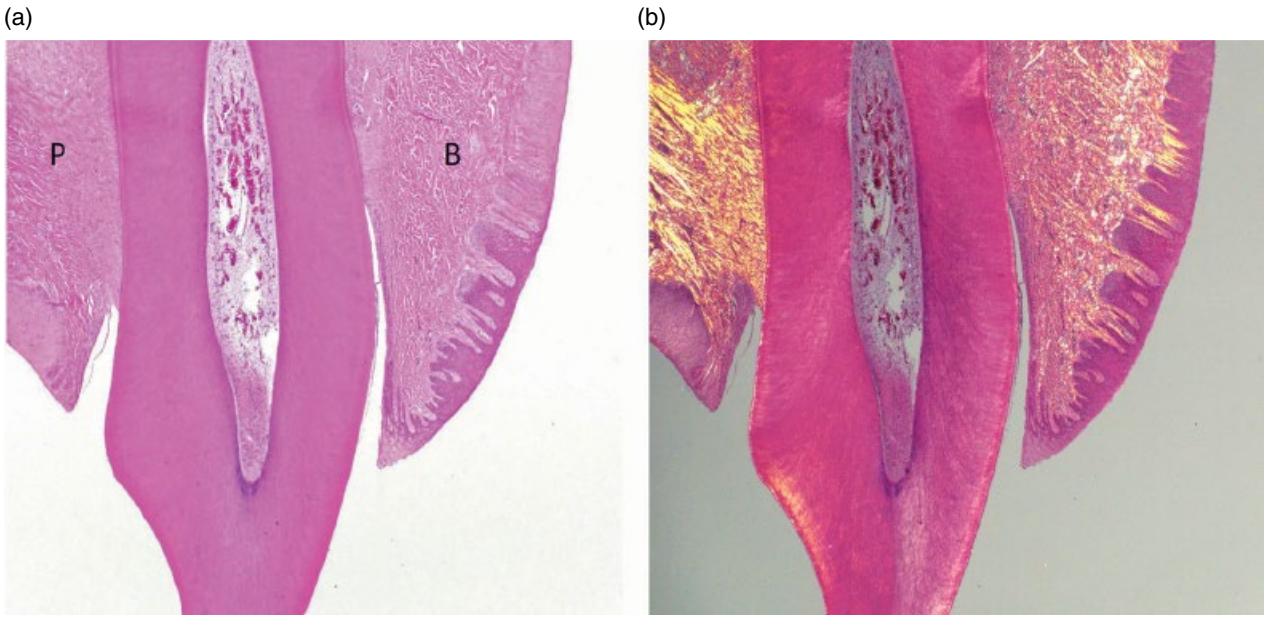


Figure 2.6 Histologic images of a normal maxillary premolar tooth from a five-month-old, male Boxer dog. Photomicrographs taken with (a) brightfield microscopy and (b) polarized light in order to demonstrate the abundance and orientation of gingival collagen fibers. There are obvious differences in the shape of the gingiva and the organization of fibers between the palatal (P) and buccal (B) sides of the tooth.

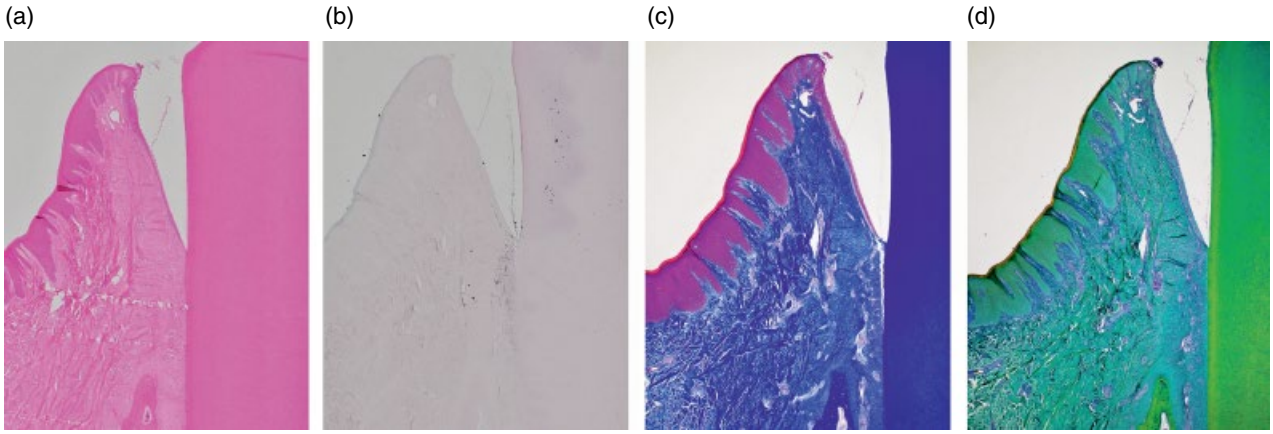


Figure 2.7 A series of low-magnification histologic images of free and attached gingiva adjacent to a tooth of a dog. (a) HE-stained section. (b) Acid Orcein–Giemsa stains elastin fibers black. (c) Masson's trichrome stains collagen blue. (d) Gomori's aldehyde fuchsin stains oxytalan fibers royal blue.

fibers, the gingiva has fibers with elastic properties, including both elastin fibers and oxytalan fibers. These fibers are abundant within the cervical portion of the attached gingiva and are often organized parallel to collagen fiber bundles (Figures 2.7 and 2.8).

2.3 Periodontal Apparatus

Periodontal apparatus refers to all those tissues and structures that anchor the tooth within the bony alveolus. The entire periodontal apparatus includes the periodontal ligament, its adjacent structures (i.e. cementum and alveolar bone), the attached gingival epithelium, and the fiber-rich gingiva that attaches to the cervical portion of a tooth. Cells within the periodontal ligament are assumed to regulate mineralization in some way that would allow a distinct fibrous layer to exist between two heavily mineralized tissues – cementum and bone. The mechanism of this regulation is not currently understood.

The periodontal ligament (PDL), or gomphosis, forms a sheath between the tooth root and surrounding alveolar bone; its functions include (i) holding the tooth in

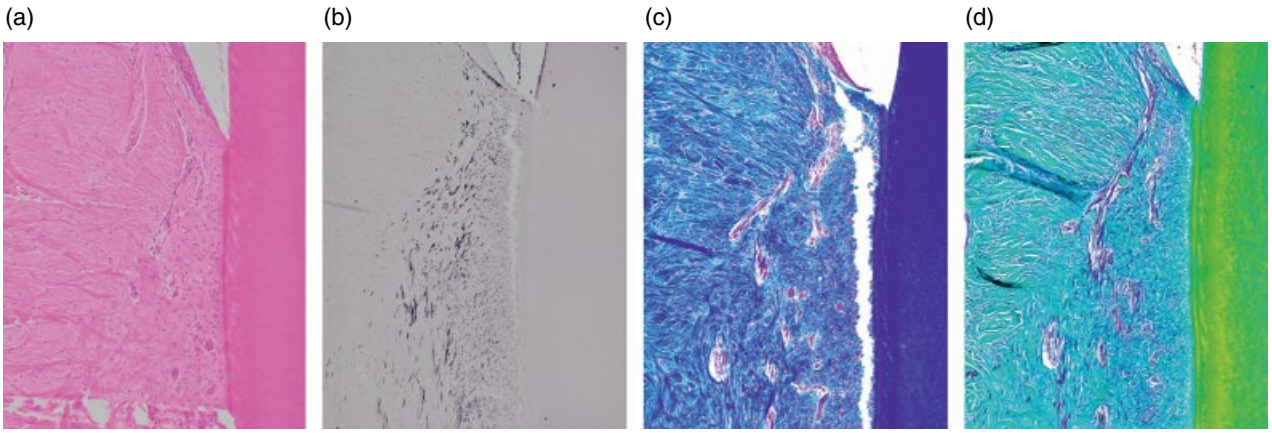


Figure 2.8 Histologic images taken at high magnification at the site of gingival attachment of the same sections shown in Figure 2.7. (a) The hematoxylin and eosin (HE)-stained tissue at the attachment site resembles PDL and is the junction between gingiva and PDL proper. (b) The acid Orcein–Giemsa stain reveals many fine elastin fibers in the attaching tissues, but elastin fibers are not present in the adjacent gingival fibrous tissue (left part of the image) or in the PDL proper (Figure 2.9b). (c) With Masson's trichrome stain, the short, fine collagen bundles near the attachment site contrast with the long, thick collagen bundles in the gingival fibrous tissue to the left. (d) The Gomori's aldehyde fuchsin stain shows that at the site of attachment, oxytalan fibers have approximately the same abundance and distribution as the elastin fibers.

Box 2.1 Components of PDL

Periodontal Ligament Components:

Mesenchymal Cells
- fibroblasts
- osteoblasts
- osteoclasts
- cementoblasts
- undifferentiated mesenchymal cells

Other Cells
- epithelial cells within odontogenic rests
- macrophages
- vessels and nerves

Extracellular Components
- collagen fiber bundles
- ground substance
- oxytalan fibers

place, (ii) acting as a sensory receptor, and (iii). providing a flexible cushion with limited movement when the tooth is subjected to forces. Lower vertebrates, like some reptiles, fish, and sharks, have teeth directly connected to the jawbone and completely lack a periodontal ligament (acrodont dentition). The periodontal ligament is a complex tissue composed of cellular and extracellular components (see Box 2.1). Undifferentiated cells are believed to have the capacity to differentiate into fibroblasts, cementoblasts, or osteoblasts. Fibroblasts produce collagen fibers that arrange in bundles and these are critically important to the structure and function of the periodontal apparatus. *Principal fibers* within the PDL are analogous to gingival fibers within the gingiva, as discussed previously. Principal fibers are composed of type I collagen fiber bundles that firmly attach tooth to bone by anchoring into cementum, spanning the PDL, and anchoring into adjacent alveolar bone. *Sharpey's fiber* refers to an end of a collagen fiber bundle where it embeds into either cementum or bone. Compared to the gingiva, the PDL has fewer oxytalan fibers, which tend to run vertically, parallel to the tooth root (Figure 2.9).

The periodontal tissues are constantly remodeling and the PDL in particular has a high rate of collagen turnover. The PDL is derived from tissues of the dental follicle that surround a forming tooth. The PDL of a young tooth can be difficult to distinguish from adjacent fibrous periosteum of the forming alveolar bone. The forces associated with a tooth in use influence modeling of a distinct PDL. In both disease and health, altered use of a tooth can significantly affect the structure and/or quality of the periodontal tissues. Increased use is expected to lead to increased width of the PDL, increased thickness of the collagen fiber bundles, and increased amount of alveolar bone. Conversely, disuse will lead to narrowing of the PDL, decreased fiber thickness and increased porosity of bone [1].

2.4 Enamel

The histological sections of decalcified teeth rarely retain enamel, which is approximately 96% inorganic mineral, 3–4% organic matrix, and less than 1% water (in comparison, bone is approximately 67% mineral and

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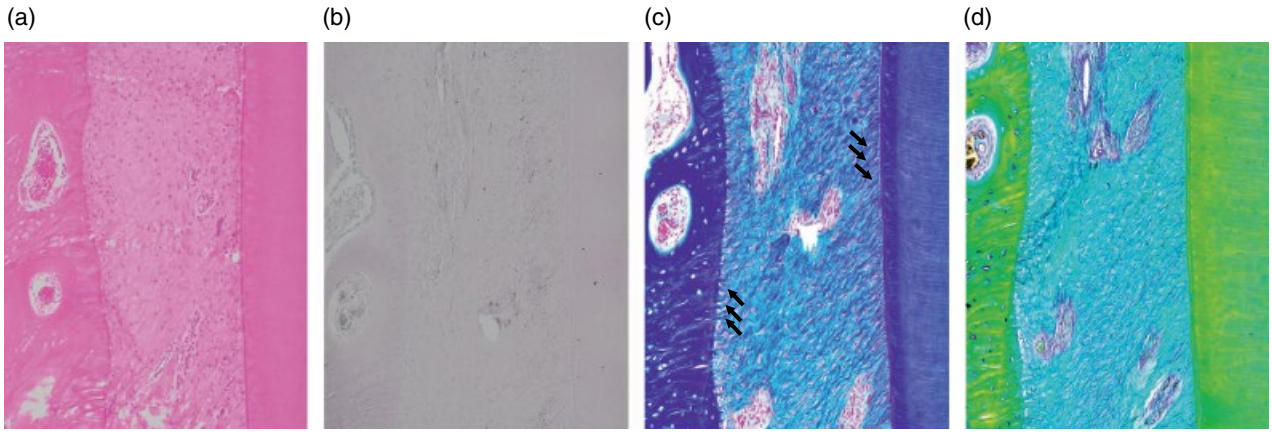


Figure 2.9 Histologic images taken at high magnification of the PDL of the same sections shown in Figure 2.7. (a) With HE stain, the PDL has a familiar pattern of stellate fibroblasts individually surrounded and separated by abundant fine collagen fibers. (b) The acid Orcein–Giemsa stain reveals nearly no elastin fibers within the PDL. (c) Masson's trichrome highlights the fine fibrillar structure of collagen and the Sharpey's fibers (arrows) that anchor PDL to bone (on the left) and PDL to cementum (on the right). (d) Gomori's aldehyde fuchsin stains fine oxytalan fibers that are interspersed throughout the collagen and considerably more abundantly around vessels.

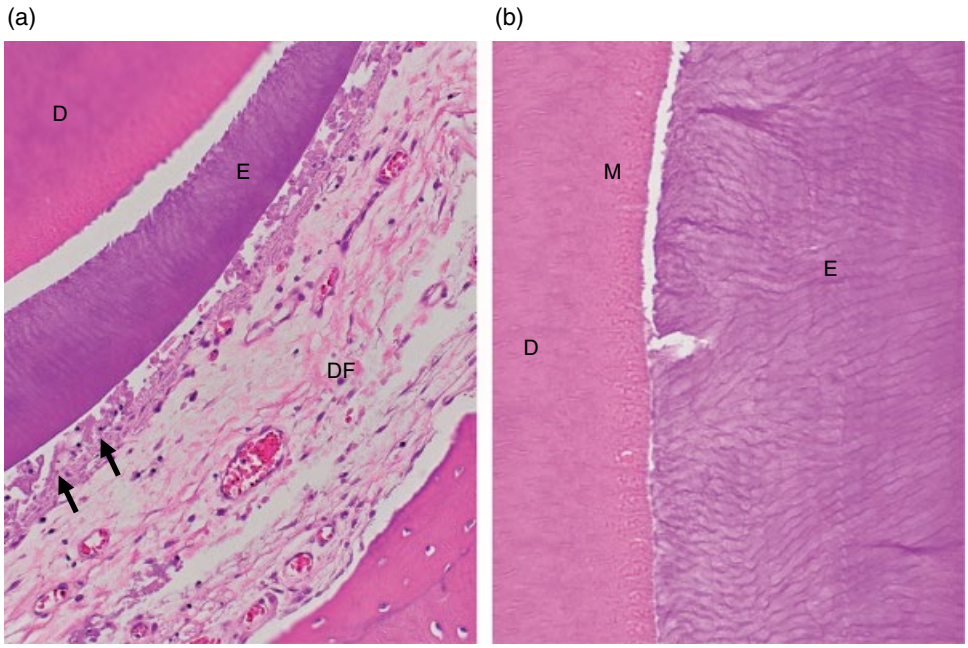


Figure 2.10 Histologic images of an unerupted tooth from a five-month-old, male Boxer dog. Because the tooth has not fully developed, the enamel has enough organic matrix to remain even in decalcified sections such as these. (a) Enamel (E) has been deposited directly onto dentin (D). A layer of degenerating ameloblasts (arrows) separates the enamel from the adjacent fibrovascular stroma of the dental follicle (DF). (b) At higher magnification, the rod (or prism) architecture of the enamel is highly organized and uniform. The mantle dentin (M) is subtly apparent as a thin, ragged outermost layer of dentin. Unlike primary dentin, this layer of mantle dentin is fibrillar rather than tubular.

33% organic) [1]. Ameloblasts secrete enamel matrix that provides the scaffold for mineralization. The matrix is produced in long tubular extensions, called rods (or prisms), that extend from the ameloblasts' basement membrane surface. Crystalline calcium phosphate (hydroxyapatite) is densely deposited within and between rods of matrix. Occasionally, a small amount of the organic enamel matrix will remain in a decalcified section. This residual enamel matrix shows the shape of the "rod sheath," which is a negative image of the regularly organized enamel rods that have been dissolved by acid demineralization (Figure 2.10). When enamel matrix remains in decalcified histological sections, there may be irregularities such as variably-sized vacuoles – these are thought to be an artifact of tissue processing. Occasionally, a *pellicle* (derived from salivary glycoproteins) is apparent

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on the outer enamel surface. *Dental plaque* forms as the pellicle is colonized by oral bacteria, creating a biofilm. Subsequently, *dental calculus* (tartar) may form when inorganic salts are deposited within plaque.

2.5 Dentin

There are three main types of dentin (primary, secondary, and tertiary) that represent two different morphological patterns. In addition, the outermost dentin layer (mantle dentin) and the innermost dentin layer (predentin) are unique. *Mantle dentin* is the first layer of odontogenic matrix to be deposited and is the initial mineralization center at the interface of enamel and dentin. Mantle dentin is deposited at the outset of dentinogenesis crown formation. As such, the mantle dentin is a thin amorphous layer of matrix along the enamel–dentin interface that serves as the initial scaffold for secretion of tubular dentin matrix. Enamel is external to the mantle dentin and primary dentin is internal.

Primary dentin and *secondary dentin* have highly organized tubular architecture – these layers comprise the majority of the dentinal wall of a normal tooth. Primary and secondary dentin are histologically identical and are distinguished from one another only by the time of deposition – primary dentin is deposited until root formation is complete, then secondary dentin accounts for all subsequent dentinogenesis throughout the life of the animal (unless disrupted, in which case tertiary dentin may form). While there is no apparent microscopic difference between primary and secondary dentin, there is occasionally an artifactual cleft that separates the two in histological sections. Although primary and secondary dentin are produced in the same way by the same cells, it is intuitive that some physiological or developmental differences must exist in order to explain (i) the sharp line of demarcation between these layers, and (ii) the fact that some dentinal disorders affect secondary dentin but not primary dentin.

An innermost layer of non-mineralized *predentin* faces the layer of odontoblasts within the pulp chamber. Predentin represents the site of new matrix deposition by odontoblasts. Normal teeth, whether immature or mature, should have a distinct predentin layer since dentinogenesis is ongoing throughout the life of the tooth. See Chapter 3 on odontogenesis for more detail.

Finally, *tertiary dentin* is produced by damaged odontoblasts or replacement odontoblasts from the pulp. As opposed to organized tubules, the tertiary dentin matrix is deposited irregularly. While some wavy or disrupted tubules may occur, the majority of the matrix is amorphous and often bone-like due to entrapment of odontoblasts; thus, *osteodentin* is a term commonly used for tertiary dentin. Tertiary dentin forms when odontoblasts are disrupted or injured for any number of reasons; as such, tertiary dentin is pathological dentin. Pathologists beware – at sites of disrupted dentinogenesis, there is often also irregular deposition and remodeling of both cementum and alveolar bone. In these cases, distinguishing osteodentin from cemento-osseous matrix is a challenge (see Section 6.2.1, Disrupted tooth development).

2.6 Cementum

Cementum is a poorly cellular, bone-like tissue produced by cementoblasts. The origin of cementoblasts is controversial – they arise either from the fibrovascular tissue of the dental follicle or the epithelial root sheath [1]. It is known that the mature periodontal ligament contains cells capable of differentiating into fibroblasts, cementoblasts or osteoblasts. In the normal tooth, *acellular cementum* forms a narrow, relatively uniform seam along the lateral surfaces of the tooth roots, directly upon the outer dentin surface and facing the periodontal ligament on the opposite side. As discussed above, numerous extracellular fibers anchor cemental matrix to the fibrous periodontal ligament matrix.

A second type of *cellular cementum* allows the periodontal apparatus to adapt to wear and tooth movement, and to assist in the repair of the periodontal tissues [1]. As the name suggests, this tissue is more cellular and may be more porous than the cementum that broadly attaches the tooth to the periodontal ligament. Because of this, cellular cementum may be histologically indistinguishable from immature woven bone. In daily practice, the authors of this textbook rarely use the modifiers "acellular" or "cellular," preferring to say just "cementum." We also favor the term "cemento-osseous matrix," which is useful when describing lesions where ankylosis and remodeling make it impossible (or nearly so) to distinguish cementum from alveolar bone.

2.7 Odontoblasts and Pulp Stroma

In a normal vital tooth, the odontoblasts may range from a robust palisading layer of tall columnar cells with cytoplasmic extensions (tubules), to an attenuated cell layer that is scarcely visible in histological sections. The latter morphology is common in aged teeth. Intuitively, the morphology correlates with rate of dentin production. In a single maturing tooth, the morphology of the odontoblast layer can vary with location in order to maintain the appropriate tooth shape (Figure 2.11).

The dental pulp is loosely arranged fibrovascular connective tissue with rich innervation. Older teeth have less abundant pulp due to deposition of secondary or tertiary dentin that narrows the pulp canal (Figure 2.12).

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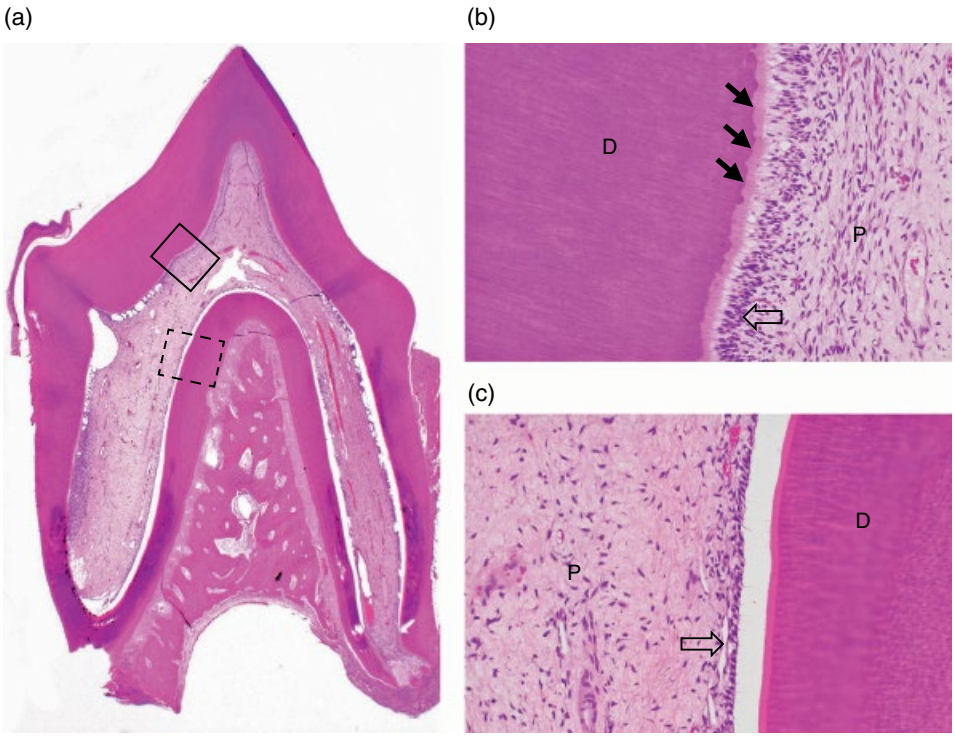
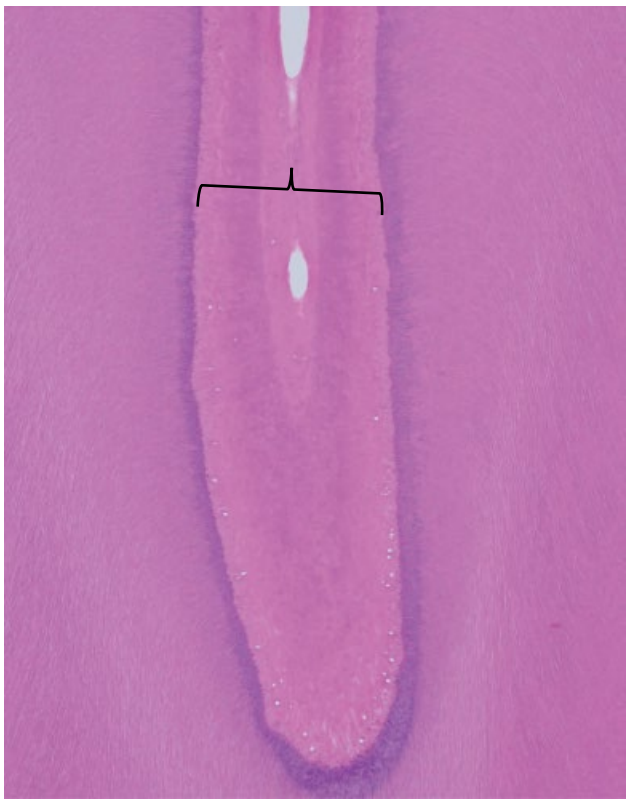


Figure 2.11 Histologic images of a maxillary fourth premolar from a young cat. (a) The pulp chamber is wide, consistent with a young animal. Differential rates of secondary dentinogenesis result as the tooth continues to mature while maintaining appropriate tooth shape and responding to physiological forces. (b) Higher magnification of the area within the solid line box demonstrates dentin (D) and pulp (P) separated by a distinct layer of predentin (arrows) and a robust layer of odontoblasts (open arrow). (c) The predentin and odontoblast layers are more attenuated in the area enclosed within the dashed line box.



The pulp stroma of older teeth also tends to have greater amounts of extracellular collagen matrix (i.e. pulp fibrosis) and dystrophic pulp calcifications that are thought to represent dystrophic mineralization of vessels or collagen fibers [1].

2.8 Maxillary and Mandibular Bone

Some unique histological features of the jawbones stem from the fact that this bone is formed by intramembranous ossification as opposed to endochondral ossification. Referring to bone density, the analogy has been made between maxillary bone as balsa wood and mandibular bone as ebony (anonymous). There is truth to this difference, particularly regarding the predominance of trabecular bone as compared to cortical bone. The mandible has a thick cortex with porous medullary (cancellous) bone. The maxillary bone is diffusely porous (cancellous)

Figure 2.12 Histologic image of a tooth from an adult dog. The entire width of what was the pulp chamber (bracket) is nearly filled by bone-like osteodentin, a process known as "pulp sclerosis." One can assume that the odontoblasts were affected by injury, inflammation or necrosis at some previous time, likely long ago.

with a thin cortex. Maxillary bone is continuous with adjacent "plates" of bone that form from different ossification centers, including incisive bone, palatine bone, and nasal bones. These plates of maxillary bone interconnect through bone–bone junctions referred to as synostoses. Except in the developing embryo or neonate, these transitions are imperceptible. Thus, although not technically correct, the term "maxilla" is often used to refer to all bones of the upper jaw/ maxillofacial region (see Figures 2.13–2.15).

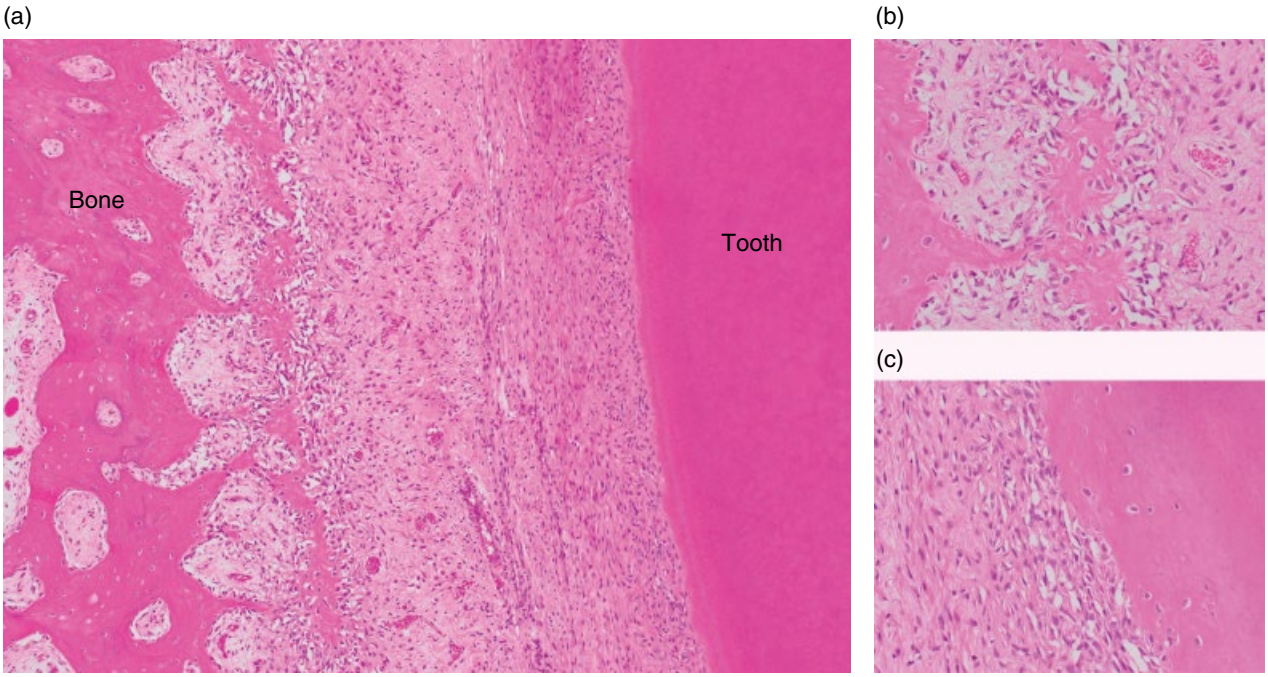


Figure 2.13 Histological images from the mandible of a young German Shepherd dog. (a) The low-magnification image shows the relationship between the tooth (right of image), periodontal ligament (middle) and alveolar bone (left of image). (b) The plump osteoblasts have similar morphology to the plump cementoblasts. (c) Both of these cell types arise in close proximity to fibrovascular tissue that was the dental follicle and is becoming the periodontal ligament. Although poorly defined in these images, the periodontal ligament would have become more distinct as the dog aged and alveolar bone became completely modeled.

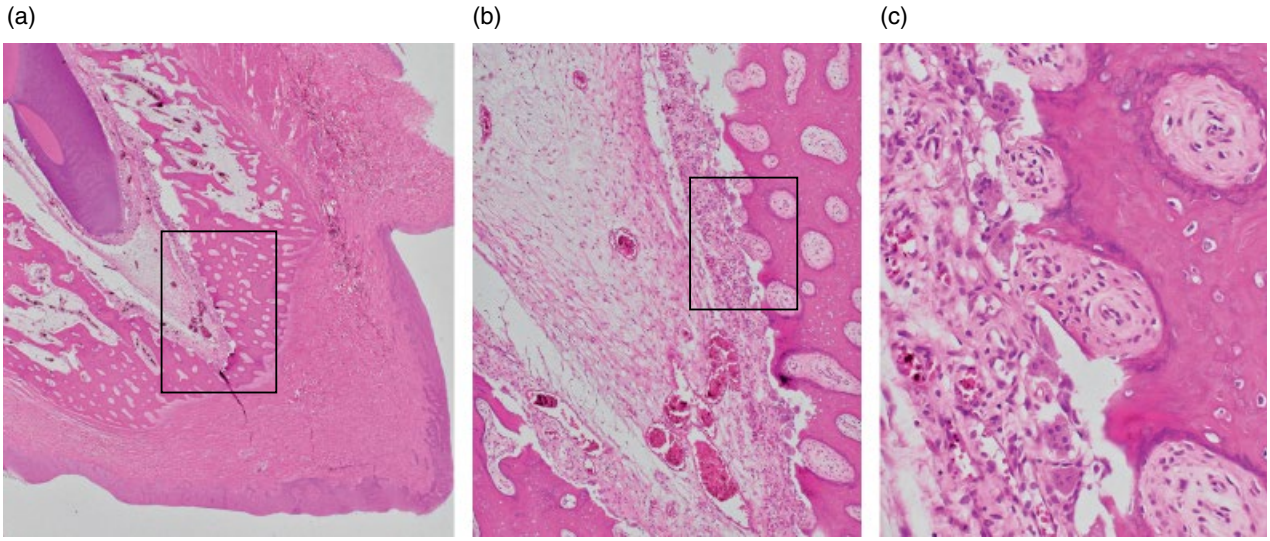


Figure 2.14 Histological images of maxillary bone from a five-month-old, male Boxer dog. (a) An incompletely erupted tooth has not emerged through the palatal mucosa, although a V-shaped area of fibrous tissue approximates the eruption pathway that this tooth would have taken. (b) The adjacent alveolar bone continues to be cut back as a result of osteoclastic activity. (c) Large numbers of osteoclasts are present and necessary for normal tooth eruption and exfoliation of the primary dentition.

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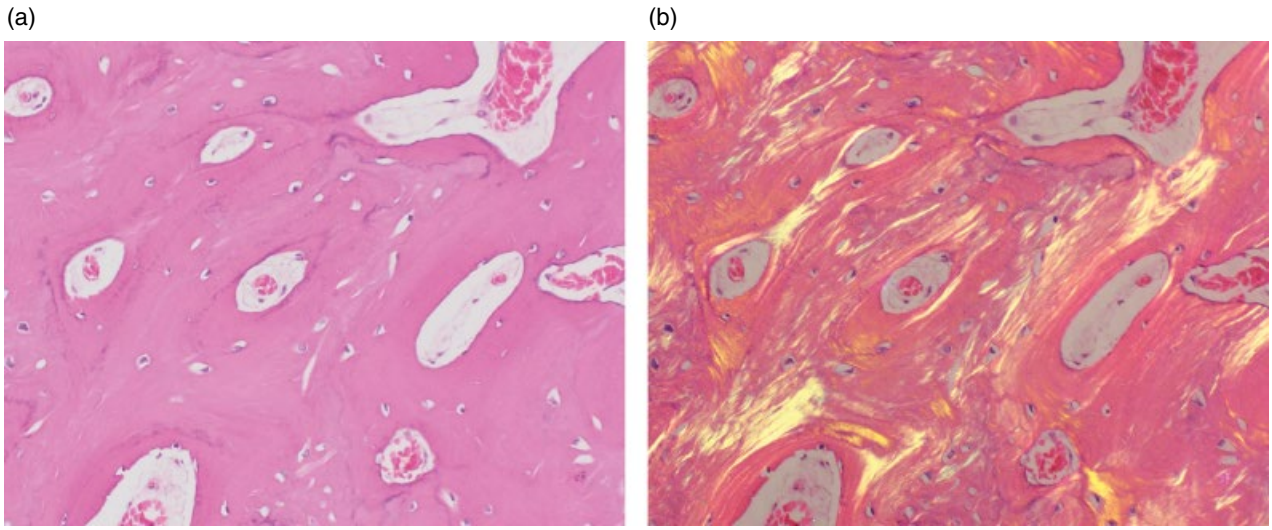


Figure 2.15 Histological images of mandibular bone from a five-month-old, male Boxer dog photographed with (a) brightfield and (b) polarized light, revealing unstructured woven bone with short intersecting fibers. Partial laminar modeling is apparent where matrix is denser, less cellular and has fibers aligned in parallel.

Immature bone can present unique challenges for the pathologist who is attempting to distinguish between a pathological process and a physiological process. In general, young animals have more cellular connective tissues, their bone is incompletely modeled, and active odontogenic tissue elements reside within the jawbones at least until all permanent teeth have erupted.

Reference

1 Nanci, A. and Ten Cate, A.R. (2008). *Ten Cate's Oral Histology: Development, Structure, and Function*, 7e. St. Louis, MO: Mosby Elsevier.

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3

Tooth Development (Odontogenesis)

One of the more complex and puzzling aspects of oral pathology is the classification of odontogenic lesions and cysts. The key to unraveling these puzzles is rooted in a solid understanding of tooth development. The study of tooth development is both a fascinating and well-described aspect of embryology. Although tooth development, or *odontogenesis*, has been well-documented elsewhere (at least for animals with brachydont dentition – short crowns and well-developed roots), we review the general embryologic features here in recognition of its central importance to the classification of odontogenic lesions.

Odontogenesis initiates within the embryo in utero; in most animals, it continues after birth for months to (in some cases) years. The process of tooth development is relatively similar for both the deciduous and permanent dentition. Development of the tooth involves the interplay between two principal tissue types, odontogenic epithelium and the subjacent neural crest-derived ectomesenchyme of the jaws. The primitive tooth germ can be simplified into three coherent parts: (i) the odontogenic epithelium (dental lamina-derived enamel organ); (ii) the surrounding ectomesenchyme-derived *dental follicle* (or *dental sac*); and (iii) the partially entrapped dental papilla, which is also derived from ectomesenchyme (Figure 3.1). The enamel organ is responsible for enamel formation, the dental follicle forms the structures associated with the periodontal ligament (PDL), and the dental papilla forms the tooth pulp and dentin.

Tooth embryogenesis moves through predictable and overlapping stages of development referred to as the *bud, cap, bell,* and *crown* stages. Each stage refers to the histologic *shape of the epithelial tooth germ*. The bud stage initiates with a proliferative focal thickening and progressive extension of oral epithelium into the subepithelial tissues, forming the *dental lamina* (Figure 3.2). For animals with two sets of teeth (deciduous and permanent), a bud off of the enamel organ, the future permanent tooth, remains in suspended development while the deciduous tooth proceeds down the developmental pathway. As the dental lamina expands to form a cap-like structure within the oral subepithelium, it induces the subjacent ectomesenchyme to differentiate and proliferate. This differentiation occurs *within a concavity* of the inner surface of the dental lamina; this tissue develops into the dental papilla (Figure 3.3). The relationship between the odontogenic epithelium of the dental lamina and the underlying ectomesenchyme is both complex and a two-way street, as we shall see.

The odontogenic epithelium continues to proliferate, eventually developing into a bell-like structure (Figure 3.4). During this metamorphosis, the epithelium differentiates into the enamel organ that is composed of multiple histologically distinct layers of cells - an inner layer of palisading columnar ameloblasts and stratum intermedium (together known as the inner enamel epithelium), a sheet of star-shaped epithelial cells known as the stellate reticulum, and an outer enamel epithelium (Figure 3.5). The ameloblasts and stellate reticulum exhibit those specific histological features (discussed below) that are commonly recognized as characteristic of odontogenic epithelium. The ameloblasts form a linear palisade, have antibasilar nuclei and often have basilar cytoplasmic clearing, which is thought to be an artifact of processing [1]. The stellate reticulum is comprised of variably sized, stellate to polygonal epithelial cells with thin and prominent cell–cell junctions (desmosomes) separated by extensive intercellular space. The wide intercellular spacing of these unusual epithelial cells is thought to be the result of extracellular deposition of water-attracting glycosaminoglycans [1]. The histological appearance of the stellate reticulum suggests that it may function as a cushion over the developing tooth. In pathologic lesions, recognition of these histological features is often key to establishing an appropriate diagnosis (discussed further in Section 7.1, Approach to Odontogenic Neoplasms). Note: One of the most commonly diagnosed odontogenic lesions in veterinary species is canine acanthomatous ameloblastoma (CAA); this lesion *does not* exhibit histologic features of stellate reticulum.

The ectomesenchymal tissue surrounding the odontogenic epithelium forms a variably distinct structure

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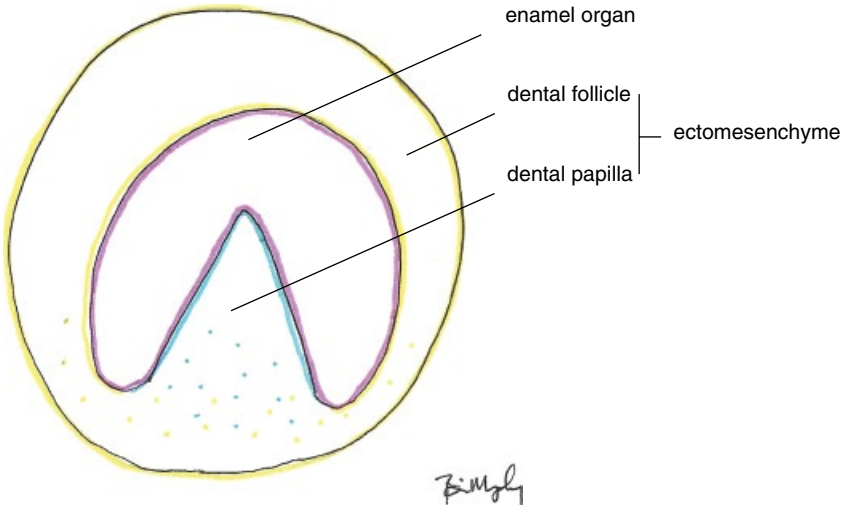
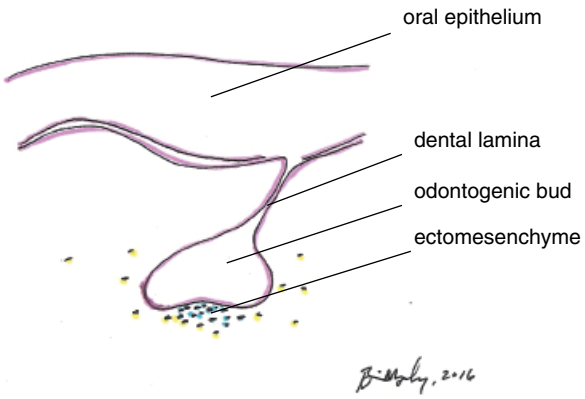


Figure 3.1 Diagram of the three primitive tooth germs.

(a)



(b)

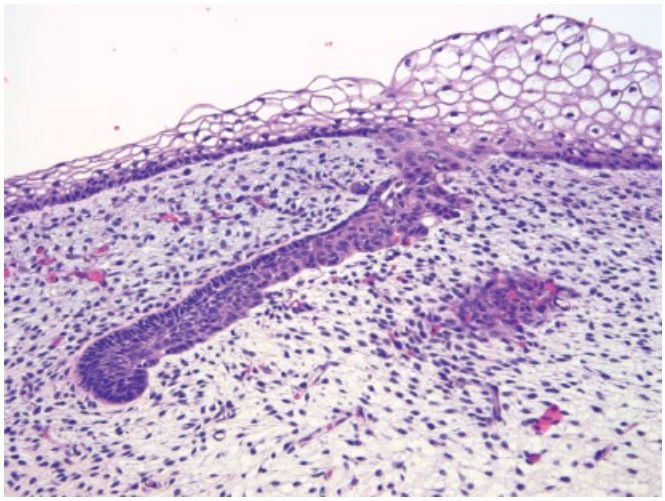
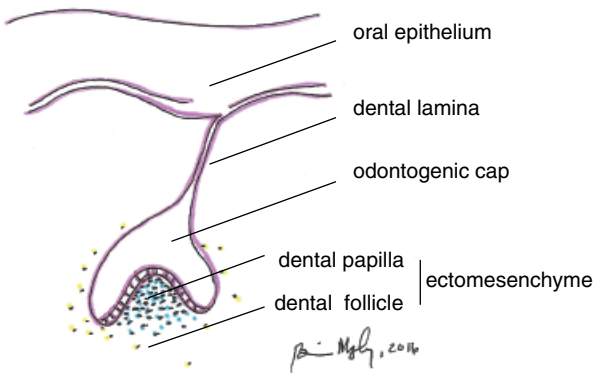


Figure 3.2 Odontogenesis, bud stage. The bud stage of odontogenesis initiates as an invagination of the overlying oral epithelium into the subjacent connective tissue. (a) Diagram of an odontogenic bud. (b) Histologic image, ~40-day gestation feline fetus.

(a)



(b)

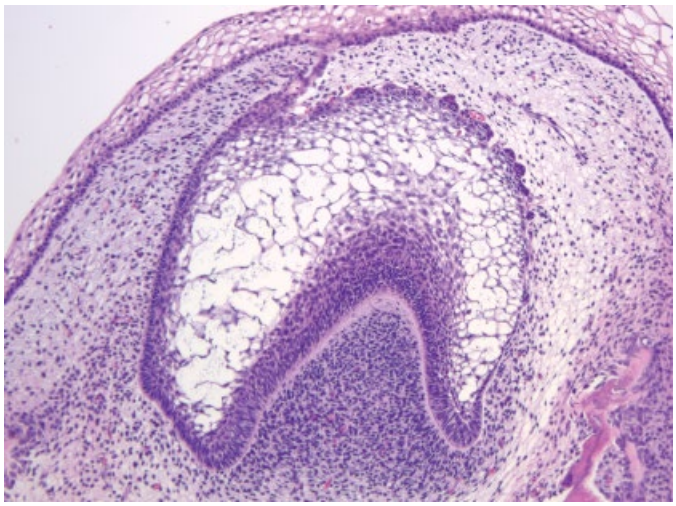


Figure 3.3 Odontogenesis, cap stage. The cap stage of odontogenesis is characterized by differentiation of the ectomesenchyme (future dental papilla) within a concavity of the dental lamina. (a) Diagram of the odontogenic cap. (b) Histologic image, ~40 day gestation feline fetus.

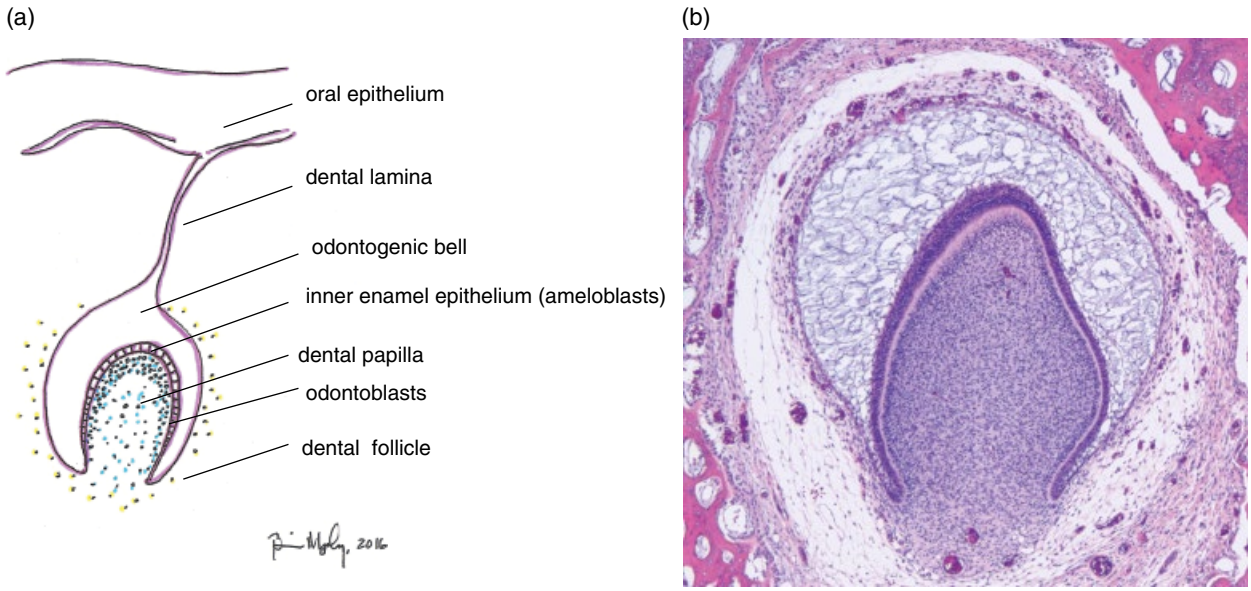


Figure 3.4 Odontogenesis, bell stage. The enamel organ forms a well-defined bell-like structure surrounding the proliferative ectomesenchyme of the dental papilla. (a) Diagram of the odontogenic bell. (b) Histologic image, ~60-day gestation (term) feline fetus.

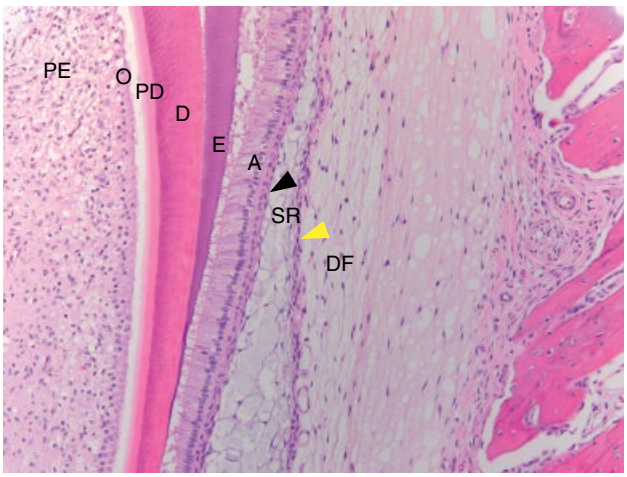


Figure 3.5 Histology of a developing tooth. In this histologic image of a developing tooth, the pulp ectomesenchyme (PE), palisading odontoblasts (O), predentin (PD), dentin (D), enamel (E), palisading ameloblasts (A), stratum intermedium (black arrowhead), stellate reticulum (SR), outer enamel epithelium (yellow arrowhead) and dental follicle (DF) are visible. The PE and odontoblasts are ectomesenchymal tissues while the ameloblasts, stratum intermedium, SR, and outer enamel epithelium are all derived from the dental lamina. Note the subtle extracellular basophilia and unusual spider-like shape of the SR. Histologic image of a developing premolar tooth (maxilla), three-week-old kitten.

called the *dental follicle* or *dental sac*. This condensed connective tissue structure separates the developing tooth from the surrounding jawbone. The dental follicle is the embryologic precursor to the PDL, which serves to anchor the tooth into the surrounding alveolar bone.

During the bell stage of development, palisading ameloblasts/ inner enamel epithelium extend down to the base of the crown and, at the cervical loop, reflect back to become contiguous with the outer enamel epithelium. Later in development, the opposed inner and outer enamel epithelium envelop the developing root (see discussion of Hertwig's epithelial root sheath below). Within the adjacent ectomesenchyme, odontoblasts differentiate and proliferate subjacent to the basement membrane of the palisading ameloblasts. Formation of the dental matrix, *dentinogenesis*, is initiated during this stage of development (Figure 3.6). The ameloblasts provide a molecular signal inducing the subjacent odontoblasts to produce dentin. Dentin is initially produced from cytoplasmic extensions of the odontoblasts as a lightly eosinophilic staining material called *predentin*. Predentin becomes dentin as it calcifies. In HE-stained tissue sections, dentin stains pink. In normal tooth structures, parallel tubules are evident within the dentinal matrix, reflecting the linear extrusion mechanism of dentinal deposition by odontoblasts.

A word or two about primary, secondary, and tertiary dentin – odontoblasts in the pulp cavity persist throughout the life of the tooth, continuing to produce *secondary dentin* and progressively narrowing the diameter of the root canal. Secondary dentin is formed after root formation is complete, and accumulates at a much slower rate than primary dentin (initial dentin laid down during odontogenesis). This process of a progressively narrowing root canal is evident radiographically as the tooth ages. Tertiary dentin is formed as a result of a pathologic stimulus, such as traumatic injury, or as a degenerative

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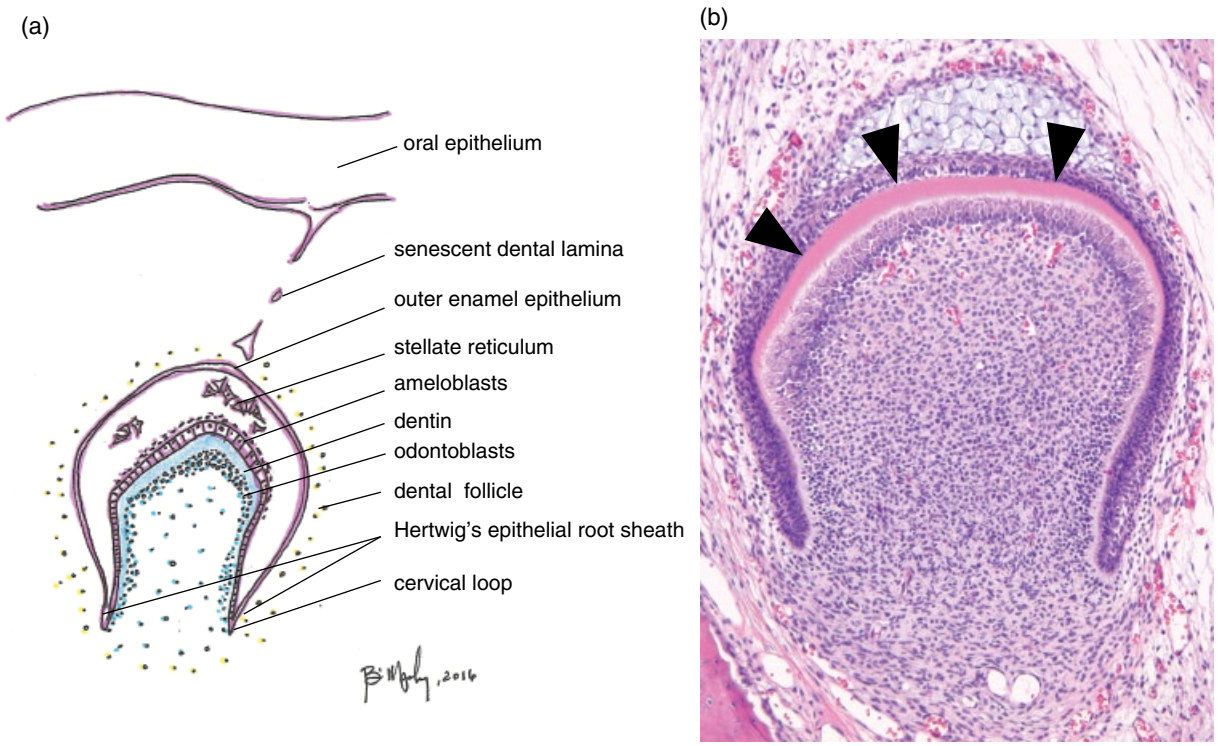


Figure 3.6 Odontogenesis, late bell stage (dentinogenesis). In the late bell stage of tooth development, ectomesenchyme-derived odontoblasts produce a strip of dentin along the basement membrane. (a) Diagram of dentinogenesis. (b) Note the ribbon of hyalinized, eosinophilic dentin (black arrowheads) in this histologic image. ~60-day gestation (term) feline fetus.

change of attrition; tertiary dentinogenesis may occur in mature or immature teeth. Primary and secondary dentin are histologically indistinguishable, both having regular tubular architecture. Tertiary dentin is deposited rapidly and consists of irregularly organized tubules, amorphous matrix, and/or bone-like osteodentin.

The earliest presence of dentin subsequently provides a signal to induce the ameloblasts to initiate synthesis of enamel on the dentinal surface during the crown stage of tooth development, *amelogenesis* (Figure 3.7). *Reciprocal induction* is the process of ameloblasts signaling odontoblasts to produce dentin followed by dentinal matrix signaling ameloblasts to produce enamel (Figure 3.8). There is a pathologic correlate of this biological scheme, as will be discussed in later chapters. As the dental matrices accrete on top of one another, the two germinal tissues, odontoblasts and ameloblasts, gradually move apart. At this time, the dental lamina also fragments into islands of epithelium referred to as the *rests of Serres*. Pathologic proliferation of these epithelial remnants is associated with the development of some odontogenic cysts and tumors.

In a mature erupted tooth, the enamel matrix is often absent in histologic sections. This is because enamel is very hard and primarily comprised of mineral (~95%), which is essentially removed during sectional processing (decalcification). However, in an unerupted tooth (or odontogenic tumor), fragments of basophilic to purple-staining enamel matrix are often evident in histologic sections, perhaps as a result of entrapment within the adjacent tissues or a greater ratio of ground substance to mineral in the immature enamel.

In animals with brachydont dentition, enamel is confined to the crown of the tooth. The purpose of the bi-layered tube of epithelium (*Hertwig's epithelial root sheath*) that surrounds the tooth root from the base of the crown to the apex is to induce the subjacent odontoblasts to form root dentin. As tooth development progresses, the epithelium of Hertwig's epithelial root sheath (Figure 3.6) partially disintegrates, resulting in isolated islands of odontogenic epithelium that persist within the PDL into adulthood as *rests of Malassez* (Figure 3.9). The rests of Malassez may play a role in regulation and maintenance of PDL, while proliferation of these epithelial remnants is thought to be associated with lesions such as odontogenic cysts and tumors.

The process of progressive epithelial disintegration facilitates contact between the evolving PDL and tooth root dentin, resulting in the differentiation of cementoblasts and the deposition of a bone-like matrical substance called cementum on the dentinal surface, referred to as *cementogenesis* (Figure 3.9). Like bone, cementum is pink-staining (with HE stains) and has variably densely arranged

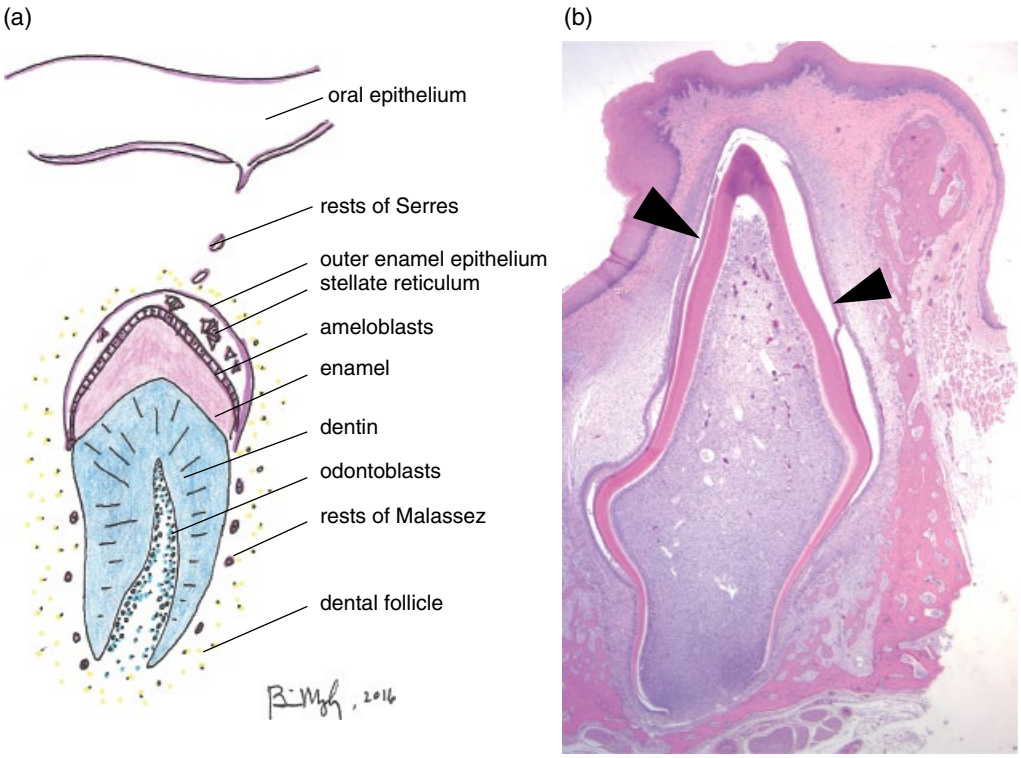
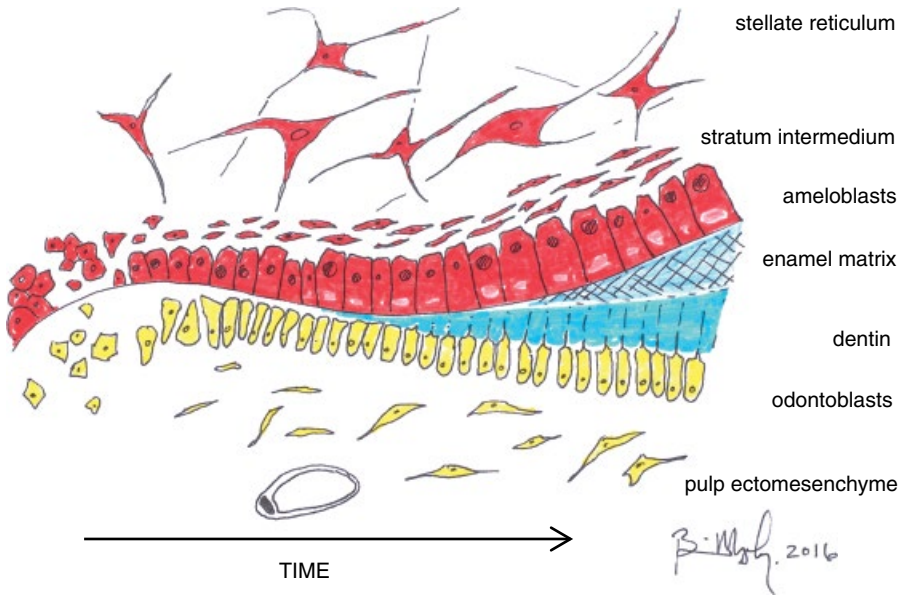


Figure 3.7 Odontogenesis, crown stage (amelogenesis). During the crown stage of odontogenesis, enamel is produced by the ameloblasts and deposited on the surface of the dentin. (a) Diagram of amelogenesis. (b) In this histologic image of the crown stage of tooth development, some of the enamel has been dissolved by tissue processing (decalcification), leaving an artifactual void delineating the tooth crown. However, a thin ribbon of purple-staining enamel remains visible in this section (black arrowheads). Three-week-old kitten.

Figure 3.8 Diagram of reciprocal induction. Odontoblast-derived dentin formation precedes ameloblast-derived enamel formation. Deposition of the two matrices gradually forces the palisading odontoblasts and ameloblasts apart. *Source:* Figure redrawn from [2].



embedded cells, called cementocytes; for the pathologist, cementum can be challenging to impossible to differentiate from immature woven bone. The ectomesenchyme of the dental follicle also facilitates the differentiation and production of unique PDL fibroblasts along with osteoblasts and cementoblasts, which form the adjacent alveolar bone and cementum. Collectively, these tissues produce the dental–alveolar joint called the *gomphosis*.

As the formation of the tooth crown completes and the nascent tooth moves toward the oral cavity, the enamel

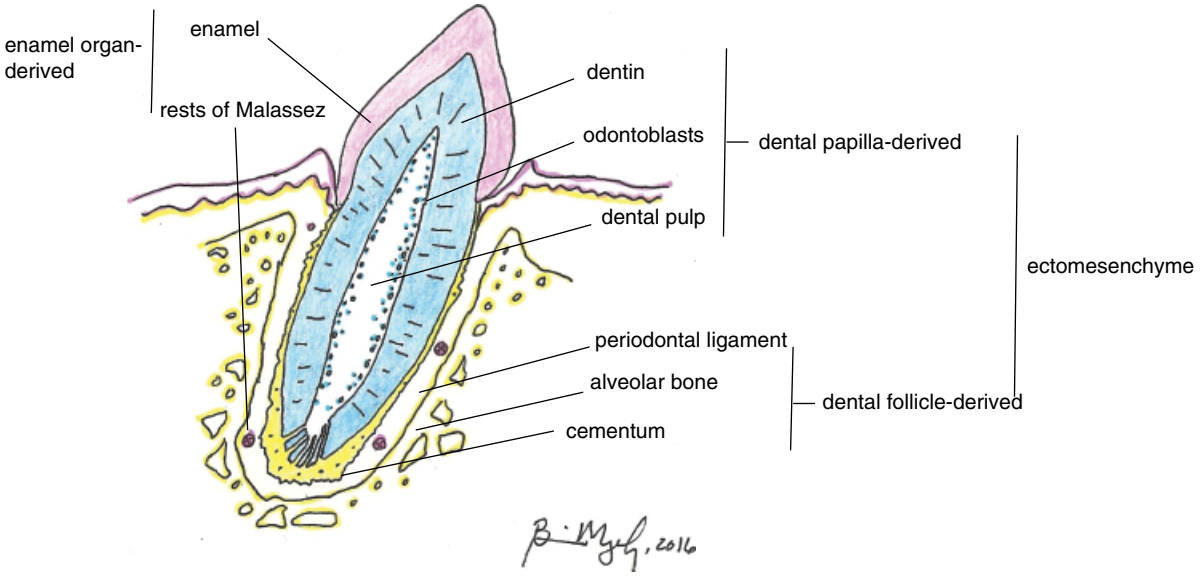


Figure 3.9 Diagram of an erupted brachydont tooth.

organ collapses and atrophies, producing the *reduced enamel epithelium*. Persistence of this epithelial structure can result in odontogenic cyst formation. Obviously, the crown of the erupted tooth is free of odontogenic epithelium. As a result, repair of damaged enamel is not possible after tooth eruption. Surprisingly, the precise mechanism of tooth eruption remains controversial.

3.1 Species Differences

It is important for the pathologist to have an understanding of the differences between brachydont and hypsodont teeth. The word "hypsodont" indicates *high crowned* or *long crowned tooth*, as the crown extends well past (underneath) the gum line. Hyposdont teeth are an anatomic and physiologic adaption of specific teeth in grazing herbivorous animals like ruminants, rodents, rabbits, and horses. Many herbivorous animals use their teeth to grind fibrous or abrasive feed material, which results in progressive dental wear. This problem of progressive dental wear over time is elegantly solved through the development of constantly erupting hyposodont teeth with long crowns and relatively short roots. Hypsodont teeth are further subdivided into *aradicular* (lacking a true root) and *radicular*. For animals with aradicular hypsodont dentition (also referred to as *elodont dentition*) like rabbits, guinea pigs and chinchillas, the teeth grow continuously throughout the animals' lives. The tooth apex (bottom) of aradicular hypsodont teeth is open and is not cone-shaped like the root of brachydont teeth. In animals with radicular hypsodont dentition, like horses and ruminants (cheek teeth), the

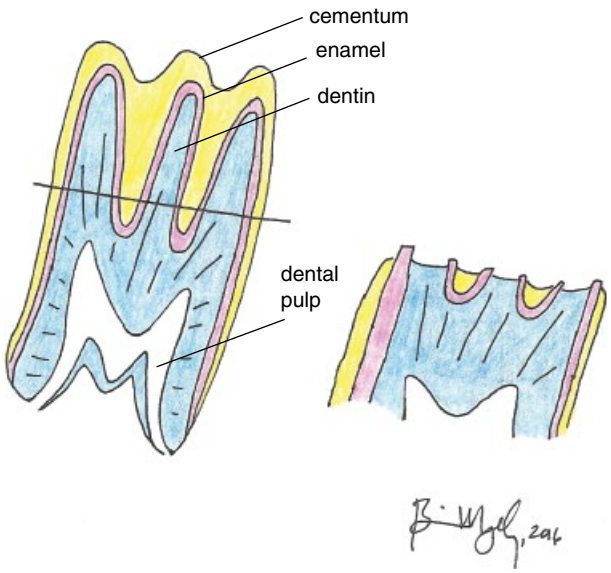


Figure 3.10 Diagram of a hypsodont tooth.

apex of the root eventually closes and the root ceases to elongate. All rodents have continuously growing, aradicular hypsodont incisors. The premolar and molar teeth of rodents, however, can be either radicular or aradicular, depending upon the species.

Unlike a brachydont tooth, the hypsodont crown has an anatomically complex convoluted pattern of cementum, enamel, and dentin arranged in layers (Figure 3.10). At the time of tooth eruption, the enamel is actually covered with a thin layer of cementum. After some wear has occurred due to mastication, a complex ridged occlusal surface emerges comprised of alternating layers

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of cementum, enamel, and dentin. The ridges are the result of the varying rates of attrition of these different odontogenic matrices, and facilitate efficient mastication of fibrous feed material. These ridge patterns are sharply delineated in certain herbivorous taxa like the Cervidae (deer, elk, moose, caribou).

Near the tooth apex, persistence of the enamel organ into adulthood is a requirement of hypsodont dentition. As the tooth grows toward the oral cavity, the enamel organ fragments, facilitating contact between the PDL and enamel surface. This results in the deposition of cementum onto the enamel surface. There are several potential pathologic consequences of the persistence of tooth germ into adulthood. For hypsodont animals, there is a delicate balance between tooth root production (growth in tooth length) and wear. A failure to maintain this balance due to inadequate wear or other mechanism can result in malocclusion, which is common in rodents, rabbits, and horses.

Rodents have only one set of teeth while rabbits have both deciduous and permanent teeth. The enamel matrix of rabbits and rodents forms a prominent and complex crisscrossing pattern that is often evident in histologic sections. Grossly, many rodents have a yellow-orange enamel pigment on the rostral surface of the incisor teeth. This is most evident in beavers, and is the result of the incorporation of iron into the enamel. The presence of iron makes the rostral surface of the tooth very hard, resulting in the sharp chisel shape of the rodent incisor. Rabbit incisors, however, are white and contain very little iron relative to rodents. Some animals (camelids, cervids, bovids, and equids) have an additional odontogenic feature of their hypsodont teeth, the *infundibulum* or dental cup. The infundibulum is a diverticulum or recess within the occlusal surface that is lined by cementum. In some of these animals, the folding pattern of the infundibulum can be extremely complicated. Caries of this structure (*infundibular necrosis*) is a relatively common condition in older horses.

Since there really is no anatomic difference between the premolar and molar teeth of many herbivorous mammals like horses and rabbits, these teeth are often referred to as *cheek teeth*. In sagittal histologic sections of the skull or mandible of small mammals with hypsodont dentition (rodents, rabbits, and guinea pigs), the cheek teeth form anatomically complex arrays (Figure 3.11). Due to the undulating odontogenic matrices, it can be difficult for the pathologist to determine where one tooth stops and another begins. Pathologic changes within the tooth structure and adjacent periodontal ligament/alveolar bone are common in such animals, and can be easily dismissed if the pathologist fails to appreciate the normal hypsodont tooth anatomy. In animals like the guinea pig and capybara (Caviidae), the crown cementum (*coronal cementum*) is cartilage-like and is referred to as *chondroid cementum* (Figure 3.11). This matrical material is less hard than enamel or dentin and presumably wears at a more rapid rate. The precise reason for the evolution of this form of cementum in the Caviidae remains controversial.

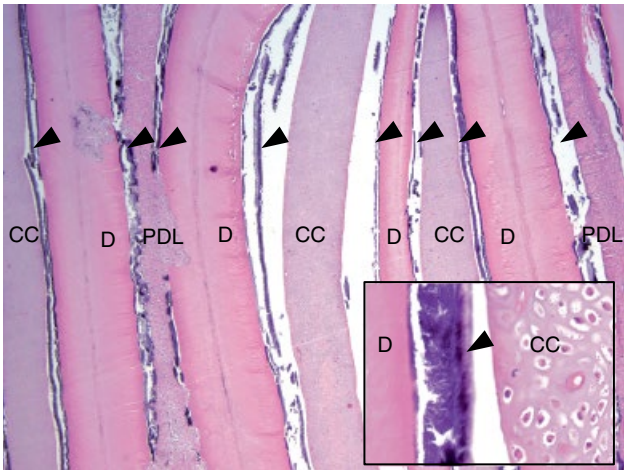


Figure 3.11 Histologic image of the hypsodont cheek teeth of a guinea pig. Histologically, it is difficult to distinguish between individual teeth. Chondroid cementum (CC), dentin (D), periodontal ligament (PDL), and enamel matrix (black arrowhead) are evident. Inset – higher magnification image to show detail of the CC. Mandibular cheek teeth, adult guinea pig.

References

1 Meuten, D.J. (2017). *Tumors in Domestic Animals*, 5e. Hoboken, NJ: John Wiley & Sons.

2 Walsh, K.M., Denholm, L.J., and Cooper, B.J. (1987). Epithelial odontogenic tumours in domestic animals. *J. Comp. Pathol.* 97: 503–521.

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4

Conditions and Diseases of Teeth

4.1 Odontogenic Developmental Anomalies and Attrition

Abnormal teeth in young animals may occur for many reasons – some are genetic but others are acquired. The distribution of abnormal teeth may be focal (one or few teeth affected) or diffuse (i.e. generalized, affecting all teeth). If possible, determining the underlying cause of such a lesion is important, as appropriate management or intervention will depend on the expected viability and functionality of the affected teeth. The pathologist's role in the diagnostic workup is to help the clinician answer the question, "Is this a cosmetic condition or are the affected teeth at risk for significant dental disease?"

Disturbances of tooth development may also be associated with dysplastic and/or hyperplastic changes in the gingiva, periodontal tissue and/or alveolar bone. We encourage clinicians to submit extracted teeth along with the surrounding bone and/or soft tissue for histopathologic examination (see Appendix). An accurate diagnosis also depends on open, collaborative communication between the clinician and the pathologist. In addition to clinical information regarding the appearance and condition of the teeth and dental radiographic findings, a thorough evaluation of the history is often required to establish the cause of odontogenic anomalies. Useful information would include known drug or toxin exposure, exposure to infectious agents, and possible pedigree evaluation.

In this chapter, we discuss primary hereditary disorders, spontaneous anomalies of unknown cause, and dental alterations due to extrinsic factors (e.g. canine distemper virus or tetracycline staining). We have not included a discussion of oral lesions that occur with craniofacial anomalies or developmental disorders of another organ system (e.g. osteopetrosis). Also, less emphasized are lesions that may be encountered by veterinary dentists, but rarely sampled or submitted for histological examination (developmental palatal disorders, malocclusions, prognathism or brachygnathism).

4.1.1 Primary Enamel Disorders

Amelogenesis imperfecta (AI) refers to a heterogeneous group of clinically indistinguishable hereditary disorders in which there is altered structure of the enamel in the absence of a systemic bone disorder. The condition diffusely affects the enamel formation of all teeth, including both the primary and permanent dentition. In humans, there are many hereditary subtypes of AI with variable patterns of inheritance. Three main phenotypic subtypes are recognized: hypoplastic (reduced amount of enamel), hypomaturation (aberrant enamel crystal structure), and hypocalcified (reduced quality of enamel) [1, 2].

In AI, mutations occur in genes that encode enamel proteins or proteases; several have been identified in humans. The AMELX gene encodes the enamel protein amelogenin, which constitutes approximately 90% of enamel matrix. The ENAM gene encodes the enamel protein enamelin, which constitutes less than 5% of enamel matrix. Mutations in the MMP-20 gene or the KLK4 gene affect the proteinases enamelysin or kallikrein-4, respectively [2].

The clinical and gross appearance of teeth with AI is highly variable but changes include loss, opacification and/or pigmentation of the enamel. Photographic documentation of enamel defects of the teeth is very important. Since enamel is predominantly inorganic mineral, virtually all of it is removed in routinely decalcified sections. Ground non-decalcified sections, which are expensive and time-consuming to process, may be necessary to characterize the histopathologic features of enamel. Such services are only available in specialized laboratories. In individuals affected with AI, the normally ordered prism structure of enamel is variable and may be highly disorganized.

AI is rarely identified in animals. Clinicopathologic evaluation and pedigree analysis of Standard poodle dogs in Sweden have identified a hereditary enamel disorder of dogs with discolored teeth; the phenotype was consistent with AI [3]. A simple recessive mutation of the enamelin (ENAM) gene has been reported in Italian

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greyhounds in which abnormalities were limited to the teeth, which had rough discolored enamel and were often abnormally small and/or pointed [4]. Affected dogs tended to maintain their teeth throughout life, suggesting that tooth hardness and strength were not compromised, unlike other clinically important enamel and dentin disorders.

Enamel hypoplasia and hypomineralization may be caused by many factors that disturb enamel matrix secretion and/or maturation. Most causes are systemic and include exposure to chemicals, infectious agents, malnutrition, and metabolic disorders [2]. Often, the enamel defects do not have a diffuse pattern since abnormal enamel will be that which forms during the period of malnutrition, infection, toxin exposure, etc. Trauma/injury and localized infection are common causes of focal defects.

Excessive fluoride is a well-known and well-characterized disruptor of enamel formation; dentin and bone may also be affected. Dental lesions occur when an animal is exposed to toxic levels of fluoride (fluorosis) during the period of tooth development, however, bone changes can occur in animals of any age [5]. Excessive fluoride is thought to inhibit ameloblasts directly, thereby decreasing the amount of secreted enamel matrix, but it also causes retention of organic matrix so that enamel, dentin and bone become hypomineralized [2]. In the veterinary literature, most reports of fluorosis are in herbivores grazing on contaminated pastures, and affected animals have stark white enamel (less often yellow to brown) and teeth that wear easily [5, 6].

Fluorosis in free-ranging red deer has been reported in areas contaminated by volcanic fluoride in Argentina and along the German–Czech border [6–8]. Complications as a result of secondary dental attrition have led to significant morbidity and premature mortality of affected deer populations. The affected deer had significant pulpitis, periodontitis and osteomyelitis of the jaws, as often occurs with loss of the tooth's natural protective mechanisms (e.g. defective enamel or disrupted periodontal attachment) [7].

Canine distemper virus causes enamel hypoplasia when puppies are systemically infected during the period of adult or deciduous tooth development. The mechanism appears to be direct viral infection of the enamel organ including ameloblasts, which can recover in dogs that survive and clear infection [9]. Therefore, like many transient disrupters of amelogenesis, the distribution of abnormal enamel on the teeth may be irregularly patchy or annular (see Figure 4.1).

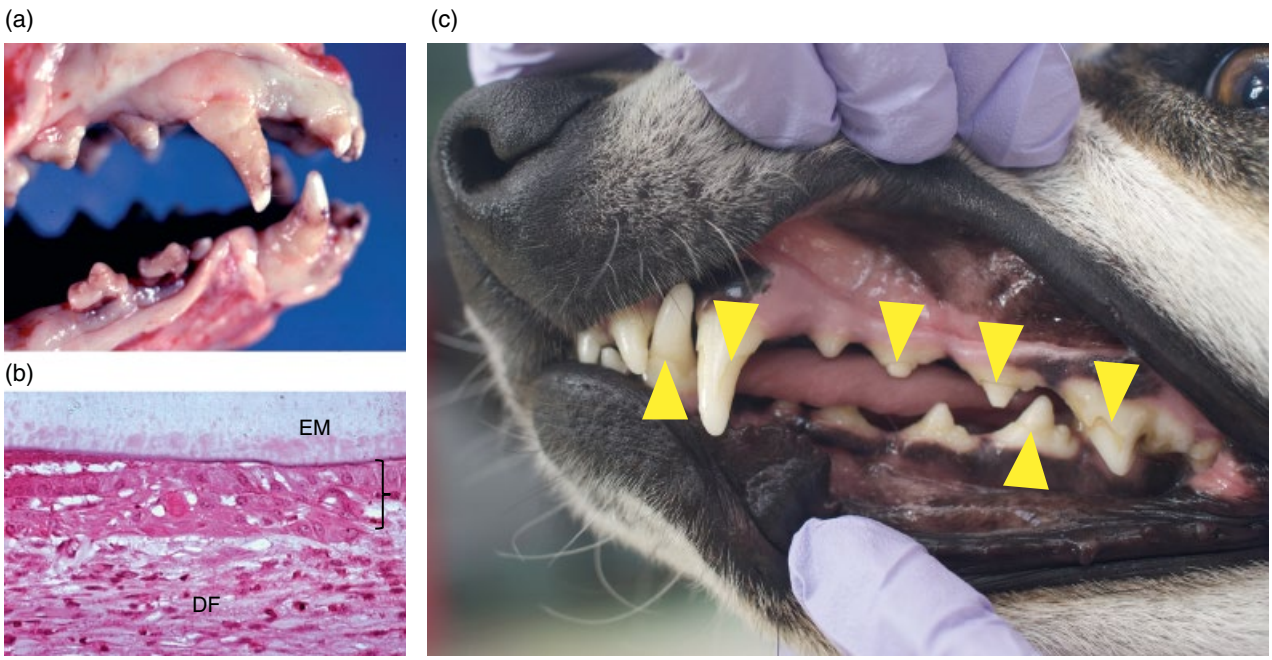


Figure 4.1 Gross and histologic images of dogs with enamel hypoplasia due to canine distemper virus infection. (a) On the canine teeth, enamel had formed normally at the tip of the crown but irregular, brown dentin is exposed on the remainder of the crown. The premolar teeth are diffusely discolored and irregular, suggesting that little to no enamel had formed on these crowns prior to the viral infection. (b) Cells in the layer of secretory ameloblasts (bracket) are jumbled among other layers of the enamel organ. The enamel matrix (EM) is wispy and rarified. There is mild vacuolization and separation at the interface of the odontogenic epithelium and the stoma of the dental follicle (DF). (c) In this two-year-old Australian Koolie dog, multiple canine, premolar and molar teeth have a loss of enamel at the tip of the crown (enamel hypoplasia, yellow arrowheads). This pattern of enamel loss is different than image (a), indicating infection at a different stage of enamel formation. *Source:* R. R. Dubielzig (a and b), University of Wisconsin-Madison; Murphy (c), University of California, Davis.

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Various enamel defects may occur in conjunction with systemic diseases or disease syndromes. In humans, dental defects often accompany childhood malnutrition, endocrine diseases, storage diseases, chromosomal abnormalities, ciliopathies, and metabolic diseases [2]. In horses, enamel defects are reported to occur in conjunction with epitheliogenesis imperfecta [10, 11]. Enamel hypoplasia has been induced experimentally in sheep by heavy parasitic infection with gastrointestinal nematodes [12].

4.1.2 Primary Dentin Disorders

Dentinogenesis imperfecta (DI) refers to a condition that affects only teeth and is associated with mutations in the DSPP gene, which encodes dentin sialophosphoprotein. For teeth, DI is phenotypically indistinguishable from some forms of osteogenesis imperfecta (discussed below), although there is bone involvement in the latter (see Figure 4.2). There are anecdotal cases of DI in dogs that have no known bone lesions, but the condition has not been thoroughly documented in domestic animals.

In DI, the enamel is structurally normal, but may chip away from the underlying abnormal dentin, creating the clinical impression of an enamel disorder. For multiple reasons, affected teeth are often discolored, including translucence of the abnormal dentin, lost enamel, or staining as a result of pulp necrosis. The presenting complaint for affected dogs may be fragility of the deciduous and permanent teeth with history of multiple tooth fractures at a young age. These tooth fractures often occur at or near the cementoenamel junction. The radiographic appearance is variable and may include excessively wide or narrow pulp, indicative of altered dentinogenesis, underdeveloped root length, and/or periapical lucencies consistent with pulpal necrosis. Histologically, the dentin lacks a regular tubular organization and is abnormally thin, resulting in a relatively wide pulp chamber.

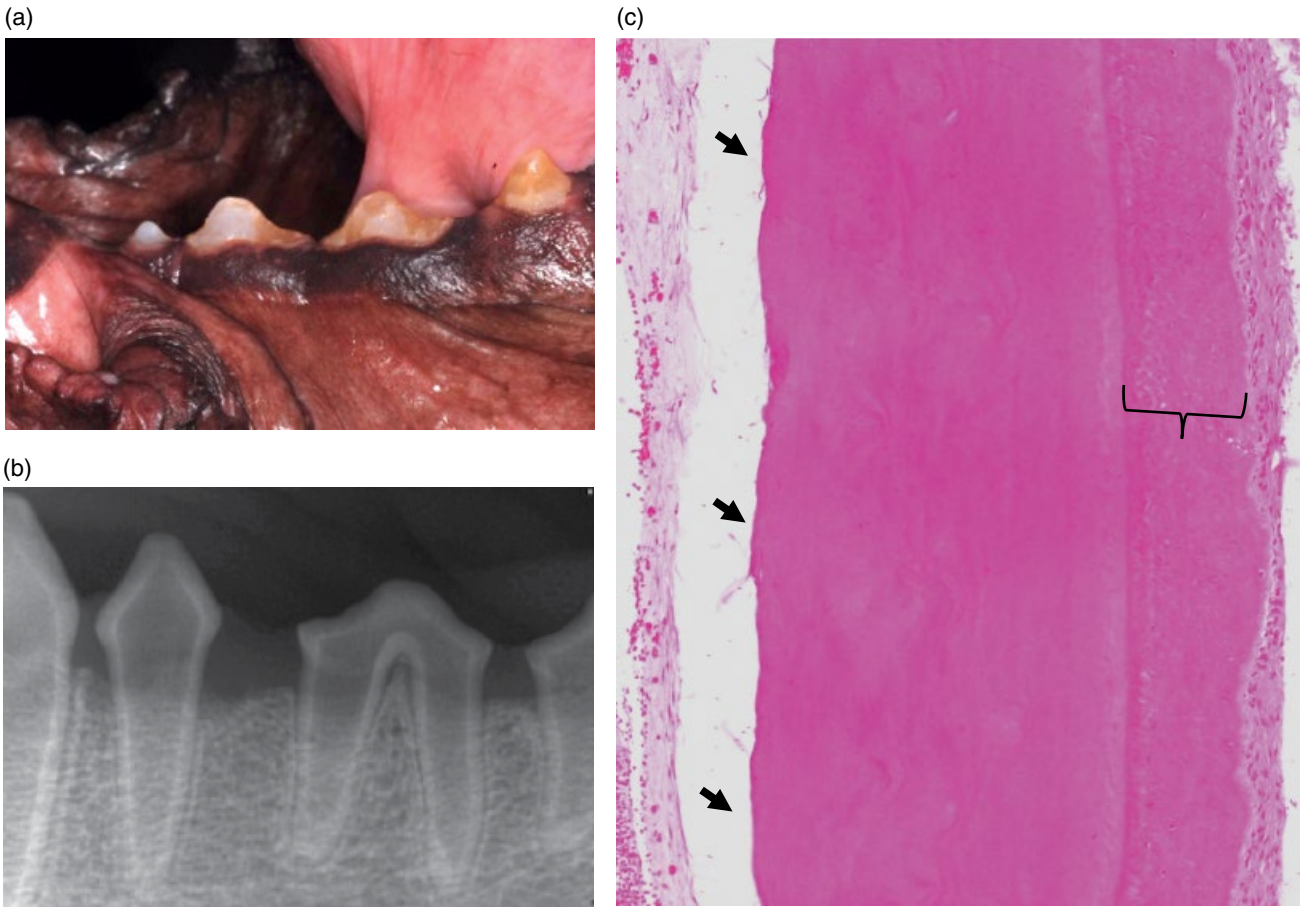


Figure 4.2 Gross, radiographic and histologic images of dentinogenesis imperfecta (DI) in a six month old, male, Cane Corso dog. (a) The enamel has chipped away from several teeth, exposing the underlying yellow-brown dentin. (b) Radiographically, the dentin is diffusely thin and the pulp chambers are wide. (c) Histologically, the dentin layer is thin relative to the thickness of the cementum (bracket) and, along the inner wall of the tooth (arrows); the odontoblast layer and the predentin that it produces are absent. Separation between the inner surface of dentin and pulpal soft tissue is an artifact of processing. *Source:* J. Riehl.

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The abnormal dentin is poorly mineralized, therefore, teeth affected by DI are prone to caries, accelerated attrition, fracture, and pulp exposure. Pulpitis and pulp necrosis may affect multiple teeth at a relatively young age. Unfortunately, secondary inflammatory changes can complicate evaluation of the primary pathology.

Osteogenesis imperfecta with opalescent teeth is a hereditary condition of teeth and bone due to genetically abnormal type I collagen. The phenotype features osteopenia and dentinopenia with both the deciduous and permanent dentition affected. *The clinical, radiological, and histological features of teeth from individuals with OI are indistinguishable from those affected by DI.* This condition has been described in animals with abnormal teeth and bones, including Dachshund dogs [13, 14] and Friesian cattle [15]. The classical forms of OI are associated with mutations in either the *COL1A1* or *COL1A2* genes, resulting in abnormal procollagen molecules. However, the OI phenotype may result, with mutations in other genes such as those involved in collagen folding. A recessive mutation in the *SERPINH1* gene, which encodes a chaperone protein, has been identified in dachshunds with osteogenesis imperfecta [13]. In affected animals, deposition of bone and dentin is quantitatively less abundant and the matrix is structurally abnormal, therefore, animals affected by OI are predisposed to pathologic skeletal fractures and all complications listed previously for DI.

Dentin dysplasia is a hereditary condition in humans that affects teeth diffusely and occurs independent of systemic disease or DI [2]. The pathology of dentin dysplasia is characterized by qualitative and quantitative changes. The quality of the dentin ranges from tubular to amorphous to osteodentin. Overproduction of dentin by odontoblasts rapidly fills and obliterates some or all of the pulp chamber. For unknown reasons, proliferation of dentin may preferentially affect a particular portion of the tooth, either the crown or the root. Classification of dentin dysplasia in humans is based, in part, on which region of the tooth is affected. In some types, the tooth roots are hypoplastic.

The clinical presentation of dentin dysplasia is highly variable in humans, ranging from no outward abnormalities to presentation for secondary complications (e.g. tooth fracture or pulp necrosis). Currently, data in animals are insufficient to justify subclassification of dentin dysplasia or what is typical for clinical presentation.

The extent of dentin dysplasia may not become apparent until dental radiographs are taken. The radiographic appearance is variable, but a key feature is that a portion of the pulp chamber is obscured by mineral radiolucency. Pulp canal mineralization in dogs can show a pattern that predominantly affects the crown or the root of affected teeth. Additionally, due to the high rate of pulpal necrosis, end-stage radiographic signs of endodontic infection (periapical lucency) is often seen (see Figure 4.3).

Grossly, the enamel surface may be normal but, on section, the pulp chamber is partially obliterated. Histologically, the primary dentin may be normal, but the secondary dentin has inconsistent tubular architecture, and amorphous or globular osteodentin occupies some portion of the pulp chamber. Root formation may be incomplete, and affected teeth are predisposed to pulp exposure and necrosis. One case has been reported in a dog, although the authors used the term "odontoblastic dysplasia," which is accurate but less conventional than dentin dysplasia [16].

In summary, primary enamel and dentin disorders occur uncommonly in animals and may be differentiated from one another based upon clinical, gross, histological, and radiographic characteristics (Table 4.1). Clinicians and pathologists are advised to be cautious about interpreting enamel surface defects as evidence of primary enamel disorders, since structurally normal enamel may chip away from abnormal dentin. Inherited (genetic) enamel and dentin disorders tend to affect teeth diffusely whereas acquired enamel hypoplasia/ hypocalcification usually does not. Confirmation of a hereditary disorder will usually require pedigree and/or genetic analyses.

4.1.3 Abnormalities in Tooth Number

Anomalies in tooth number, size or shape may be incidental findings of the deciduous or permanent dentition. While the absence of all teeth (complete anodontia) is rare, *hypodontia* (partial anodontia) is common in domestic animals and may be a normal finding in a particular species or breed of dog.

Causes of congenital hypodontia include genetic alteration/ mutation and injury to the tooth early in development. Several domestic animal species are represented in individual case reports of abnormalities in tooth shape and/or number – most of these have unknown etiology or pathogenesis. Hypodontia with abnormally shaped teeth (often conical "peg teeth") is associated with various forms of ectodermal dysplasia, and has been reported in cats, horses, and cattle [17–19]. Some forms of ectodermal dysplasia involve Ectodysplasin 1 (*ED-1*), which is involved in fetal development of hair follicles, sweat glands, and tooth buds. Cattle affected by *ED-1* mutation are reported to have hypotrichosis and oligodontia with absence of secondary dentition, although the primary dentition persists to function as the permanent dentition [17].

Pseudoanodontia is the condition of clinically absent teeth as a result of impaction or delayed eruption. Impacted teeth appear to be clinically absent but can be identified radiographically. A tooth is considered to be

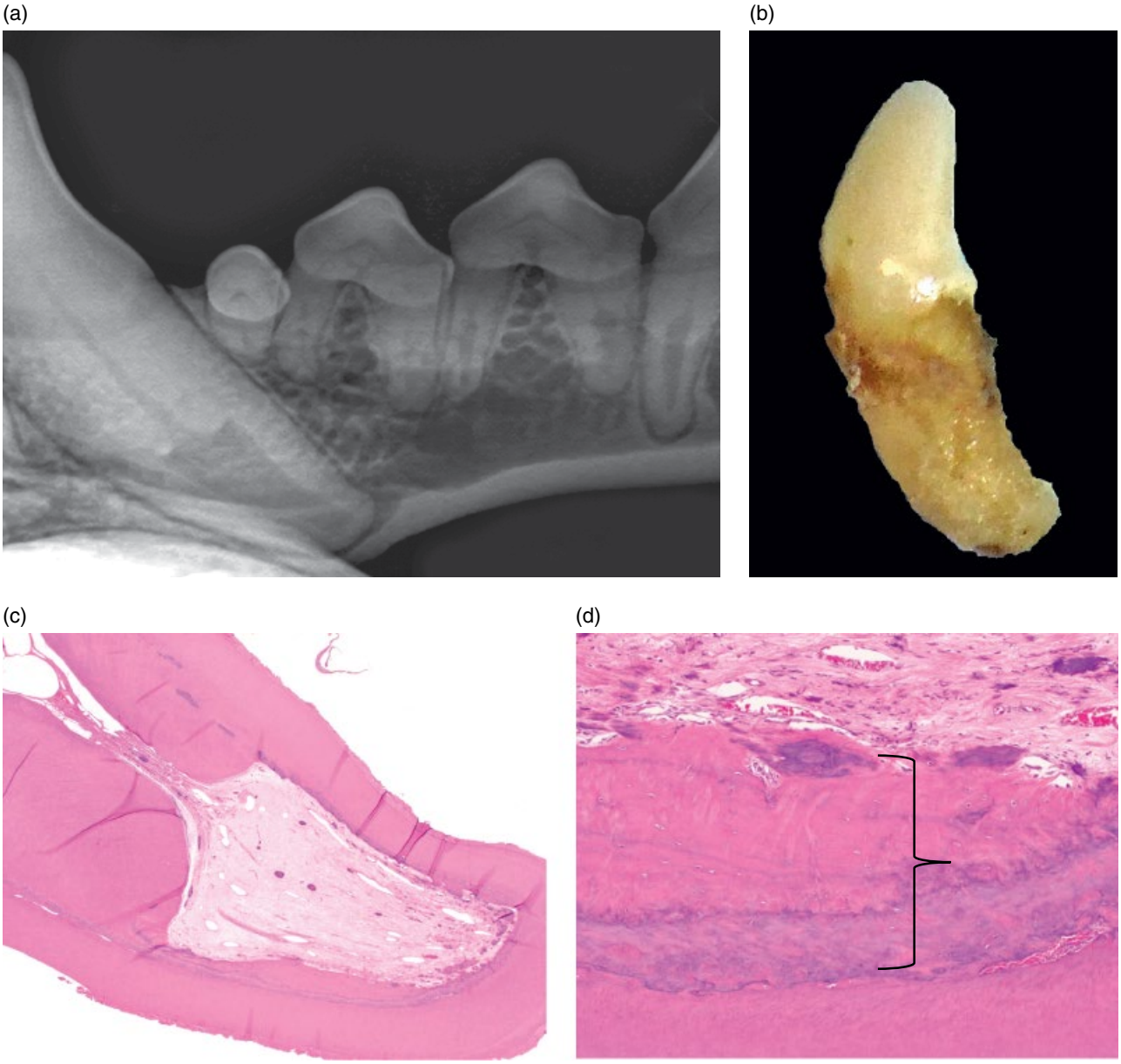


Figure 4.3 Radiographic, gross and histologic images of diffuse dentin dysplasia in a four-year-old, neutered male, terrier cross. (a) The radiograph demonstrates that there is over-proliferation of dentin that fills the majority of the pulp chamber, but notably sparing the apical segment. All teeth are affected similarly. (b) The enamel-covered crown of extracted tooth 104 (right maxillary canine) is grossly normal. (c) The photomicrograph corroborates abrupt widening of the apical pulp canal, as seen radiographically. The coronal portion of the pulp canal (top left of image) is replaced by dentin. (d) The outer primary dentin is well-organized compared to amorphous dentin (bracket) that has irregular zones of basophilia. Odontoblasts cannot be identified. *Source:* J. Alterman.

Table 4.1 Primary disorders of teeth.

	Pattern	Rapid attrition	Described in animals
Enamel disorders			
Amelogenesis imperfecta	diffusely affects teeth	no	yes
Hypoplasia/hypocalcification	non-diffuse in teeth +/– bone depending on cause	possible depending on cause	yes
Dentin disorders			
Osteogenesis imperfecta	diffusely affects teeth and bone	yes	yes
Dentinogenesis imperfecta	diffusely affects teeth	yes	anecdotal evidence
Dentin dysplasia	diffusely affects teeth	variable	yes

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impacted when eruption is prevented by an opposing force. Causes of impaction include obstruction from crowding (as in brachycephalic breeds), ankylosis of the primary dentition, malorientation of the tooth germ, or other physical barrier to eruption.

Impacted teeth in cats and dogs have been associated with individual dysplastic teeth [20], suspected traumatic alteration of deciduous teeth [21, 22], and the presence of a supernumerary tooth [23]. Impacted teeth are often extracted surgically as a prophylactic measure to prevent dentigerous cyst formation (for more information see Chapter 11, focused on odontogenic cysts).

Currently, there is no evidence that tooth impaction increases the risk of an odontogenic tumor developing at the site. Nevertheless, there is a relationship between some odontogenic tumors and tooth impaction (or absence of a tooth), since development of an odontogenic tumor in a young animal can prevent tooth eruption or development. Put another way – the tumor causes impaction rather than the impacted tooth causing the tumor.

Supernumerary teeth result from continued proliferation of the dental lamina with formation of a third tooth germ, usually occurring in the permanent dentition rather than the deciduous dentition [1]. The supernumerary tooth may or may not erupt. Some dentigerous cysts in dogs are associated with a supernumerary tooth, particularly at the site of a first premolar (see Chapter 11 on odontogenic cysts). Horses may have supernumerary incisors or cheek teeth, which tend to occur in the caudal maxillary dentition [24].

4.1.4 Abnormalities in Tooth Shape

Abnormalities in tooth shape can be the result of dysplastic teeth that occur in the presence of otherwise normal dentition and not as a result of a primary enamel or dentin disorder. Table 4.2 provides terminology and definitions for several abnormalities of tooth shape. Many of these

Table 4.2 Abnormalities of tooth shape.

Condition	Definition
Gemination	Tooth with a double crown, single root and usually a single root canal
Fusion	Two teeth that are joined with confluence of dentin
Concrescence	Two teeth joined by cementum but not dentin
Dilaceration	Abnormal curvature of a tooth, usually the root
Deflection	Deviation of a tooth from its normal eruption pattern
Microdontia	An abnormally small tooth
Macrodontia	An abnormally large tooth

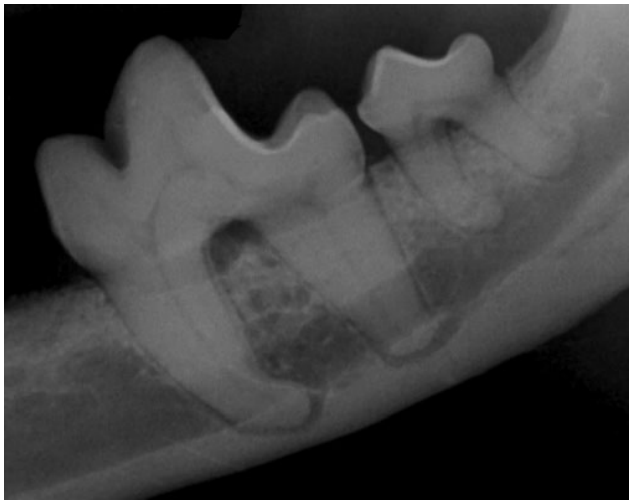


Figure 4.4 Radiographic image of a 1st mandibular molar with dilaceration of the mesial root apex, 10-year-old FS Maltese/poodle mix. *Source:* B. Arzi, Dentistry Oral Surgery Service, University of California, Davis.

conditions are incidental and may be of no clinical concern unless the abnormal conformation exposes periodontal tissues, thereby increasing the risk of periodontal disease at the site. In such situations, tooth extraction is often elected. *Dilaceration* is among the most common conditions and it may be congenital or acquired secondary to trauma to the developing tooth, compression by a space-occupying lesion such as a cyst or tumor, or interference by cortical bone (e.g. first mandibular molar in small breed dogs) (Figure 4.4). *Deflection* is most often caused by a retained deciduous tooth and the most common complication is malocclusion (Figure 4.5).

Dens invaginatus is a specific developmental abnormality of the tooth shape that results from focal or multifocal infolding (invagination) of the tooth. At the affected area of the tooth, organized hard tissues of the tooth (odontogenic matrices) are disorganized, often forming a dense knot of dysplastic enamel with less abundant dentin (Figure 4.6). The malformation usually occurs at the base of the crown. The term "dens in dente" is sometimes used to refer to dens invaginatus since large invaginations may result in a tooth-within-a-tooth appearance on dental radiographs. Dens invaginatus in dogs generally occurs on an isolated tooth, usually the mandibular first molar tooth, and may be bilateral [25, 26]. In our experience, dens invaginatus is more likely to occur in small-breed dogs; Yorkshire terriers in particular may be over-represented. Teeth affected by dens invaginatus may be at risk for pulpitis and/or endodontic disease if the surface enamel is incomplete or if the gingivoperiodontal attachment to the tooth is abnormal. A report of dental dysplasia in two young uremic dogs with concurrent renal dysplasia describes symmetrical malformation

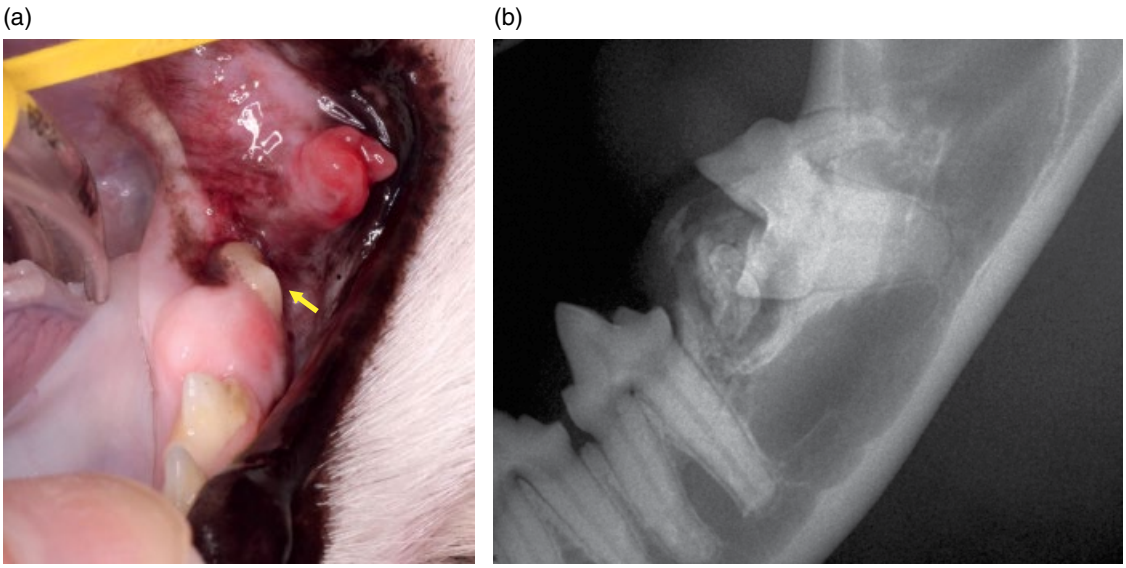


Figure 4.5 Gross and radiographic images of a cat with a dysplastic, impacted deciduous tooth. (a) The permanent left mandibular first molar (309) is incompletely erupted with only a portion of the crown visible (arrow) and, mesial to the erupted portion, the gingiva is swollen over the site of the impacted deciduous tooth. A bright pink pyogenic granuloma on the mucosa, buccal to 309, is presumably secondary to contact with the opposing maxillary 4th premolar (208). (b) The radiograph demonstrates deflection and incomplete eruption of tooth 309, plus the embedded deciduous tooth. *Source:* C. Schor.

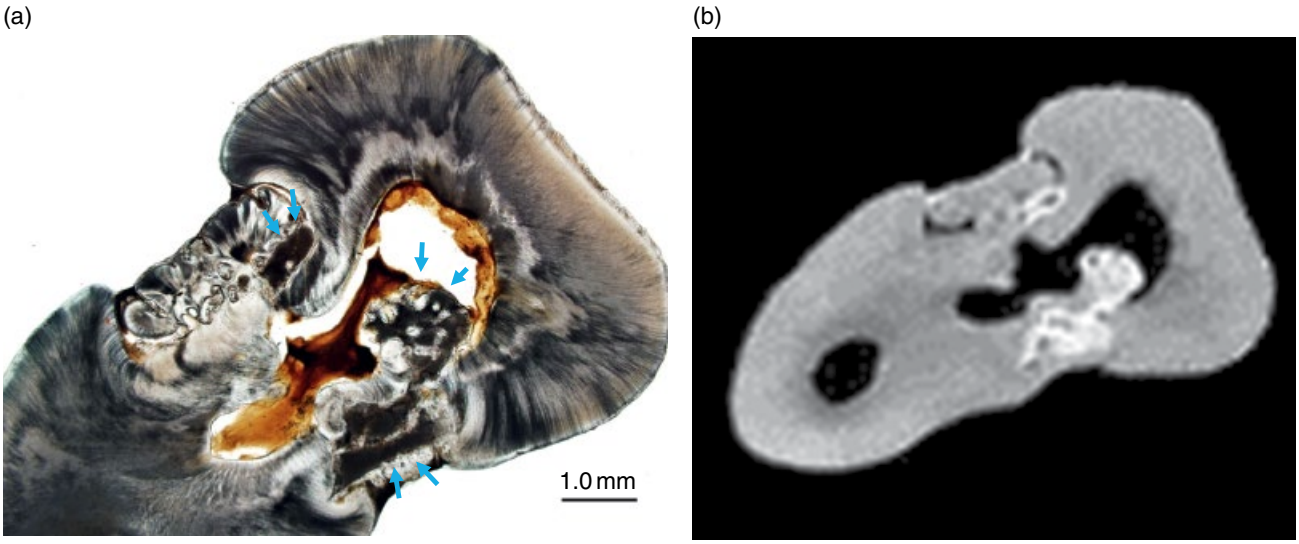


Figure 4.6 Histologic and radiographic images of Dens invaginatus affecting the mandibular first molar from a dog. (a) Plastic-embedded, non-decalcified ground section stained with Goldner's trichrome. The tooth was cut in the coronal plane in order to demonstrate the irregularly infolded dentin wall of the tooth, as well as the enamel that stains black (arrows). (b) The radiograph of an adjacent section from the non-decalcified tooth shows the radio-opaque enamel invaginated into the irregular dentin and bulging into the pulp chamber.

of isolated mandibular molars and premolars; although not diagnosed as such, the reported findings closely resemble dens invaginatus [27].

Enamel pearl, or "enameloma," is a dysplastic nodule on the tooth surface that consists of enamel only. Enamel pearls are seen occasionally in companion animals, particularly at the furcation of a multi-rooted tooth [28]. These structures can interfere with normal periodontal attachment, predisposing the tooth to focal periodontitis. Dens invaginatus and enamel pearl can appear similarly; the former is generally larger and involves the dentinal wall of the tooth.

Focal odontodysplasia, affecting one or few contiguous teeth, is often caused by trauma in early life (see Section 6.2 on traumatic lesions for a more complete discussion of this process). Crown and root shape will be influenced by

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alterations in the spatial distribution of the enamel organ, particularly as it relates to adjacent odontogenic ectomesenchyme and dental follicle. As these tissues continue to proliferate and differentiate, the consequence is an abnormally shaped and frequently impacted or under-erupted tooth (Figure 4.5). In the authors' opinion, the term focal may still apply even if multiple teeth are affected. *Localized* and *segmental* are also acceptable descriptors of distribution, but the term "regional" should be avoided because it implies a specific entity.

Regional odontodysplasia refers to a specific condition in humans in which an entire quadrant of the maxilla or mandible has malformed teeth. Both enamel and dentin are poorly mineralized and hypoplastic. Diagnosis of this condition is largely based on radiological evidence of "ghost teeth" that have a very thin shell of dentin, short roots, and large pulp chambers. Clinically, the condition may present as partial anodontia because eruption of affected teeth is delayed or does not occur. There is no known cause or suspected genetic alteration [2] and there are no published reports in animals that adequately match the definition of regional odontodysplasia.

Box 4.1 Differential Diagnoses for Tooth Discoloration

- Extrinsic staining
  - Pigments produced by plaque bacteria
  - Plant-derived pigments
  - Metals (e.g. iron)
- Intrinsic staining
  - Pulpal hemorrhage
  - Pulpitis/pulp necrosis
  - Incorporation of exogenous pigments
    - Tetracycline
    - Fluoride
  - Incorporation of intrinsic pigments
    - Bilirubin pigments
    - Hemoglobin pigments (e.g. porphyria)

4.1.5 Tooth Discoloration

Teeth tend to become discolored from white to yellow, dark brown, pink, purple, or gray. Tooth discoloration is classified as intrinsic or extrinsic. Extrinsic stains are outside the tooth substance, usually on the tooth surface, due to by-products of chromogenic bacteria within plaque or pigments in dietary substances (plant-derived pigments in herbivores). Exposure to various metals may exacerbate extrinsic staining from metabolic pigments produced by bacteria (Figure 4.7).

Intrinsic staining occurs when pigmented compounds are incorporated into the structure of dentin and/or enamel. Major types of intrinsic staining include:

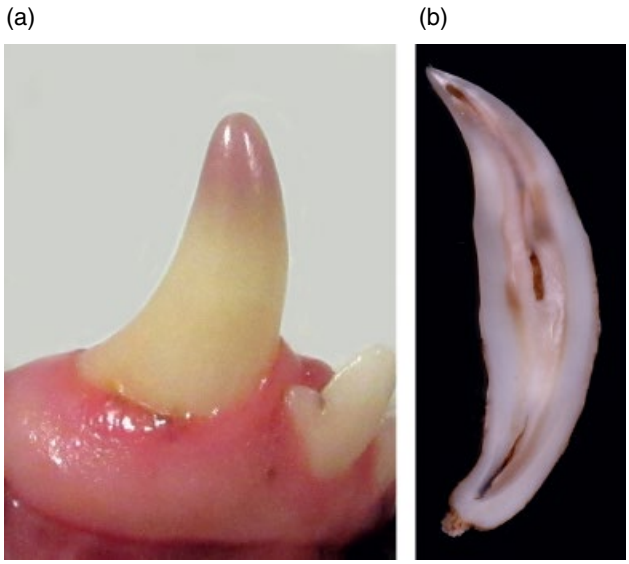


Figure 4.7 Gross images of an intrinsically stained canine tooth of a dog. (a) Clinically, the tooth had pink discoloration at the tip of the crown. (b) The extracted tooth was fixed and decalcified and, on cut section, there was dilated pulp chamber and intrinsic staining of both crown and root dentin. *Source:* K. Feigin.

1) Direct imbibition of pigment, such as products of hemorrhage and necrosis, within the pulp chamber
2) Incorporation of hematogenous or otherwise systemically distributed pigments during tooth development

Traumatized teeth are believed to become discolored (pink, blue, purple) by pulpal hemorrhage, subsequent lysis of erythrocytes, and accumulation of hemoglobin and/or hemosiderin pigments [29]. Generally, darker pigments occur in teeth that are infected or otherwise affected by pulpitis or pulp necrosis. In the presence of bacterial or leukocytic enzymes, the hemoglobin will be further metabolized to additional pigmented products including black iron sulfide [29]. Pulpitis/pulp necrosis is reported to be the most common reason for intrinsic tooth discoloration in dogs [30].

Causes of intrinsic staining in young animals during tooth development include tetracycline therapy, fluorosis, congenital porphyria, and hyperbilirubinemia. Both tetracycline and porphyrin may fluoresce with ultraviolet light. Icterus or hemolysis in young children is an observed cause of tooth discoloration in humans, and would logically apply to young animals as well [1]. Congenital erythropoietic porphyria is reported in humans and animals as a cause of pink to brown discoloration of teeth. Congenital erythropoietic porphyria is caused by mutation of uroprophyrinogen III cosynthase, which has been reported in domestic animals, particularly cats [31]. In affected individuals, pigmented heme precursors accumulate in tissues and are preferentially

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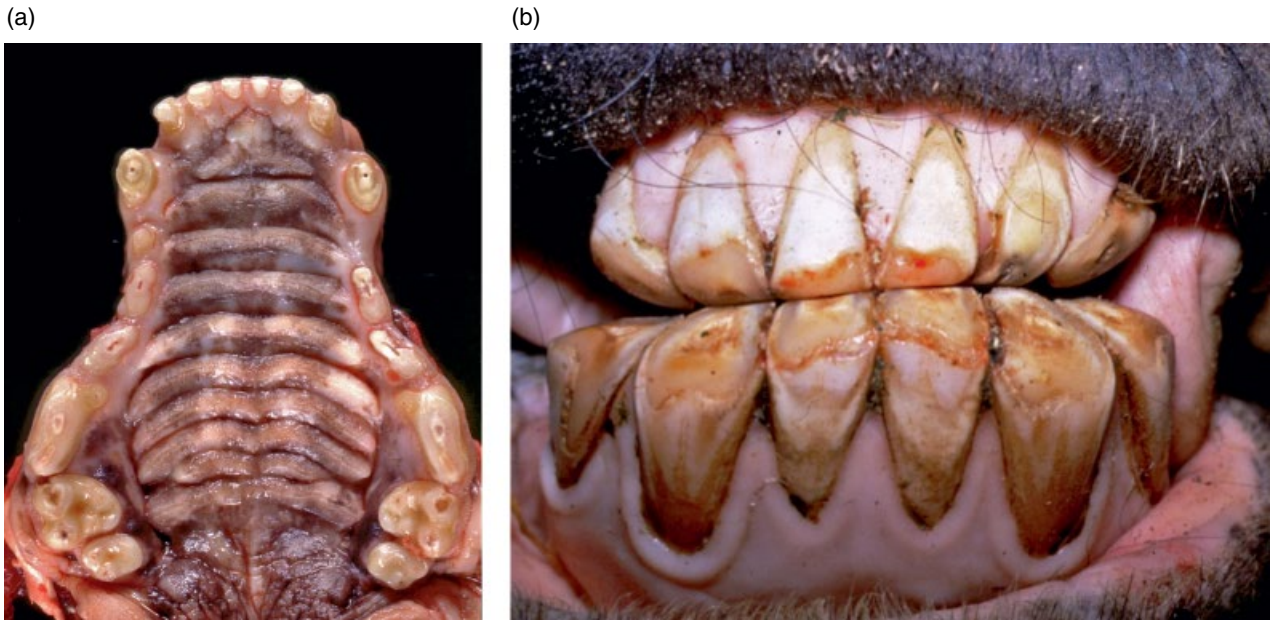


Figure 4.8 Gross images depicting forms of tooth wear: (a) attrition of the maxillary dentition of a dog and (b) abrasion of the maxillary and mandibular incisors of a horse as a result of cribbing. *Source:* R.R. Dubielzig, University of Wisconsin-Madison.

deposited in teeth and bones. There is evidence that erythrodontia in cats may be more often the result of acute intermittent porphyria, a hepatic porphyria, rather than congenital erythropoietic porphyria [32].

4.1.6 Dental Attrition, Abrasion, and Erosion

While attrition is often used as a general term for tooth wear, *dental attrition* is specifically defined as loss of tooth structure (enamel and/or dentin) due to mechanical forces from opposing teeth (i.e. occlusal forces). *Dental abrasion* is loss of tooth structure due to mechanical forces against a foreign object. Finally, *dental erosion* is loss of tooth structure at the surface due to chemical reactions (e.g. acidic demineralization). Enamel erosion is rare as a natural occurrence in companion animals, although it may be induced experimentally by exposing animals to acidic feed or water. For example, bovine teeth exposed to acidic sweet potato cannery waste showed erosion at pH 3.2, but not when the feed was neutralized to pH 5.5 [33].

In dogs, malocclusion is a common cause of attrition [28]. Attrition can be accelerated by abrasive material (e.g. rough forage, hair chewing), but the force resulting in wear remains occlusal. Tertiary dentin is produced on the worn and flattened occlusal surface in order to protect the tooth from pulp exposure; this may be evident as yellow-brown discoloration in the center of the wear facet (Figure 4.8a). Distal abrasion of the canine teeth due to cage chewing is one of the more common forms of tooth abrasion in dogs. Similarly, horses may wear their incisors as a result of cribbing (Figure 4.8b). The incisors are often more severely affected by wear due to their importance as cutting teeth and because the occlusal surface area of incisors have proportionately less enamel than premolars and molars, particularly in grazing herbivores.

Dental wear rarely comes to the attention of pathologists except when noted at post-mortem examination, in which case tooth wear is usually an incidental finding. Nevertheless, a pathologist who can recognize patterns of excessive or unusual tooth wear will be better able to correctly identify underlying causes for other oral lesions. For example, teeth affected by advanced attrition are at increased risk for pulpal changes (pulpitis, pulp necrosis, pulp stones, or partial/complete obliteration of the pulp canal by tertiary dentin).

References

1 Regezi, J.A., Sciubba, J.J., and Jordan, R.C.K. (2012). *Oral Pathology: Clinical Pathologic Correlations*, 6e. St. Louis, MO: Elsevier/Saunders.

2 Neville, B.W., Damm, D.D., Allen, C.M., and Chi, A.C. (2016). *Oral and Maxillofacial Pathology*, 4e. St. Louis, MO: Elsevier.

VetBooks.ir

3 Mannerfelt, T. and Lindgren, I. (2009). Enamel defects in standard poodle dogs in Sweden. *J. Vet. Dent.* 26: 213–215.
4 Gandolfi, B., Liu, H., Griffioen, L., and Pedersen, N.C. (2013). Simple recessive mutation in ENAM is associated with amelogenesis imperfecta in Italian Greyhounds. *Anim. Genet.* 44: 569–578.
5 Shupe, J.L. (1980). Clinicopathologic features of fluoride toxicosis in cattle. *J. Anim. Sci.* 51: 746–758.
6 Kierdorf, U., Kierdorf, H., Sedlacek, F., and Fejerskov, O. (1996). Structural changes in fluorosed dental enamel of red deer (*Cervus elaphus* L.) from a region with severe environmental pollution by fluorides. *J. Anat.* 188 (Pt 1): 183–195.
7 Schultz, M., Kierdorf, U., Sedlacek, F., and Kierdorf, H. (1998). Pathological bone changes in the mandibles of wild red deer (*Cervus elaphus* L.) exposed to high environmental levels of fluoride. *J. Anat.* 193 (Pt 3): 431–442.
8 Flueck, W.T. and Smith-Flueck, J.A. (2013). Severe dental fluorosis in juvenile deer linked to a recent volcanic eruption in Patagonia. *J. Wildl. Dis.* 49: 355–366.
9 Dubielzig, R.R., Higgins, R.J., and Krakowka, S. (1981). Lesions of the enamel organ of developing dog teeth following experimental inoculation of gnotobiotic puppies with canine distemper virus. *Vet. Pathol.* 18: 684–689.
10 Dubielzig, R.R., Wilson, J.W., Beck, K.A., and Robbins, T. (1986). Dental dysplasia and epitheliogenesis imperfecta in a foal. *Vet. Pathol.* 23: 325–327.
11 Lieto, L.D., Swerczek, T.W., and Cothran, E.G. (2002). Equine epitheliogenesis imperfecta in two american saddlebred foals is a lamina lucida defect. *Vet. Pathol.* 39: 576–580.
12 Suckling, G., Elliott, D.C., and Thurley, D.C. (1986). The macroscopic appearance and associated histological changes in the enamel organ of hypoplastic lesions of sheep incisor teeth resulting from induced parasitism. *Arch. Oral. Biol.* 31: 427–439.
13 Drogemuller, C., Becker, D., Brunner, A. et al. (2009). A missense mutation in the SERPINH1 gene in Dachshunds with osteogenesis imperfecta. *PLoS Genet.* 5: e1000579.
14 Seeliger, F., Leeb, T., Peters, M. et al. (2003). Osteogenesis imperfecta in two litters of dachshunds. *Vet. Pathol.* 40: 530–539.
15 Denholm, L.J. and Cole, W.G. (1983). Heritable bone fragility, joint laxity and dysplastic dentin in Friesian calves: a bovine syndrome of osteogenesis imperfecta. *Aust. Vet. J.* 60: 9–17.
16 Smithson, C.W., Smith, M.M., and Gamble, D.A. (2010). Multifocal odontoblastic dysplasia in a dog. *J. Vet. Dent.* 27: 242–247.
17 Drogemuller, C., Kuiper, H., Peters, M. et al. (2002). Congenital hypotrichosis with anodontia in cattle: a genetic, clinical and histological analysis. *Vet. Dermatol.* 13: 307–313.
18 Vieira, A.L., Ocarino Ndem, M., Boelonim, J.N., and Serakidesm, R. (2009). Congenital oligodontia of the deciduous teeth and anodontia of the permanent teeth in a cat. *J. Feline Med. Surg.* 11: 156–158.
19 Ramzan, P.H., Dixont, P.M., Kempson, S.A., and Rossdale, P.D. (2001). Dental dysplasia and oligodontia in a thoroughbred colt. *Equine Vet. J.* 33: 99–104.
20 Hoffman, S. (2008). Abnormal tooth eruption in a cat. *J. Vet. Dent.* 25: 118–122.
21 Mendoza, K.A., Marretta, S.M., Behr, M.J., and Klippert, L.S. (2001). Facial swelling associated with impaction of the deciduous and permanent maxillary fourth premolars in a dog with patent ductus arteriosus. *J. Vet. Dent.* 18: 69–74.
22 Taney, K.G. and Smith, M.M. (2006). Surgical extraction of impacted teeth in a dog. *J. Vet. Dent.* 23: 168–177.
23 Stapleton, B.L. and Clarke, L.L. (1999). Mandibular canine tooth impaction in a young dog – treatment and subsequent eruption: a case report. *J. Vet. Dent.* 16: 105–108.
24 Dixon, P.M., Tremaine, W.H., Pickles, K. et al. (1999). Equine dental disease part 2: a long-term study of 400 cases: disorders of development and eruption and variations in position of the cheek teeth. *Equine Vet. J.* 31: 519–528.
25 Duncan, H.L. (2010). Diagnostic imaging in veterinary dental practice. Dens invaginatus leading to arrested maturation of the right and left mandibular first molar teeth. *J. Am. Vet. Med. Assoc.* 237: 1251–1253.
26 Stein, K.E., Marretta, S.M., and Eurell, J.A. (2005). Dens invaginatus of the mandibular first molars in a dog. *J. Vet. Dent.* 22: 21–25.
27 Dubielzig, R.R., Beck, K.A., Wilson, J.W., and Ribble, G.A. (1986). Dental dysplasia in two young uremic dogs. *Vet. Pathol.* 23: 333–335.
28 Wiggs, R.B. and Lobprise, H.B. (1997). *Veterinary Dentistry: Principles and Practice*. Philadelphia. PA: Lippincott–Raven Publishers.
29 Watts, A. and Addy, M. (2001). Tooth discolouration and staining: a review of the literature. *Br. Dent. J.* 190: 309–316.
30 Hale, F.A. (2001). Localized intrinsic staining of teeth due to pulpitis and pulp necrosis in dogs. *J. Vet. Dent.* 18: 14–20.
31 Clavero, S., Bishop, D.F., Giger, U. et al. (2010). Feline congenital erythropoietic porphyria: two homozygous UROS missense mutations cause the enzyme deficiency and porphyrin accumulation. *Mol. Med.* 16: 381–388.
32 Clavero, S., Ahuja, Y., Bishop, D.F. et al. (2013). Diagnosis of feline acute intermittent porphyria presenting with erythrodontia requires molecular analyses. *Vet. J.* 198: 720–722.
33 Rogers, G.M., Poore, M.H., Ferko, B.L. et al. (1999). Dental wear and growth performance in steers fed sweetpotato cannery waste. *J. Am. Vet. Med. Assoc.* 214: 681–687.

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4.2 Degenerative and Inflammatory Disorders of Teeth

4.2.1 Pulpitis

Pulpitis is inflammation of the fibrovascular stroma that occupies the central pulp chamber of the tooth. The primary function of the pulp stroma is to support and provide nutrition for the layer of odontoblasts that produce and line the inner surface of the tooth dentin. Throughout the life of the tooth, odontoblasts are active in ongoing synthesis of dentin and physiological regulation of the dentin matrix via cytoplasmic extensions that travel along the dentin tubules. Vascular nourishment from the pulp stroma is essential to the vitality of the entire tooth.

Pulpitis may be septic or sterile and is usually initiated by one of four noxious stimuli: mechanical, thermal, chemical, or bacterial [34]. Common causes of pulpitis in animals include traumatic injury, extension of local infection (e.g. periodontitis), and pulp exposure (e.g. secondary to tooth fracture, severe attrition, or tooth resorption.

The ability of pulp to respond to injury is limited by its enclosure within a rigid shell of dentin. Progressive deposition of dentin causes the pulp chamber to become progressively narrower with age. Typical inflammatory responses, such as edema and active congestion, may increase pressure within the pulp chamber and thereby exacerbate pulpal injury through ischemia. In general, the following changes occur with pulpal injury: accumulation of inflammatory cell infiltrates, fibrosis, calcification, hemorrhage, and/or necrosis.

Clinically, there is a distinction to be made between reversible and irreversible pulpitis. Irreversible pulpitis inevitably leads to pulp necrosis and death of the tooth. From a pathologist's viewpoint, this distinction may be irrelevant, unless the fate of the tooth could be predicted. Discoloration is the most common clinical finding associated with pulpitis and radiographs support the diagnosis when there is periapical lucency of the affected tooth (Figure 4.9). This lucency represents the loss of

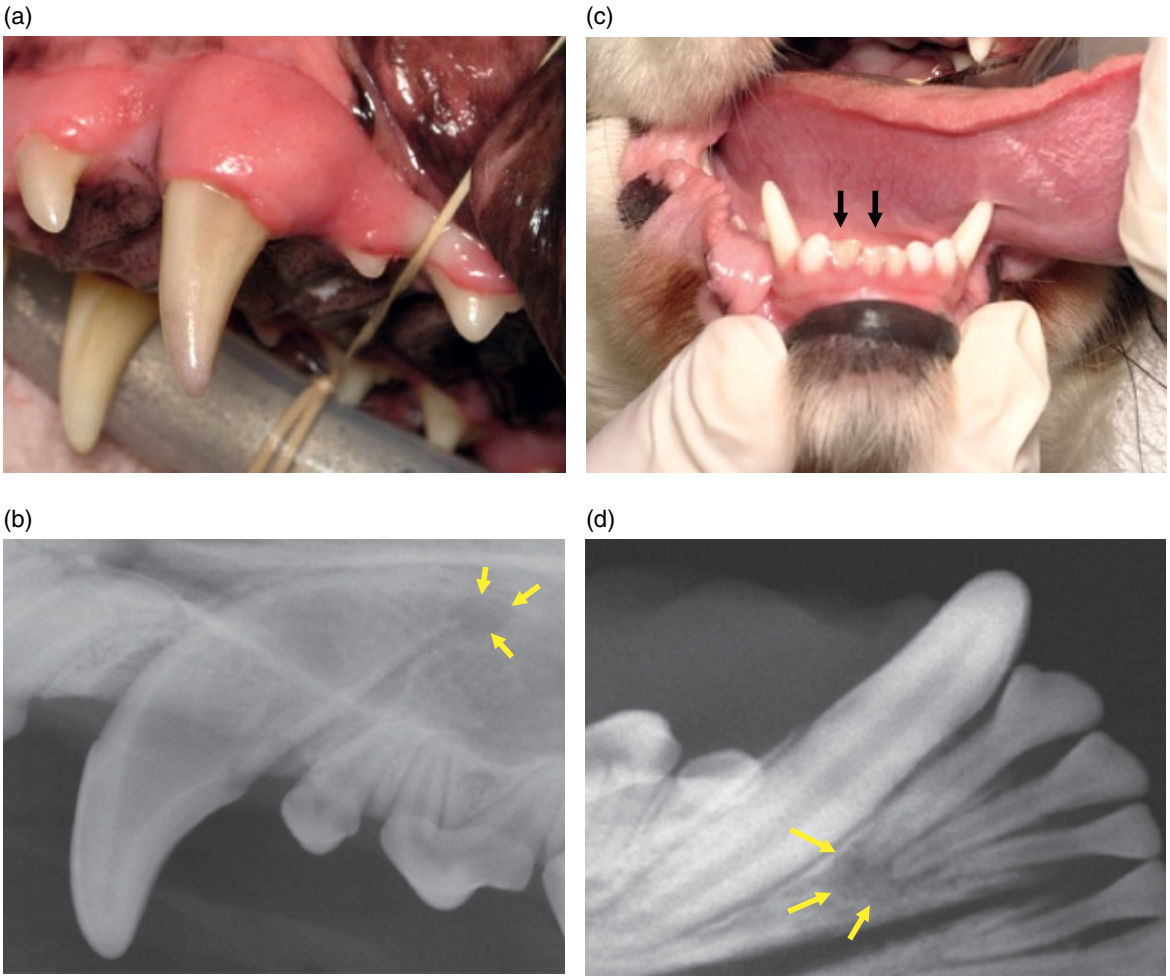


Figure 4.9 Gross and radiographic images of teeth affected by disease of the pulp (i.e. endodontic disease). (a) A canine tooth is discolored pink and (b) the corresponding radiograph has a periapical lucency (yellow arrows). (c) Adjacent incisor teeth (arrows) are discolored brown-gray and have (d) corresponding periapical lucencies. *Source:* D. Hansen.

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alveolar bone, secondary to local inflammation, that surrounds the apical foramen of the pulp canal. Pulpitis is thought to be painful, although the pain may abate with pulp necrosis.

Pulpitis is one of the pathologic processes for which a pathologist may be called upon to examine a tooth histologically. (See the Appendix for more information on preparing teeth for histological examination.) Multiple cross-sections of the tooth root, in lieu of one to two sagittal sections, provide the pathologist with multiple opportunities to assess the pulp cavity. Histologically, various changes may be seen in decalcified teeth that are affected by pulpitis or pulp necrosis (Figure 4.10). Pulpitis is usually neutrophilic. While macrophages may be seen, lymphoplasmacytic infiltrates within the pulp stroma are unusual since suppurative pulpitis is likely to progress to pulp necrosis. That said, cases of chronic, low-grade pulpitis certainly occur. In a non-vital tooth, the pulp stroma is replaced by amorphous or necrotic granular debris, hemorrhage, and/or pigment deposition. The pigments may be impossible to characterize, but likely sources are hemorrhage and bacterial metabolites. Quite often, tertiary dentin (osteodentin) can be seen lining the inner surface of an infected or non-vital tooth, suggesting that pulpitis or pulp necrosis is sufficient injury to trigger transition from secondary dentinogenesis to tertiary dentinogenesis.

4.2.2 Pulp Degeneration

Chronic degenerative changes may occur in injured teeth in the absence of pulpitis or pulp necrosis. Histologically, these changes include pulpal fibrosis, pulpal calcification, atrophy and/or loss of odontoblasts, and a seam of bone-like tertiary dentin (osteodentin) that is deposited along the inner surface of the dentin wall (Figure 4.11). In the presence of hypercementosis, the apical pulp chamber and foramen may become narrowed and partially filled by cementum. In some cases, ischemia secondary to cementification and stenosis of the apical foramen may account for pulp necrosis.

Pulp calcifications or "stones" that arise from mineralization of soft tissue tend to grow concentrically and

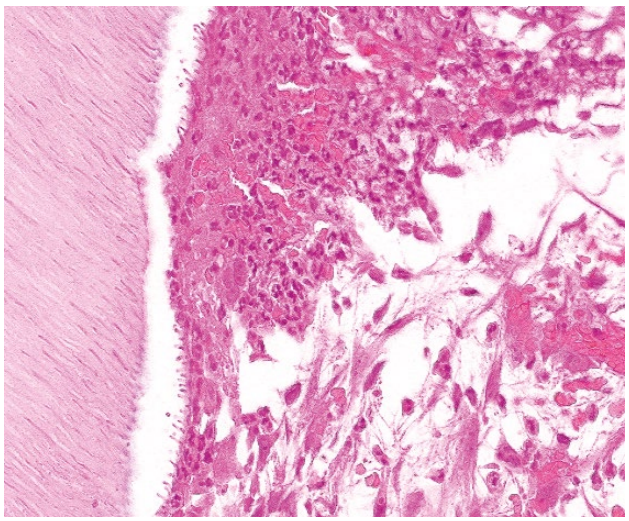


Figure 4.10 Histologic image of neutrophilic pulpitis. The predentin and odontoblast layers are absent. The pulp stroma is densely infiltrated by neutrophils, suggesting irreversible pulpitis and incipient pulp necrosis.

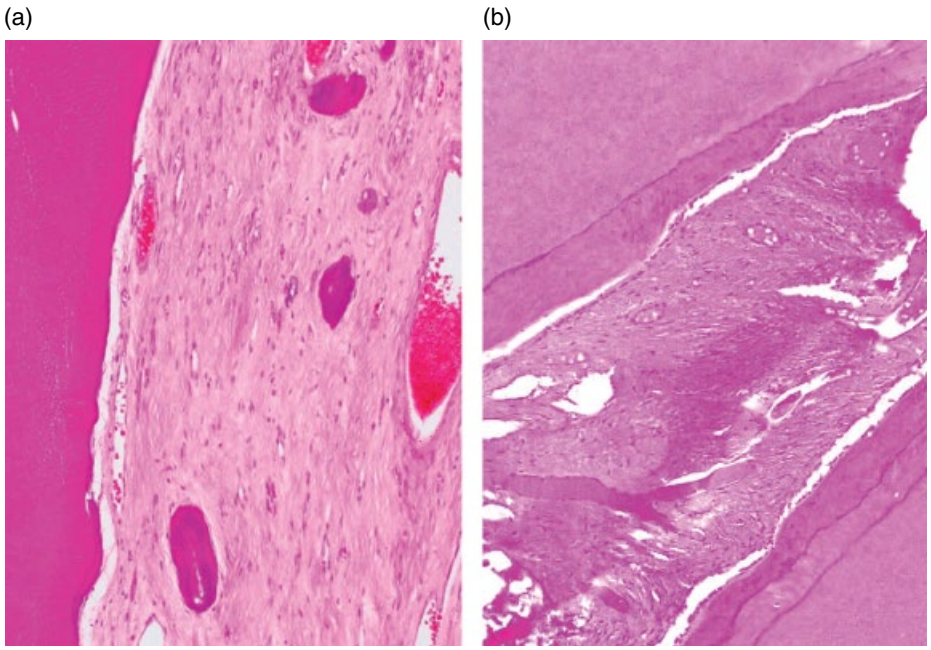


Figure 4.11 Histologic images of vital teeth that have chronic degenerative changes including loss of both the predentin and odontoblast layers although the pulp has remained vital. (a) This tooth has moderate pulp fibrosis and multifocal calcifications. (b) The inner surface of the dentin is lined by an irregular layer of osteodentin with wavy reversal lines.

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are thought to arise from a nidus of necrotic debris or degenerate collagen, implicating chronic pulpitis and/or ischemia as etiological factors. One of the authors (CB) has observed that these amorphous concretions are most often seen in conjunction with increased collagen matrix (pulpal fibrosis) in the teeth of dogs. Calcification of pulp is relatively common in humans and the prevalence increases with age [34]. The authors' observation is that the same is true for companion animals, although most pulpal calcifications, or "pulp stones" are incidental findings on dental radiographs.

4.2.3 Periapical Periodontitis

Periapical periodontitis refers to inflammation of the periodontal tissues at the tooth root apex, including the surrounding alveolar bone. This pattern of inflammation occurs secondary to pulpitis and/or pulp necrosis (Figure 4.12). The term periapical periodontitis is preferred over the terms "abscess" or "granuloma" since these lesions may not demonstrate either suppuration or granulomatous inflammation. Histologically, proliferative fibrovascular tissue (i.e. granulation tissue) replaces

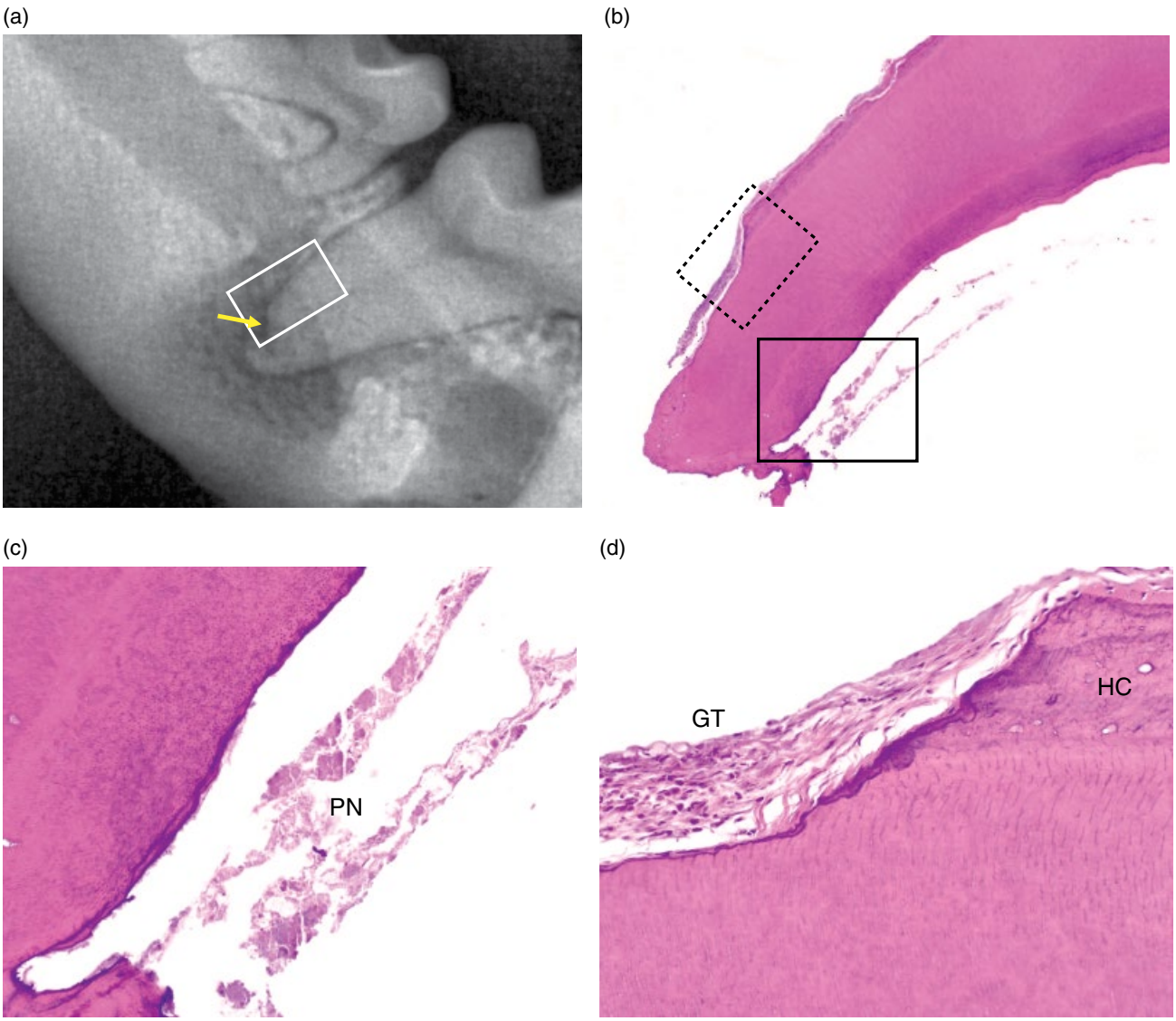


Figure 4.12 Radiographic and histologic images of periapical periodontitis at the site of a non-vital mandibular first molar in a six year-old, male Chihuahua. (a) There is a large periapical lucency at the mesial root and mild apical root resorption (arrow). (b) Low magnification of a portion of the apical mesial root (area within the solid line box from a). (c) The pulp chamber contains only amorphous debris due to pulp necrosis (PN) and a seam of basophilia along the inner dentin wall suggests internal resorption and remodeling (area within the solid line box from b). (d) Adjacent to hypercementosis (HC) is an area of external resorption that has a similar line of basophilia and is bordered by a small amount of granulation tissue (GT), which would have replaced the periapical bone (area within the dashed line box from b). *Source:* E. Vicari.

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the alveolar bone that surrounds the apex of an affected tooth, and mixed inflammatory cell infiltrates are expected, including neutrophils, lymphocytes, and plasma cells. Occasionally, the proliferative tissue includes hyperplastic rests of odontogenic epithelium. In this situation, periapical (radicular) cysts may arise with cystic degeneration and expansion of these rests. Draining sinus tracts may also develop with chronic periapical inflammation [35]. Both periodontitis (see Section 5.1.1) and periodontal osteomyelitis (see Section 5.2.1) are discussed elsewhere.

4.2.4 Caries

Caries, focal decay of the dental matrices, do occur in dogs, but they are uncommon. Although caries commonly occur in human beings, they are less common in veterinary species. One study found that prevalence of dental caries in dogs was approximately 5% and affected dogs tended to be middle age to geriatric [36]. Two types of caries occur relatively commonly in horses: peripheral and infundibular; both are most likely to develop within cementum of the erupted crown of cheek teeth. See Section 4.3 on equine dental diseases.

Caries are the result of demineralization and loss of enamel and dentin due to exposure to acidic products of microbial fermentation. An animal's risk for dental caries is dependent upon the amount of fermentable carbohydrates in the diet and genetic/ species factors (e.g. tooth shape, salivary pH, amount of salivary amylase). The microbes involved may vary from specific cariogenic pathogens to dysregulated oral flora to normal oral flora that opportunistically ferment available substrates.

The colloquial term "cavity" is derived from the fact that as caries progress, an expanding area of softened crown dentin undermines the enamel, which eventually breaks away and, when the soft dentin is removed, a cavity is left in the crown of the tooth (Figure 4.13). Grossly and clinically, caries appear as dark brown lesions on the occlusal surface of teeth; in dogs, the molar teeth are most likely to be affected (Figure 4.14) [34]. The degree of distribution of tooth demineralization cannot be adequately evaluated in decalcified histological sections; however, the presence of bacteria on the surface and within crown dentin can be confirmed histologically. Teeth submitted for pathologic evaluation should be photographed prior to decalcification (see Appendix).

4.2.5 Plaque and Calculus

The enamel surfaces of teeth are covered by a protective film of organic material called the pellicle. The pellicle is composed of salivary proteins and other macromolecules, including enzymes and immunoglobulins. Plaque is the microbial biofilm that binds to and combines with



Figure 4.13 Gross images of a baboon skull with multiple dental caries. During its life, this animal was regularly rewarded with candy. *Source:* R. R. Dubielzig, University of Wisconsin-Madison.

the pellicle. In time, plaque may become mineralized to form dental calculus, also known as tartar.

Calculus forms when calcium carbonate and calcium phosphate salts, derived from saliva, precipitate upon the tooth surface. Once formed, calculus must be removed mechanically. Dental calculus facilitates adherence of additional plaque bacteria, especially subgingivally and at the gingival margin, which is a known risk factor for periodontal disease. Cats and dogs typically have alkaline saliva, which predisposes them to calculus formation (but is potentially protective against caries!).

Histologically, evidence of the plaque biofilm can be seen in decalcified dental calculus, particularly in *en bloc* specimens that include teeth in situ. The true distribution of plaque on a tooth surface is difficult to determine histologically due to the loss of enamel during decalcification. However, plaque is easily seen when adhered to tooth/ bone surfaces that remain within the histological section, including dentin where enamel has been lost, exposed cementum at sites of gingival recession or periodontal pocketing, necrotic bone, and foreign material.

The presence of plaque alone is not sufficient to cause caries or periodontal disease. These conditions may occur when there are shifts in the population of plaque-associated bacteria and/or other host and environmental factors (e.g. diets, systemic disease). The prevalence of periodontal disease in dogs and cats increases with age and it is generally associated with *non-specific* plaque microbes [34]. However, a theory of *specific plaque pathogens* (i.e. particular disease-causing bacterial species) might explain why severe periodontitis occurs in some younger individuals [34].

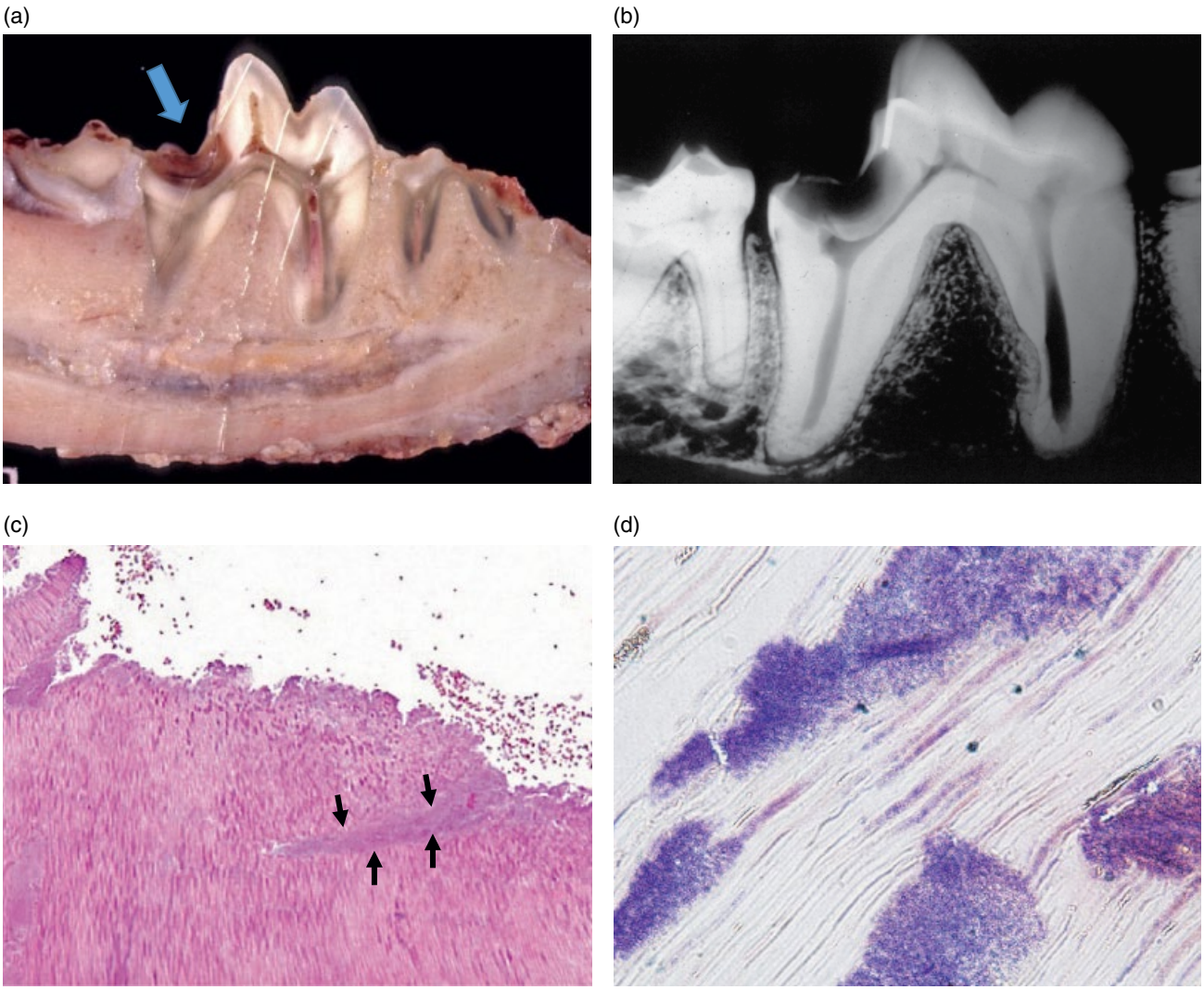


Figure 4.14 Gross, radiographic, and histologic images of a dental caries lesion affecting a mandibular first molar of a dog. (a) The distal cusp of the tooth has a grossly brown depression (arrow). (b) A radiolucent defect corresponds to the area and the entire brown portion of the tooth appears to be absent since demineralized (brown) dentin is grossly visible but radiolucent. (c) Although decalcified histological sections cannot truly demonstrate the fundamental change of caries (i.e. demineralization of tooth matrix), histopathology of the lesion demonstrates irregular and tattered dentin at the exposed surface and bacteria dissecting into the dentin (arrows). (d) A Gram stain renders the bacteria easily visible. *Source:* R. R. Dubielzig, University of Wisconsin-Madison.

4.2.6 Tooth Resorption

Tooth resorption (TR; with the modifier "odontoclastic" having been dropped in the recent literature) is physiological or pathological removal of tooth structure that is mediated by odontoclasts. In contrast, caries are lesions in which tooth structure degenerates secondary to demineralization by acidic bacterial metabolites. Some trigger is necessary to initiate the process of TR. Recruitment and differentiation of odontoclasts (histologically indistinguishable from osteoclasts) are mediated by periodontal ligament fibroblasts (external resorption) or pulp stromal fibroblasts (internal resorption) [37]. In addition to being classified anatomically as internal or external, there are two main patterns in which TR occurs – inflammatory and replacement. Inflammatory TR is triggered by pro-inflammatory mediators and the resorbed portion of tooth is replaced by granulation tissue. Usually, the process is local and affects a single tooth. External inflammatory resorption usually occurs in conjunction with periodontal disease. Inflammatory internal resorption is frequently associated with endodontic disease/ pulpitis or physical trauma [34, 35].

In replacement resorption (*resorption with replacement*), the resorbed tooth is replaced by bone or cementum-like bone. External replacement resorption has been demonstrated to be common in humans where approximately

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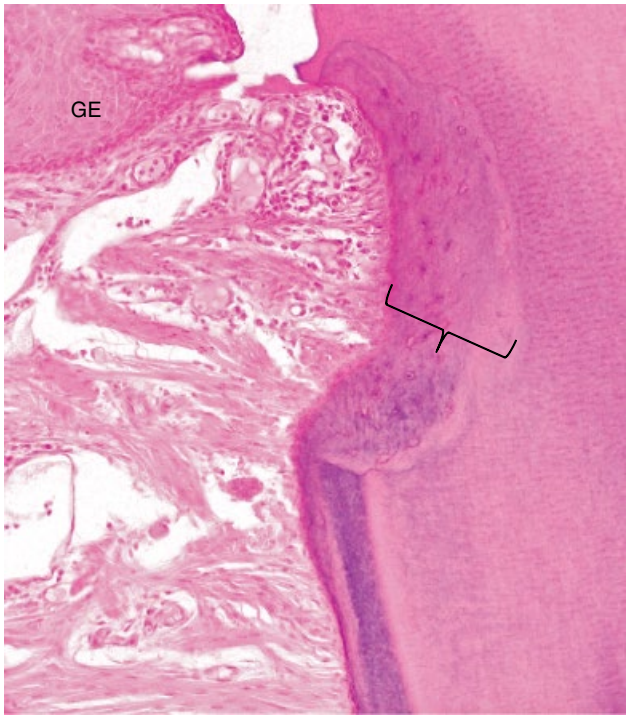


Figure 4.15 Histologic images of a tooth where a concave defect at the cementoenamel junction (CEJ) has evidence of both inflammatory and replacement resorption. A thick seam of cementoosseous matrix (bracket) lines the affected area. This lesion probably developed slowly in the presence of relatively mild inflammation, which can be seen extending from immediately below the gingival epithelium (GE) to deep into the periodontal tissues.

90% of teeth with radiographic evidence of resorption have mild lesions of no clinical significance [34]. Interestingly, inflammatory and replacement resorption can occur together, or at least sequentially, so that both patterns are simultaneously present (Figure 4.15). Replacement resorption is often accompanied by hypercementosis and ankylosis of the tooth root. *Hypercementosis* refers to deposition of excessive cementum upon the native root cementum, which is a pathophysiological process in response to stimuli such as local inflammation and occlusal trauma (in horses, this lesion should be differentiated from nodular hypercementosis/ cementoma). *Ankylosis* is the anatomic fusion of the cementum or dentin to alveolar bone. Ankylosis results when the periodontal ligament is bridged by cementum or bone and is often visible radiographically. Ankylosis prior to or during tooth eruption will result in an impacted or incompletely erupted tooth. Factors that contribute to hypercementosis and ankylosis include local inflammation and abnormal physical forces on the tooth.

The pathogenesis of external replacement TR is poorly understood; many cases in humans are considered to be idiopathic. Replacement resorption that occurs without an apparent cause also occurs in domestic animals and, as in humans, the incidence increases with age. In the following discussion of TR in different species of animals, we acknowledge an incomplete understanding of cause and mechanism, but aim to demonstrate typical morphological changes that occur in various TR lesions in animals.

4.2.6.1 Tooth Resorption in Cats

TR is very common in cats, and lesions are most apparent clinically when they occur in the cervical region of the tooth, i.e. near the cementoenamel junction (CEJ). The terms "feline resorptive neck lesion" and "neck lesions," are considered to be obsolete and we will refer to these as TR. While the mandibular premolars and molars are most affected in cats [37, 38], feline TR is often a generalized disorder that occurs as part of a syndrome with other dental diseases (e.g. periodontal ligament degeneration, hypercementosis, alveolar bone expansion, and tooth extrusion) [39]. Studies designed to address the pathogenesis and early lesions of feline TR have shown that degeneration of the periodontal ligament is a consistent early change [40, 41]. In early lesions, the periodontal ligament may become less distinct on radiographs and resorption can be limited to the cementum. Inflammation of the periodontal ligament is rarely apparent histologically [41]. Systemic mediators are likely involved as well. For example, compared to cats without TR lesions, cats with lesions had significantly higher mean serum concentration of 25-hydroxy vitamin D and significantly lower mean urine specific gravity even when corrected for age [42]. While these associations have been observed, cause and effect has not (yet) been established.

In cats, TR initiates at one or more places along the external surface of the tooth root. The CEJ may not be a predisposed site for initiation, but TR does seem to progress most rapidly and extensively in this area. The apical root is likely to become ankylosed to the surrounding alveolar bone while loss of cervical dentin may undermine the tooth structure to the point that the crown fractures away (Figure 4.16). The retained ankylosed root dentin will be gradually replaced by bone. In some cats, this process is subclinical. In other cats, the retained root becomes a nidus of inflammation that contributes to smoldering osteomyelitis until the root is removed and the alveolus is debrided (Figure 4.17). The inflammatory scenario is more likely to occur if significant periodontitis or endodontic disease was present during the resorptive process.

There is an analog to feline TR in humans called "invasive cervical resorption," which is a type of idiopathic external TR that affects the CEJ immediately below the gingival epithelial attachment [43]. In this condition, resorption is progressive and eventually leads to loss of the tooth, just as in cats. A compelling explanation for the progression and tooth loss associated with cervical TR lesions is that cementum and bone are less abundant in proximity to the CEJ. Lacking capacity for reparative

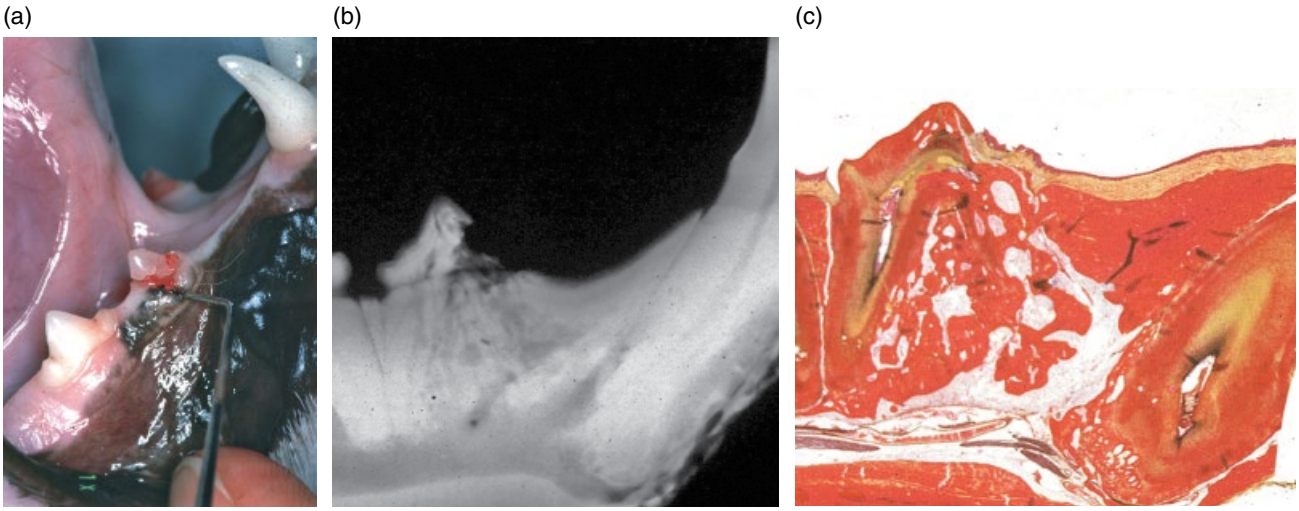


Figure 4.16 Gross, radiographic, and histologic images of a second mandibular premolar tooth in a cat that was affected by TR. (a) The tooth had grossly visible fissures in the crown. (b) The radiograph of a different but similarly affected tooth has significant crown loss and irregular modeling of the mesial root. (c) The same pattern of crown and root loss are apparent in the picrosirius red stained tissue section. *Source:* R. R. Dubielzig, University of Wisconsin-Madison.

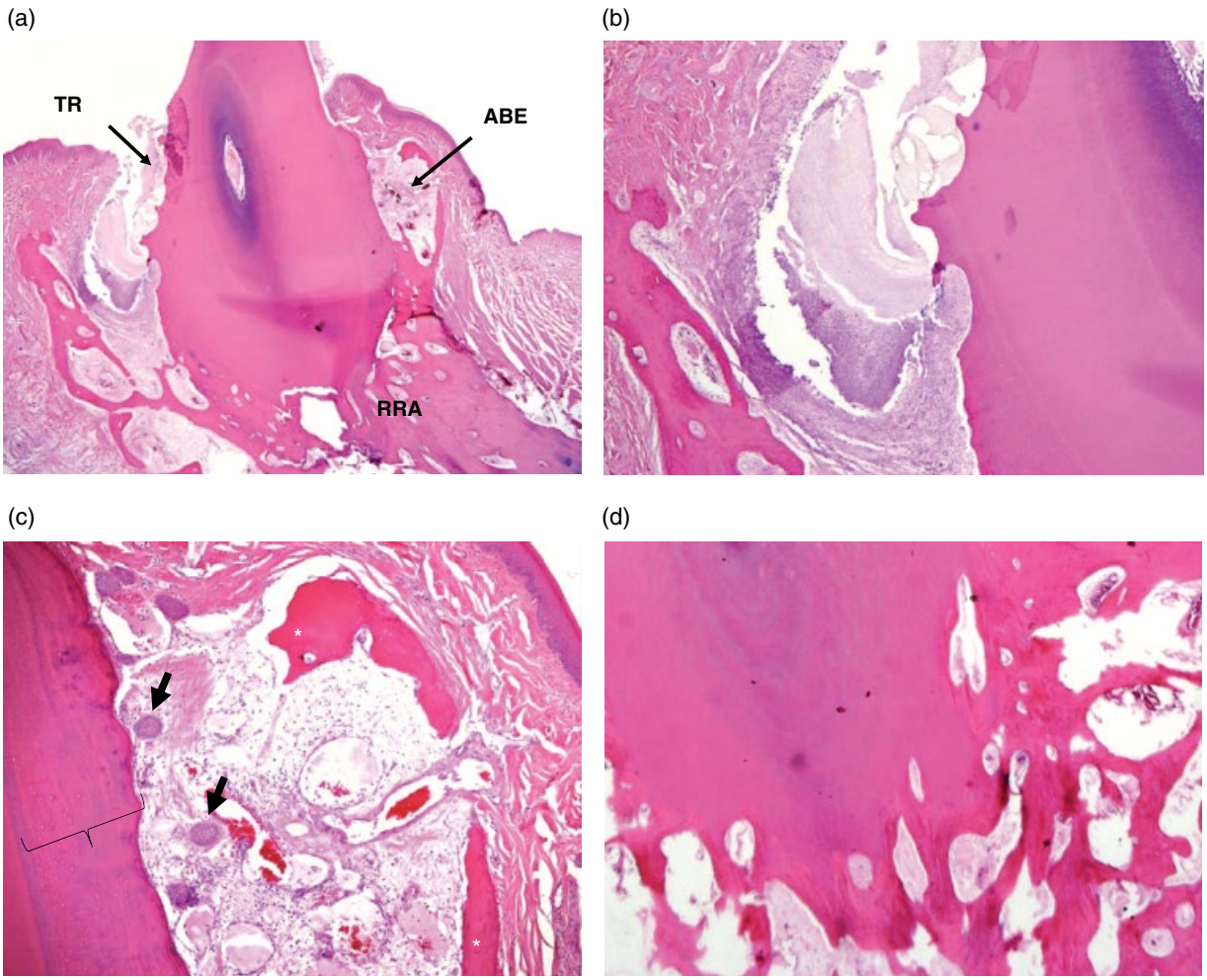


Figure 4.17 Histologic images of a mandibular canine tooth from a cat that is affected by severe periodontitis. (a) This tooth has an inflammatory tooth resorption (TR) lesion on one side, osteomyelitis with alveolar bone expansion (ABE) on the opposite side, and apical replacement resorption with ankyloses (RRA). (b) The inflammatory TR lesion demonstrates scalloping of the external tooth surface where dentin has been lost. The adjacent periodontal tissues, including alveolar bone, are replaced by a cavitated area bordered by granulation tissue and containing suppurative exudate and amorphous necrotic debris. (c) The opposite area of bone inflammation and expansion has hypercementosis (bracket) and bone of the alveolar crest (white asterisks) has been displaced away from the tooth due to proliferation of loosely arranged fibrovascular connective tissue with inflammation and few hyperplastic rests of odontogenic epithelium (arrows). (d) The apical portion of the tooth root has been partially replaced by bone, which is broadly continuous with (ankylosed to) adjacent trabecular bone of the alveolus.

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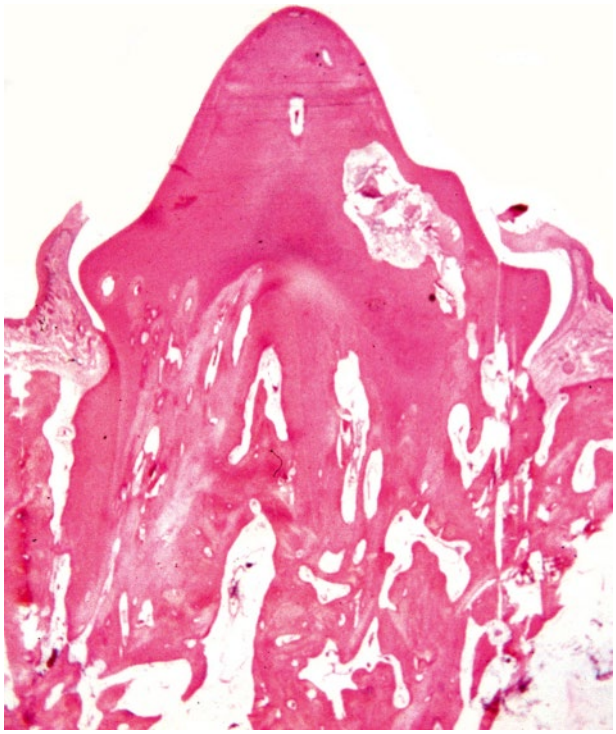


Figure 4.18 Histologic image of a feline premolar with extensive tooth resorption. The root has been replaced by bone and there is hypercementosis and ankylosis of remaining root dentin. Extending from the cementoenamel junction (CEJ) at the right of the image, an area of resorbed crown dentin is replaced by soft tissue. *Source:* R. R. Dubielzig, University of Wisconsin-Madison.

cementum or bone, granulation tissue replaces resorptive dentin defects in the cervical region of the tooth [39]. In contrast, TR lesions of the apical root are more likely to exist in conjunction with hypercementosis and/or ankyloses. These processes could help fuse the tooth to bone and thereby retain the affected tooth despite significant TR. This illustrates the complexity of TR in cats, which seem to have replacement resorption of root dentin but inflammatory resorption of the cervical and crown dentin (Figure 4.18).

4.2.6.2 Tooth Resorption in Dogs

Relative to cats, TR in dogs is less common. However, it is safe to say that with widespread implementation of dental radiography in veterinary practice, canine TR is recognized more frequently than it has ever been in the past. In the most comprehensive study of TR in dogs to date, investigators identified six different patterns of TR – four external (replacement, inflammatory, cervical, and surface) and two internal (inflammatory and surface) [44, 45]. This classification scheme of TR in dogs is based on radiographic features. While we find the terminology to be useful, these are not histological categories.

The incidence of TR in dogs increases with age and body weight such that older and larger-breed dogs are most likely to have TR lesions, especially external replacement TR [45]. Premolar and canine teeth are affected more often than incisors or molars. Replacement resorption in dogs is characterized by replacement of cementum and dentin by bone (ankylosis) (Figures 4.19 and 4.20). Inflammatory TR in dogs usually occurs in the

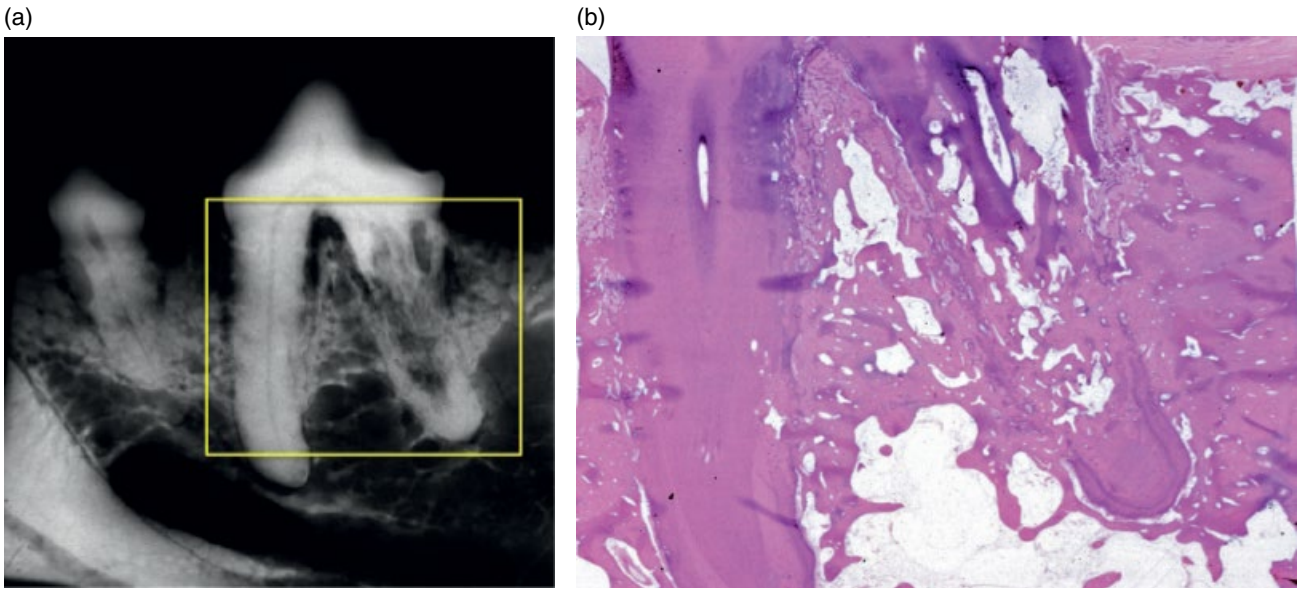


Figure 4.19 Radiographic and histologic images of a second mandibular premolar tooth from a dog. Replacement resorption and dentoalveolar ankyloses are mirrored in the radiograph (a) and the decalcified tissue section (b). *Source:* R. R. Dubielzig, University of Wisconsin-Madison.

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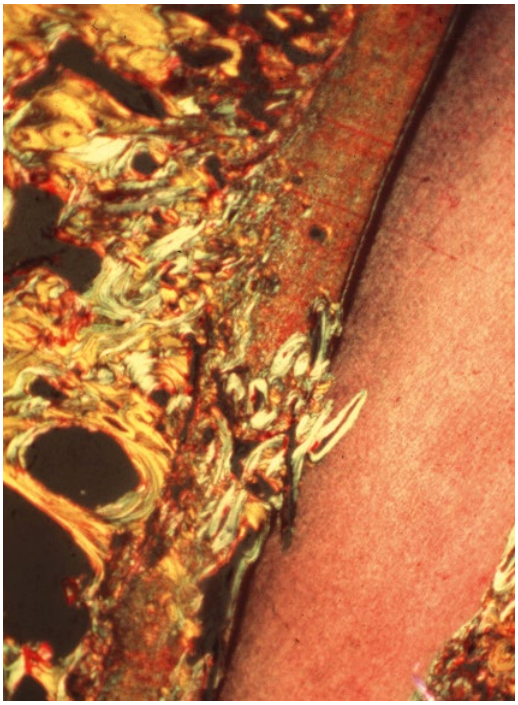


Figure 4.20 Histologic section of a tooth from a dog that was affected by dentoalveolar anklyosis and early replacement tooth resorption. Matrix fibers from the adjacent alveolar bone have reorganized a segment of cementum and few fibers extend into the dentin. Stained with picrosirius red and photographed with polarized light. *Source:* R. R. Dubielzig, University of Wisconsin-Madison.

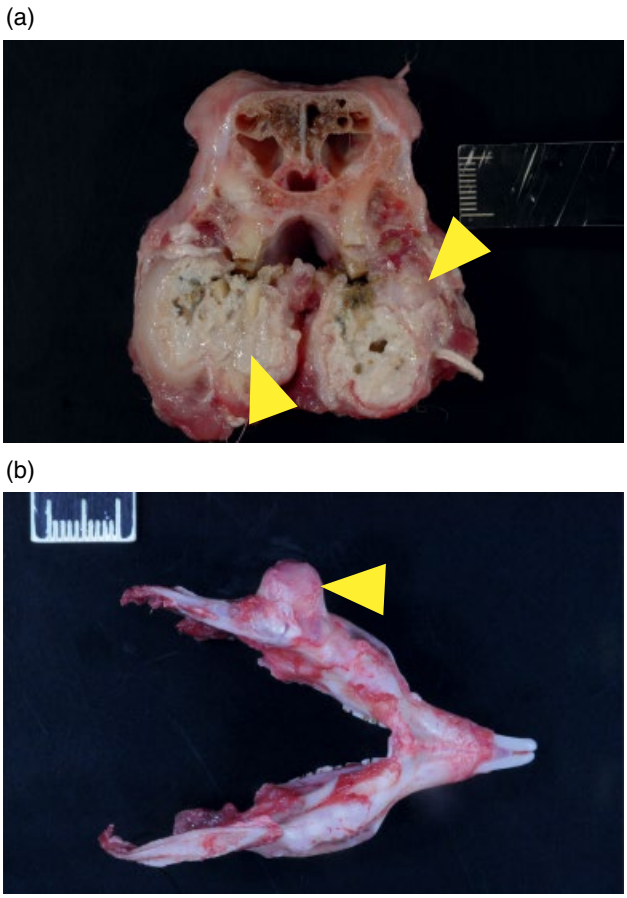


Figure 4.21 Gross images of a rabbit and guinea pig with odontogenic dysplasia. (a) A three-year-old female domestic rabbit has bilateral mandibular osteomyelitis and odontogenic dysplasia (yellow arrowheads). *Source:* Dr. K. M. Casey, University of California, Davis. (b) An adult male guinea pig has a focal expansion of the mandible associated with the root of the right third molar tooth (yellow arrowhead, odontogenic dysplasia). *Source:* A. O. Michel, University of California, Davis.

context of periodontal disease and/or endodontic disease. The maxillary fourth premolar was the most common site for external inflammatory TR, which may be due to this being a frequent location of periodontal disease [45].

4.2.7 Odontogenic Dysplasia

In animals with continuously erupting dentition, trauma, infection or other injury to the base of the tooth can result in a striking proliferative lesion within the jawbone referred to as odontogenic dysplasia (OD). OD in aging rodents and lagomorphs should be distinguished from the similarly named focal or regional odontodysplasia (see Section 4.1.4, Abnormalities in tooth shape). Importantly, rodents and lagomorphs with OD have an enamel organ that persists throughout life. Enamel organ persistence occurs in teeth lacking a true root (aradicular), which are continuously erupting (elodont) and high crowned (hypsodont). Such teeth include the incisor teeth of rodents and rabbits and the canines/tusks of pigs. OD can also occur in animals equipped with elodont cheek teeth – rabbits, guinea pigs, chinchillas, degus, and voles [46] (see Figure 4.21). Most of the animals with elodont dentition, with noted exception of pigs, are herbivorous; continuous tooth eruption is an adaptation to food-associated tooth wear. OD occurs in the cheek teeth of horses, as well (see below).

OD becomes more common as animals age, affecting as many as 25% of aged rodents in some populations [47]. In a population of voles, OD was present in 63% of the animals and was often associated with cortical perforation of the mandible, or in some cases, projection of the lesion into the cranial vault [48]. Irritation, inflammation, or mechanical disruption of the embryonic enamel organ can result in a proliferative mass-like lesion of disorganized odontogenic matrices. As a result, OD has been interpreted to be an odontogenic neoplasm (odontoma) and investigators have used terms like *pseudo-odontoma* or *elodontoma* [48, 49]. The term elodontoma was originally defined for odontoma-like lesions in southern African tree squirrels (*Paraxerus cepapi*) [49]. This term

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has subsequently has been used to describe similar odontoma-like lesions in guinea pigs [46]. Although the controversy continues, some investigators regard these lesions to be *pseudoneoplastic* [50].

Histologically, OD is a dysplastic proliferation of the odontogenic germinal tissue (odontogenic epithelium and ectomesenchyme) and dental matrix (dentin and enamel). Tissues derived from the dental follicle like bone and cementum may also be present in the OD lesion. OD is characterized as a disorganized mass of eosinophilic matrix (dentin and cementum) and intermixed basophilic matrix (enamel). Cemental matrix is distinguished by multiple, variably spaced and generally empty lacunae with numerous basophilic cementing lines organized into a mosaic "topographic map" like structure. Although dentin typically demonstrates parallel "dentinal tubules," it may lack tubules altogether (atubular dentin) or may have multiple empty lacunae, mimicking bone (osteodentin). Enamel matrix is typically basophilic to purple, may be organized into rings or undulating ribbons, or more commonly, will be intermixed and embedded within the other dental matrices as complex, swirling, basophilic–eosinophilic–gray material. In some OD lesions, clear clefts within the histology section indicate the former presence of enamel, removed during the decalcification process (Figure 4.22).

If the cause of the OD lesion is infectious (as it often is), the adjacent periodontia and alveolar bone will have evidence of inflammation, with large numbers of neutrophils/heterophils orienting around bacterial colonies, embedded plant material or hair shafts. Rabbits frequently have abscessing osteomyelitis associated with OD. The surrounding alveolar bone is often heavily remodeled with evidence of both bone formation (palisading hypertrophied osteoblasts, unmineralized osteoid) and bone lysis (multinucleate osteoclasts within scalloped bone resorption bays). Parallel plates of proliferative woven bone at the periphery of the lesion is a common finding.

OD of hypsodont teeth shares some clinical and histological features with two other important lesions: nodular hypercementosis of horses (cementoma), and odontoma. The interested reader is encouraged to review sections 4.3.3 and 7.4.1 respectively, focused on these subjects. One of the authors (BGM) has identified several cases of OD in horses associated with nasal sinusitis and the apices of the cheek teeth. This anatomic location also happens to be a common location for nodular hypercementosis (cementoma), a lesion that is also associated with sinusitis/periodontitis. Why a particular equine tooth root infection results in nodular hypercementosis vs. OD may be dependent upon proportional involvement of the persistent enamel organ (OD) vs. the dental follicle (nodular hypercementosis). Clinically and radiographically, these lesions present in a very similar manner, although nodular hypercementosis (cementoma) is more common.

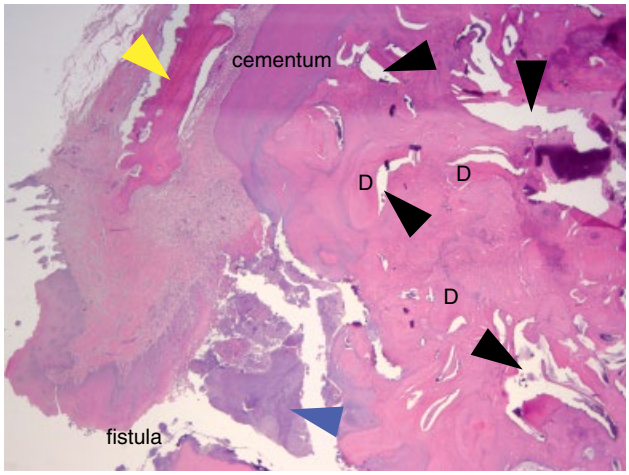


Figure 4.22 Histologic image of mandibular odontogenic dysplasia, periapical periodontitis, and osteomyelitis, seven-year-old dwarf rabbit. In this image, a hard mass is formed by disorganized deposits of dentin (D), cementum, and clear clefts presumed to have contained multiple irregular deposits of enamel matrix (black arrowheads). A bacterial biofilm is evident (blue arrowhead) and an epithelium-lined fistula drains to the ventral skin. Remnant mandibular cortical bone is also present (yellow arrowhead) (a).

References

34 Neville, B.W., Damm, D.D., Allen, C.M., and Chi, A.C. (2016). *Oral and Maxillofacial Pathology*, 4the. St. Louis, Missouri: Elsevier.

35 Wiggs, R.B. and Lobprise, H.B. (1997). *Veterinary Dentistry : Principles and Practice*. Philadelphia: Lippincott-Raven Publishers.

36 Hale, F.A. (1998). Dental caries in the dog. *J. Vet. Dent.* 15: 79–83.

37 Sokos, D., Everts, V., and de Vries, T.J. (2015). Role of periodontal ligament fibroblasts in osteoclastogenesis: a review. *J. Periodontal Res.* 50: 152–159.

38 Reiter, A.M., Lyon, K.F., Nachreiner, R.F., and Shofer, F.S. (2005). Evaluation of calciotropic hormones in cats with odontoclastic resorptive lesions. *Am. J. Vet. Res.* 66: 1446–1452.

VetBooks.ir

39 DeLaurier, A., Boyde, A., Jackson, B. et al. (2009). Identifying early osteoclastic resorptive lesions in feline teeth: a model for understanding the origin of multiple idiopathic root resorption. *J. Periodontal Res.* 44: 248–257.

40 Lewis, J.R., Okuda, A., Shofer, F.S. et al. (2008). Significant association between tooth extrusion and tooth resorption in domestic cats. *J. Vet. Dent.* 25: 86–95.

41 Roux, P., Berger, M., Stoffel, M. et al. (2005). Observations of the periodontal ligament and cementum in cats with dental resorptive lesions. *J. Vet. Dent.* 22: 74–85.

42 Gorrel, C. and Larsson, A. (2002). Feline odontoclastic resorptive lesions: unveiling the early lesion. *J. Small Anim. Pract.* 43: 482–488.

43 Regezi, J.A., Sciubba, J.J., and Jordan, R.C.K. (2012). *Oral Pathology : Clinical Pathologic Correlations*, 6e. St. Louis, MO: Elsevier/Saunders.

44 Peralta, S., Verstraete, F.J., and Kass, P.H. (2010). Radiographic evaluation of the classification of the extent of tooth resorption in dogs. *Am. J. Vet. Res.* 71: 794–798.

45 Peralta, S., Verstraete, F.J., and Kass, P.H. (2010). Radiographic evaluation of the types of tooth resorption in dogs. *Am. J. Vet. Res.* 71: 784–793.

46 Capello, V., Lennox, A., and Ghisleni, G. (2015). Elodontoma in two guinea pigs. *J. Vet. Dent.* 32: 111–119.

47 Head, K.W., Armed Forces Institute of Pathology (US), American Registry of Pathology, and WHO Collaborating Center for Worldwide Reference on Comparative Oncology (2003). *Histological Classification of Tumors of the Alimentary System of Domestic Animals*. Washington, DC: Armed Forces Institute of Pathology in cooperation with the American Registry of Pathology and the World Health Organization Collaborating Center for Worldwide Reference on Comparative Oncology,.

48 Imai, D.M., Pesapane, R., Conroy, C.J. et al. (2018). Apical elongation of molar teeth in captive Microtus voles. *Vet. Pathol.* 55 (4): 572–583.

49 Boy, S.C. and Steenkamp, G. (2006). Odontoma-like tumours of squirrel elodont incisors – elodontomas. *J. Comp. Pathol.* 135: 56–61.

50 Wong, H.E., Hedley, J., Stapleton, N. et al. (2018). Odontoameloblastoma with extensive chondroid matrix deposition in a guinea pig. *J. Vet. Diagn. Investig.* 30 (5): 793–797.

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4.3 Equine Dental Diseases

Although horses primarily have hypsodont dentition, their deciduous incisors are brachydont. The permanent teeth continue to erupt throughout the life of the horse, with the exception of the canine teeth. The horse's so-called "wolf teeth," rudimentary/ vestigial maxillary PM1 teeth, may or may not be present. The mandibular PM1 is generally absent and the mare's canine teeth may be small and fail to erupt. As a result, the horse may have 36–42 permanent teeth. Equine teeth also have an anatomic structure which carnivores lack, the infundibulum. The relative state of wear of the infundibulum provides a useful gauge to age a horse. Pathologists should be aware of the technical challenges associated with preparing large mineralized specimens like equine teeth for histological examination (see Appendix).

In a survey of horses presented for slaughter, "the most common oral pathologies included sharp edges, buccal abrasions, calculus, lingual ulcers, gingival recession, periodontal pockets, ramps, and waves" [51]. Tooth-associated infections, loss, fractures, and calculus accumulation are also common. In older horses, various forms of malocclusion ("step mouth"/"wave mouth") and tooth wear/ attrition are common. The following section is not intended to be an exhaustive survey covering all of the pathologies of equine teeth; it covers several of the more common equine dental diseases and a few dental pathologies unique to equids.

4.3.1 Equine Odontoclastic Tooth Resorption and Hypercementosis

The term equine odontoclastic tooth resorption and hypercementosis (EOTRH) refers to an interesting syndrome of tooth *resorption* and *proliferation* of calcified tissue that affects the roots of multiple incisor, canine, and less often, cheek teeth in aged horses. The descriptive name of this common and progressive lesion defines the principal radiographic and histologic lesions – concurrent dental resorption and hypercementosis. EOTRH is likely underdiagnosed, and typically progresses from the third to the first incisor [52]. Early lesions may be asymptomatic, becoming progressively more painful as the lesions advance. Ankylosis is common in advanced EOTRH lesions.

Histologically, there is evidence of resorption of the mineralized dental matrices (cementum and/or dentin) with attached odontoclasts (osteoclasts) along the scalloped surface of the tooth. As the name suggests, moderate to profound hyperplasia of the cemental tissues is concurrently present. Some investigators have coined the term *irregular cementum* [53] to describe this reparative tissue, as its florid and irregular proliferation results

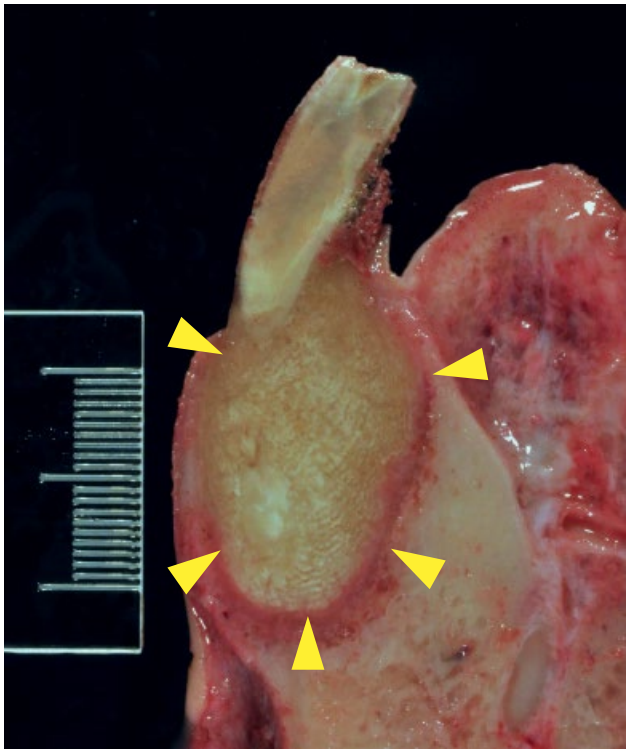


Figure 4.23 Gross image of incisor tooth affected by EOTRH, 20-year-old Standardbred gelding. Hypercementosis of the tooth root is grossly evident (yellow arrowheads). *Source:* A.L. Johnson, University of California, Davis

in a characteristic bulbous dental enlargement in the intraalveolar portion (reserve crown) of the tooth (Figures 4.23 and 4.24). The associated periodontal tissues typically have evidence of inflammation, with moderate to large numbers of infiltrating neutrophils, lymphocytes, and plasma cells. Lesions may be characterized by predominant tooth resorption, predominant hypercementosis or a balance of these two processes [52]. It is important for the pathologist to recognize the hypercementosis associated with EOTRH as a reactive process (non-neoplastic), and to avoid using the terms "cementoma" or "cementoblastoma."

Radiographs are critical to establishing a diagnosis, and in conjunction with signalment and clinical signs, radiographs may be diagnostic (Figure 4.25). Although EOTRH is commonly seen by clinicians, the diagnosis of EOTRH is rarely made by pathologists. Evaluation of EOTRH in diagnostic or study specimens is complicated by how difficult it is to obtain high-quality, demineralized histology sections (see Appendix).

Mechanical (occlusal) stress of the periodontal ligament (PDL) has been proposed as the initiating factor of EOTRH resulting from progressively shorter reserve crowns in the incisor teeth as horses age [3]. EOTRH shares some features with tooth resorption in cats, which

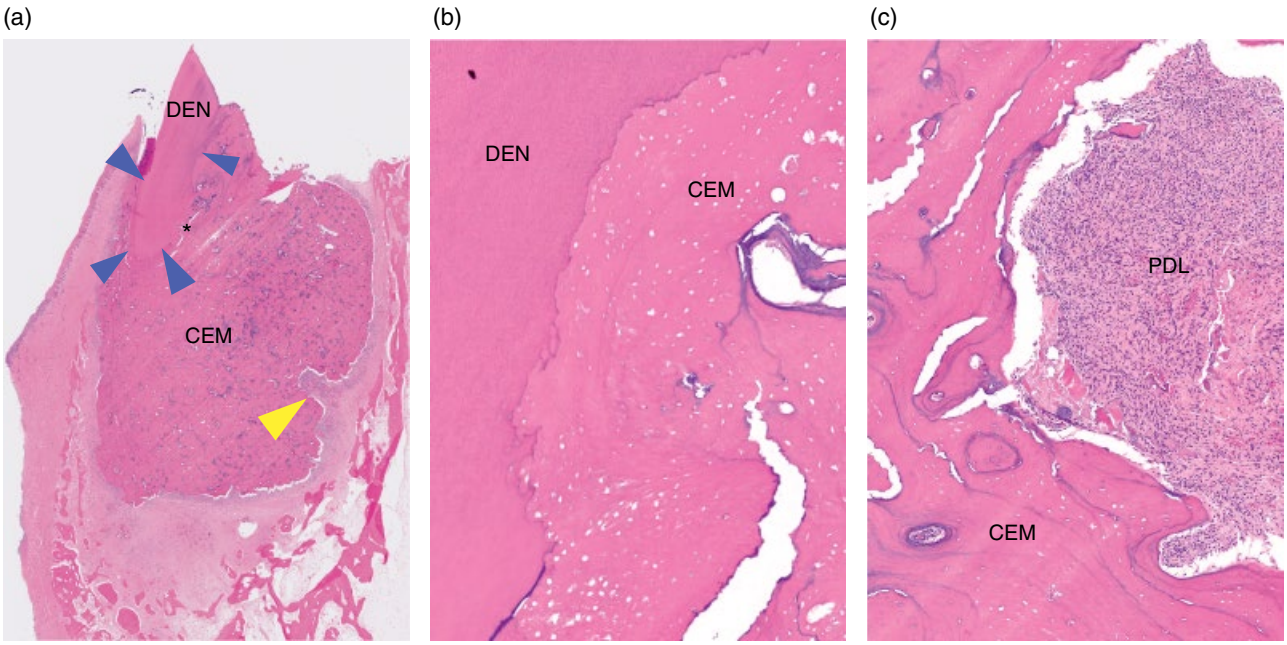


Figure 4.24 Histologic image of EOTRH, 20-year-old Standardbred gelding (same lesion as Figure 4.23). (a) Proliferative cementum (CEM) is present adjacent to the root dentin (blue arrowheads). (b) Proliferative CEM fills a resorbed focus of dentin characterized by a scalloped margin (* detail of a). (c) The inflamed periodontal ligament (PDL) is adjacent to the proliferative CEM. Note that the proliferative CEM is characterized by numerous *topographic* basophilic cementing lines. This region is delineated by the yellow arrowhead in (a).



Figure 4.25 Radiographic image of equine mandible, 28-year-old Thoroughbred gelding. In this radiographic image, both hypercementosis (yellow arrowheads) and multifocal lysis of the incisor teeth are evident (red arrowheads). *Source:* N. Pusterla, University of California, Davis.

generally targets cheek teeth. The profound hypercementosis in the equine lesion appears to be unique. At present, the treatment of choice is extraction of the affected teeth (see Figure 4.26).

4.3.2 Periodontitis and Pulpitis of Cheek Teeth

Periodontitis and pulpitis of cheek teeth is a common dental disease of horses. Early diagnosis and treatment is important to minimize morbidity and complications subsequent to periapical osteomyelitis. Clinical signs (bone swelling or nasal discharge) occur late in disease. Where diagnostic imaging is not available, one study suggested that correlating defects in secondary dentin on the occlusal surface with pulpitis could lead to earlier diagnosis in approximately 50% of cheek teeth [54]. A recent study on diagnostic imaging showed that apical infections in maxillary cheek teeth were apparent in radiographs in slightly over half of affected teeth, whereas 97% of examined teeth had agreement between computed tomography findings and pathological changes noted grossly and histologically [55].

Dacre, Kempson, and Dixon evaluated decalcified and non-decalcified sections of normal and apically infected equine cheek teeth [56–58]. Pathological features of chronic apical infections of cheek teeth included pulp necrosis or obliteration of pulp, lysis of internal dentin, feed material impacted within pulp horns, bacteria embedded within dentin, and hypercementosis. For both mandibular [58] and maxillary [57] cheek teeth, slightly over 50% of those examined showed no apparent portal for apical infection. Identifiable causes of apical infection included fractured teeth, periodontitis, caries, and dysplastic changes [57, 58].

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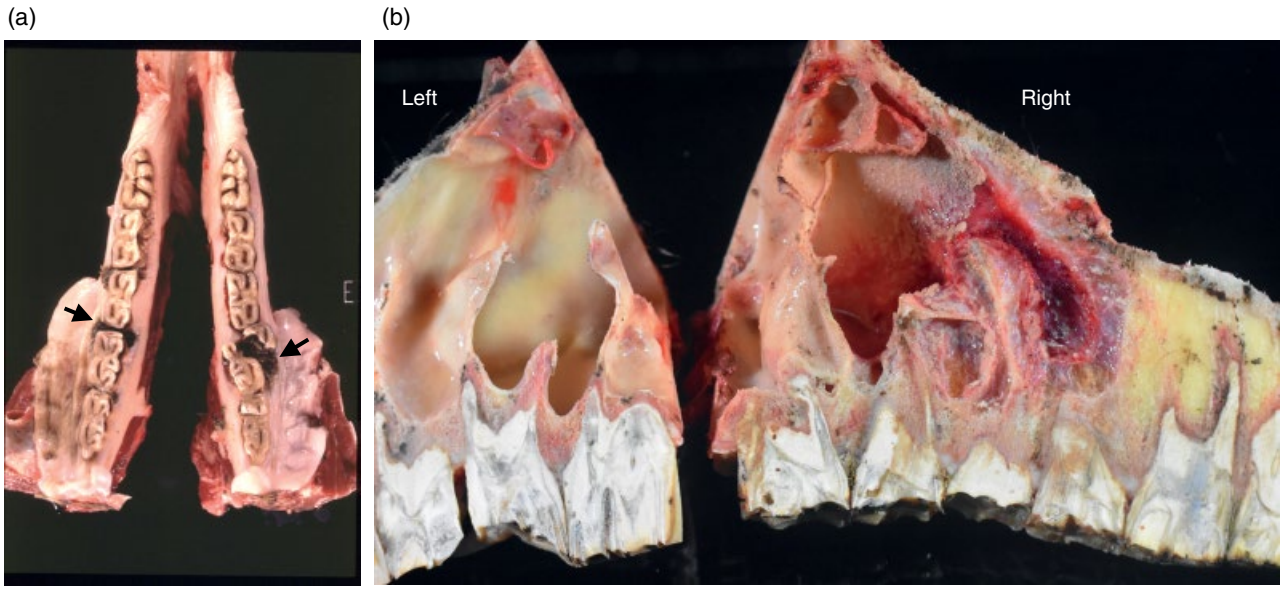


Figure 4.26 Gross images from a 20-year-old Quarter Horse mare. (a) Diastema between cheek teeth contain impacted feed material (arrows). (b) The left maxillary sinus is clear and dry; however, erythema and edema on the right are consistent with maxillary sinusitis secondary to periapical periodontitis.

Box 4.2 Differential Diagnoses for Nodular Hypercementosis

Odontogenic dysplasia
Cementoblastoma
Hypercementosis associated with tooth resorption (EOTRH)

4.3.3 Nodular Hypercementosis (Cementoma)

Nodular hypercementosis (NH) is a focal to multifocal, tooth root-associated, reactive/hyperplastic/dysplastic nodular concretion of cementum most often identified in horses. Classically, this lesion has been referred to by the term cementoma, however, many pathologists feel that cementoma is a misnomer, as there is little to no evidence that NH is actually neoplastic. NH is most often identified in the cheek teeth of herbivorous animals with hypsodont (high crowned) dentition, and is rarely seen in carnivores.

NH is characterized grossly as a variably sized, highly mineralized concretion of cementum that may or may not be attached to the tooth root (Figure 4.27). NH can be associated with dental displacement, dental loss and periodontal inflammation [59]. Due to mineralization, these lesions are very hard, often radiographically visible (radiopaque), and are associated with the roots of teeth. NH lesions can be difficult to section and may require extensive demineralization. Histologically, the lesion is comprised of mineralized and disorganized cementum with variably thick, basophilic cementing lines akin to a "topographic map" (Figure 4.28). Lacunae distributed throughout the cementum may or may not contain embedded cementocytes. In some areas, the eosinophilic cementum may be indistinguishable from woven bone, although it typically forms broad sheets with some degree of basophilia. Whether the empty lacunae devoid of cementocytes represent a real pathologic finding (e.g. cemental necrosis) or are artifacts of decalcification has not been determined.

The pathogenesis of NH involves a stimulus that acts on the tooth root and adjacent structures such as inflammation (periodontitis, rhinitis, sinusitis), skull/ tooth trauma, or other abnormal forces. Histological evidence of inflammation or microbial infection may be present and should be sought out. The associated connective tissue or PDL may be inflamed. The NH lesion may have an attached biofilm of acellular debris, bacteria and/or fungal hyphae. NH needs to be distinguished from proliferative cementum associated with tooth resorption in horses, dogs, and cats. Such a distinction may require knowledge of the gross or radiographic features of the lesion.

There is some histological overlap between NH and *odontogenic dysplasia* (see Section 4.2.7, Odontogenic dysplasia). Odontogenic dysplasia is also often associated with tooth root inflammation in animals with hypsodont dentition but involves dysplastic proliferation of dentin and/or enamel matrices in addition to cementum. NH should also be distinguished from the rare tumor of cemental origin, cementoblastoma (see Section 7.5,

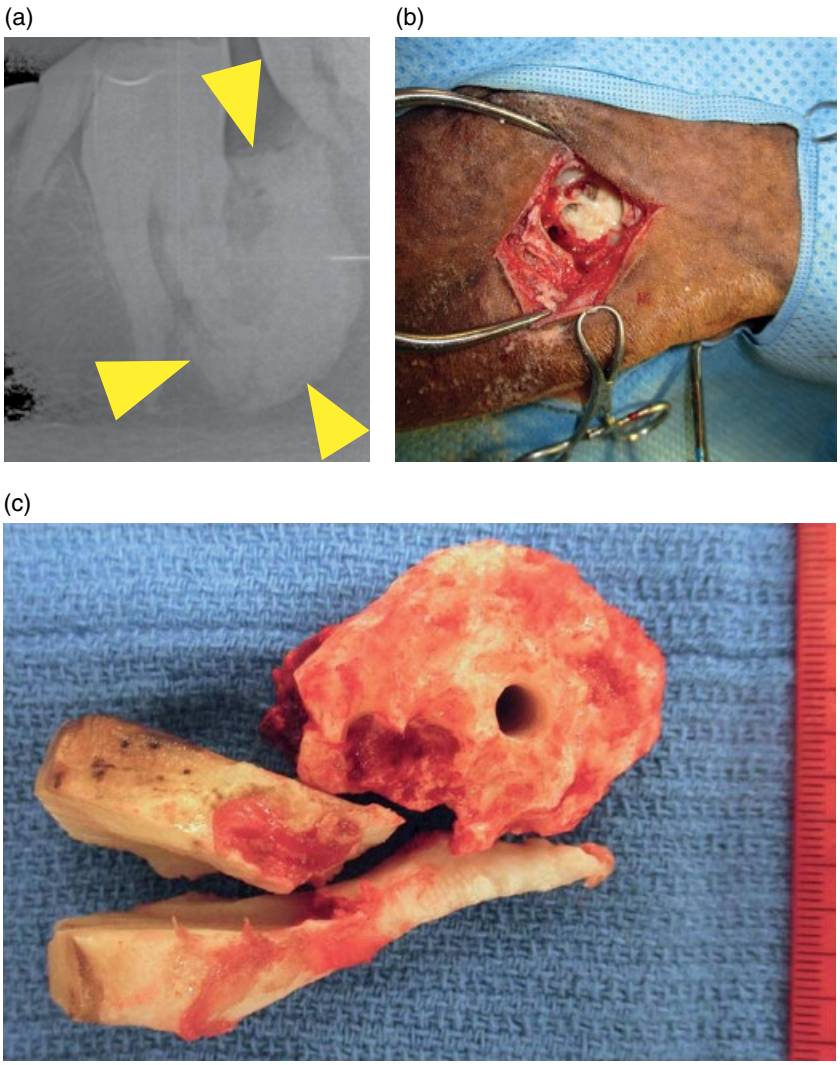


Figure 4.27 Radiographic, surgical, and gross images of equine nodular hypercementosis (NH, cementoma), 30-year-old Quarter Horse gelding. A chronic draining tract was associated with an infection of the root of a mandibular premolar tooth. (a) Intraoral radiographic image of NH closely associated with the tooth (yellow arrowheads). (b) A lateral surgical approach was necessary to remove the affected tooth root and NH lesion. (c) Gross appearance of NH and associated tooth root. *Source:* N. Pusterla, University of California, Davis.

Cementoblastoma). While NH is essentially comprised of cemental matrix with embedded cementocytes, cementoblastoma has regions of proliferative and, presumably neoplastic, cementoblasts.

4.3.4 Tooth Fractures

Fractures of the tooth crown are a significant cause of pulpitis and periapical infection of equine cheek teeth. The incidence of equine tooth fracture is likely much higher than is apparent, since some tooth cracks and fractures resolve by deposition of osteodentin (Figure 4.29). In a detailed evaluation of idiopathic fractures of cheek teeth [60], the most common pattern was a buccal slab fracture and, in most cases, the fracture plane involved the pulp chambers. Fractures that did not involve the pulp chambers were associated with infundibular caries. In this study, the idiopathic buccal slab fracture most frequently involved a maxillary first molar [60].

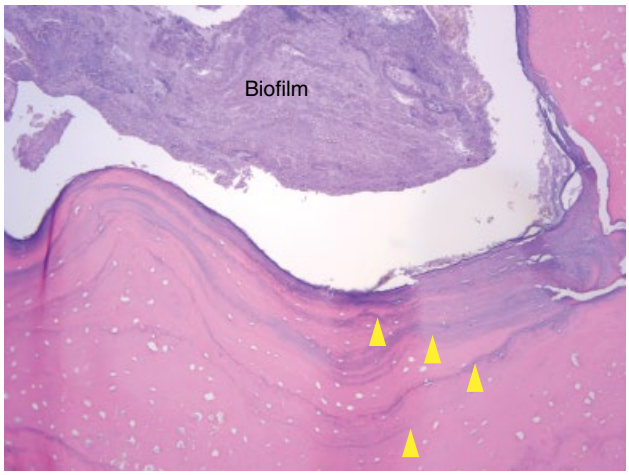
4.3.5 Caries

Peripheral caries in horses occur on the caudal-most cheek teeth, distributed approximately equally between the maxillary and mandibular arcades [61]. A histopathological study of peripheral dental caries of equine cheek teeth showed abundant bacteria within the affected cementum and within the associated plaque, but subgingival extension to periodontal disease was rare [62]. Peripheral and infundibular caries are reported in donkeys with histopathological changes similar to horses, including loss of occlusal secondary dentin, and pulp necrosis in cases of pulpar exposure [63].

Infundibular necrosis is a common type of equine caries, frequently developing on the occlusal surface of the maxillary first molar [64]. Equine teeth naturally have a deep invagination (infundibulum or "cup") in the occlusal crown which is *partially* filled with cementum and oral debris comprised of food material and bacteria.

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(a)



(b)

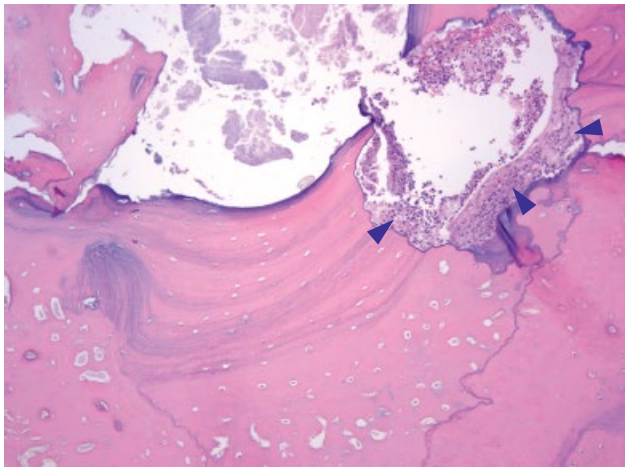
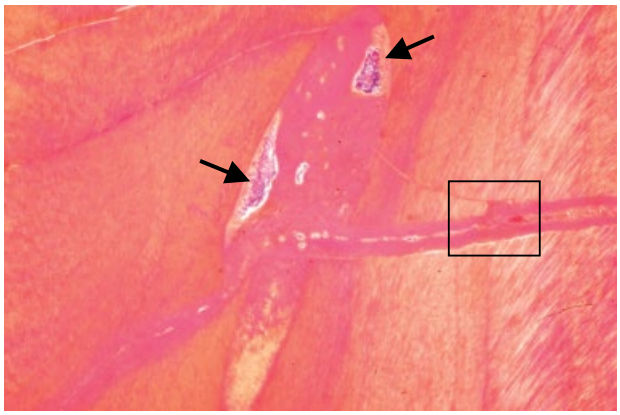


Figure 4.28 Histologic images of nodular hypercementosis (cementoma) associated with the right maxillary first molar tooth, 18-year-old Quarter Horse mare. This lesion was associated with right-sided nasal discharge and sinusitis of three years duration. (a) The nodular hypercementosis lesion (bottom) is characterized by eosinophilic matrix with empty lacunae and multiple, variably thick, basophilic cementing lines arranged in a *topographic pattern* (yellow arrowheads). The associated biofilm is a conglomerate of basophilic necrotic debris with intermixed bacteria and fungal elements. (b) A resorption bay with a scalloped margin is partially filled with infiltrating leukocytes and acellular debris (blue arrowheads).

(a)



(b)

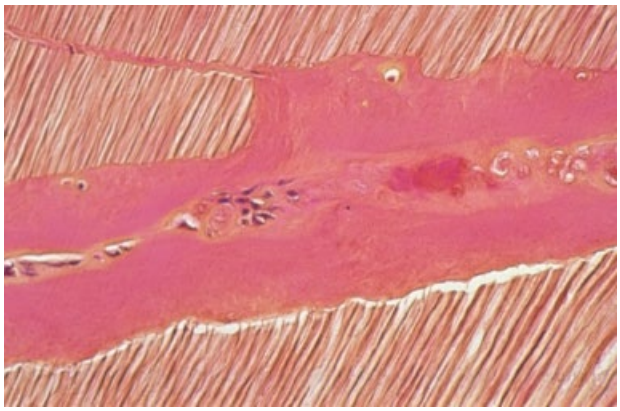


Figure 4.29 Histologic images from an equine cheek tooth. (a) Multiple fracture lines are filled by osteodentin, which also partially fills the pulp cavity where vital osteoblasts and pulp occupy what remains of the narrowed canal (arrows). (b) Higher magnification of one of the healed fracture lines (area within the box of a) demonstrates the avascular tubular organization of dentin versus the vascular osteodentin. *Source:* R.R. Dubielzig, University of Wisconsin-Madison.

Fermentation of food material by bacteria can result in acid formation and lysis of the cementum, underlying enamel and dentin. The incidence of infundibular necrosis increases with age, and 80–100 % of horses older than 12 years may have the lesion [64].

References

51 Anthony, J., Waldner, C., Grier, C., and Laycock, A.R. (2010). A survey of equine oral pathology. *J. Vet. Dent.* 27: 12–15.

52 Smedley, R.C., Earley, E.T., Galloway, S.S. et al. (2015). Equine odontoclastic tooth resorption and hypercementosis: histopathologic features. *Vet. Pathol.* 52: 903–909.

53 Staszyk, C., Bienert, A., Kreutzer, R. et al. (2008). Equine odontoclastic tooth resorption and hypercementosis. *Vet. J.* 178: 372–379.

54 Casey, M.B. and Tremaine, W.H. (2010). The prevalence of secondary dentinal lesions in cheek teeth from horses with clinical signs of pulpitis compared to controls. *Equine Vet. J.* 42: 30–36.

VetBooks.ir

55 Liuti, T., Smith, S., and Dixon, P.M. (2018). Radiographic, computed tomographic, gross pathological and histological findings with suspected apical infection in 32 equine maxillary cheek teeth (2012–2015). *Equine Vet. J.* 50: 41–47.

56 Dacre, I.T., Kempson, S., and Dixon, P.M. (2008). Pathological studies of cheek teeth apical infections in the horse: 1. Normal endodontic anatomy and dentinal structure of equine cheek teeth. *Vet. J.* 178: 311–320.

57 Dacre, I., Kempson, S., and Dixon, P.M. (2008). Pathological studies of cheek teeth apical infections in the horse: 5. Aetiopathological findings in 57 apically infected maxillary cheek teeth and histological and ultrastructural findings. *Vet. J.* 178: 352–363.

58 Dacre, I.T., Kempson, S., and Dixon, P.M. (2008). Pathological studies of cheek teeth apical infections in the horse: 4. Aetiopathological findings in 41 apically infected mandibular cheek teeth. *Vet. J.* 178: 341–351.

59 Head, K.W. and Armed Forces Institute of Pathology (U.S.), American Registry of Pathology., & WHO Collaborating Center for Worldwide Reference on Comparative Oncology (2003). *Histological Classification of Tumors of the Alimentary System of Domestic Animals*. Washington, DC: Published by the Armed Forces Institute of Pathology in cooperation with the American Registry of Pathology, & the World Health Organization Collaborating Center for Worldwide Reference on Comparative Oncology.

60 Dacre, I., Kempson, S., and Dixon, P.M. (2007). Equine idiopathic cheek teeth fractures. Part 1: pathological studies on 35 fractured cheek teeth. *Equine Vet. J.* 39: 310–318.

61 Ramzan, P.H. and Palmer, L. (2011). The incidence and distribution of peripheral caries in the cheek teeth of horses and its association with diastemata and gingival recession. *Vet. J.* 190: 90–93.

62 Erridge, M.E., Cox, A.L., and Dixon, P.M. (2012). A histological study of peripheral dental caries of equine cheek teeth. *J. Vet. Dent.* 29: 150–156.

63 Toit, N., Burden, F.A., Kempson, S.A., and Dixon, P.M. (2008). Pathological investigation of caries and occlusal pulpar exposure in donkey cheek teeth using computerised axial tomography with histological and ultrastructural examinations. *Vet. J.* 178: 387–395.

64 Maxie, M.G. (2016). *Jubb, Kennedy, and Palmer's Pathology of Domestic Animals*, 6e. St. Louis, Missouri: Elsevier.

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5

Inflammatory Lesions of the Oral Mucosa and Jaws

5.1 Inflammation of the Oral Mucosa

5.1.1 Gingivitis and Periodontitis

Gingivitis is defined as inflammation of the oral soft tissues surrounding the tooth, excluding the underlying periodontal apparatus. Periodontitis refers to inflammation of this apparatus, which includes gingiva as well as periodontal ligament, cementum, and alveolar bone. Periodontal disease encompasses inflammation of the periodontal tissues (periodontitis) as well as the state of alteration of these tissues (e.g. recession or attachment loss). In humans and animals, periodontal disease is usually characterized by cyclic episodes of active inflammatory disease and remission that lead to progressive loss of attachment between the affected tooth and the supporting periodontium [1, 2]. As such, an animal with no active inflammation could still have an altered periodontal attachment – in other words, periodontal disease without active periodontitis.

Gingivitis always precedes and accompanies periodontitis, although not all cases of gingivitis will progress to periodontitis. These conditions have a multifactorial etiopathogenesis that is influenced by a number of different factors that disrupt oral homeostasis. Various mechanisms may alter populations of plaque-associated bacteria, change the quality and quantity of saliva, and/or alter host immune response; examples include medications, allergy, systemic infections, hormones, stress, and poor oral hygiene (see Figures 5.1 and 5.2).

Bacterial plaque is considered to play a key role in both the initiation of periodontitis and episodes of destructive inflammation. Plaque biofilm research in companion animals has shown that the oral flora of dogs and cats is unlike that of humans, bacterial species that are early colonizers of the biofilm tend to be non-pathogenic/ beneficial. Supragingival plaque is less mature and more diverse than subgingival plaque [3, 4]. An individual dog or cat may be at risk for periodontitis when oral bacterial populations shift toward increased numbers of subgingival Gram positive bacteria [5–8]. Future work will likely translate this knowledge into new prophylactic treatments and therapies. At present, these studies support current clinical recommendations that emphasize plaque control. Daily at-home oral care for companion animals is the most economical and most effective way to prevent accumulation of subgingival plaque and avoid detrimental shifts in bacterial populations (see Figures 5.3 and 5.4).

Grossly, gingivitis is characterized by red, swollen gums due to congestion and edema (Figure 5.3). Histologically, plasma cells typically outnumber lymphocytes and neutrophils within the superficial gingival stroma, which also shows vasodilation and congestion of stromal capillaries (Figure 5.4). Epithelial changes include hyperplasia, erosion, hydropic degeneration, and spongiosis. Inflammation is often more severe along the sulcular surface since it is in direct contact with subgingival plaque on the tooth surface (Figure 5.5).

Sites of gingivitis and periodontal inflammation are commonly biopsied in clinical practice since the extent of soft tissue proliferation and/or bone loss may suggest a neoplastic process. Biopsy samples from sites of periodontitis are likely to have the same histological features as gingivitis (Figure 5.6). They are also likely to be small and fragmented, so tissue architecture may be challenging or impossible to orient. The lesions are often proliferative, with hyperplasia of the gingival and crevicular epithelium, neovascularization within granulation tissue, and mixed inflammatory infiltrates. Periodontitis-associated proliferative epithelium must be distinguished from an epithelial neoplasm (Figure 5.7). Communication with the submitting clinician may clarify critical clinical features, such as whether or not a tooth-associated mass was identified. It is worth noting that the diagnosis of periodontitis will not be readily apparent to the pathologist unless the examined section is a decalcified *en bloc* specimen of tooth, gingiva and bone. Ideally, the case history should specify the site of biopsy as subgingival tissue and/or provide clinical and radiographic findings.

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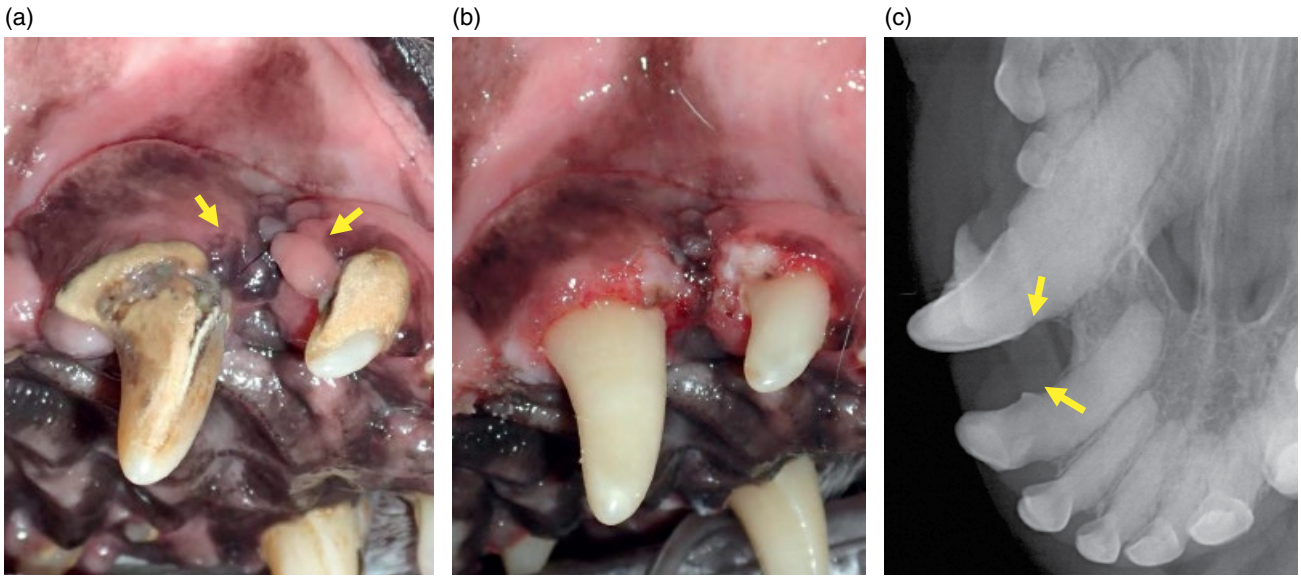


Figure 5.1 Gross and radiographic images of inflammatory dental disease in a 12-year-old, neutered male beagle dog. (a) There is heavy accumulation of calculus on the surface of the teeth and proliferative gingiva in the diastema of 103–104 (arrows). (b) After scaling and gingivectomy, the tissues have a healthy appearance and the gingiva has been restored to a more normal profile. (c) However, radiographs show significant horizontal bone loss below the normal level of alveolar bone (arrows), consistent with periodontal disease at this site. *Source:* D. Otten.

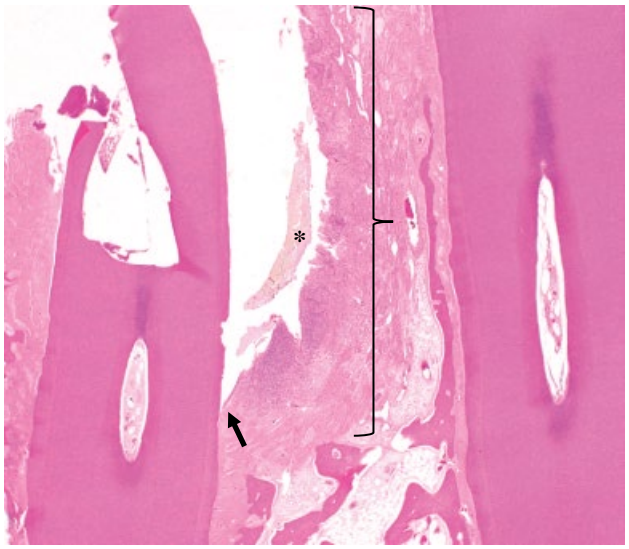


Figure 5.2 Histologic image of periodontitis at the left maxillary 1st incisor (tooth 201) of a 12-year-old, spayed female, Boxer cross dog. Loss of gingiva, periodontal ligament and bone has resulted in a deep periodontal cleft (correlating clinically with a periodontal pocket). The gingiva remains anchored to the tooth (arrow) but is severely recessed. There is subgingival plaque within the cleft (asterisk). The bracket represents the zone of horizontal bone loss where inflamed granulation tissue replaces bone and lines the cleft. A rostral maxillectomy was performed on this dog for excision of a tumor and the periodontal disease at this site was an incidental finding.



Figure 5.3 Gross image of gingivitis in a 14-year-old, neutered male, DSH cat. The gingival margin labial and distal to tooth 104 is mildly proliferative and erythematous. *Source:* B. Beckman.

Because of their thinner gingiva and alveolar bone, toy and small breed dogs are predisposed to more severe periodontitis compared to dogs with robust gingiva [9]. Crowding or malocclusion of teeth also predispose specific anatomic sites to periodontal disease. The prevalence and severity of periodontitis in companion animals generally increases with age, although some young cats are an exception.

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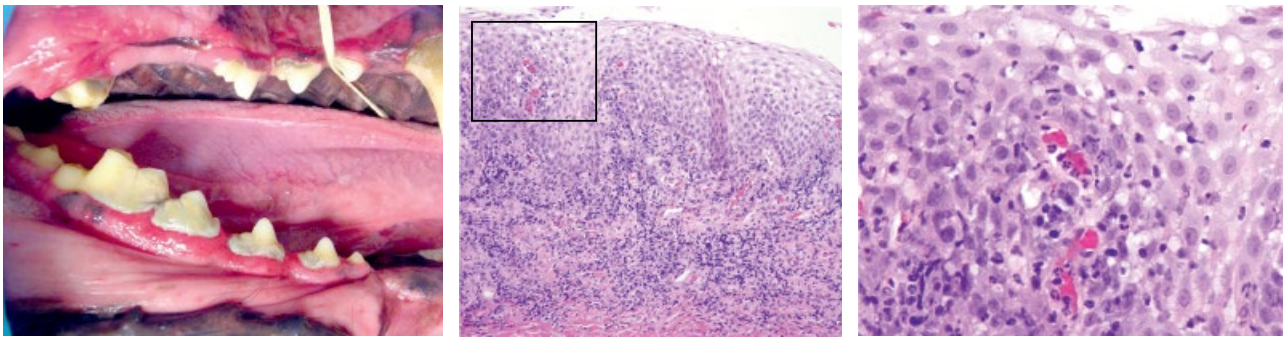


Figure 5.4 Gross and histologic images of gingivitis in a 12-year-old, neutered male Plott hound. (a) The gingiva is diffusely red and swollen. (b) The microscopic lesion consists of hyperplasia of the surface epithelium and a densely cellular zone of superficial inflammation. (c) There is hydropic degeneration and spongiosis of the epithelium with intraepithelial neutrophils and small lymphocytes. *Source:* E. Brine.

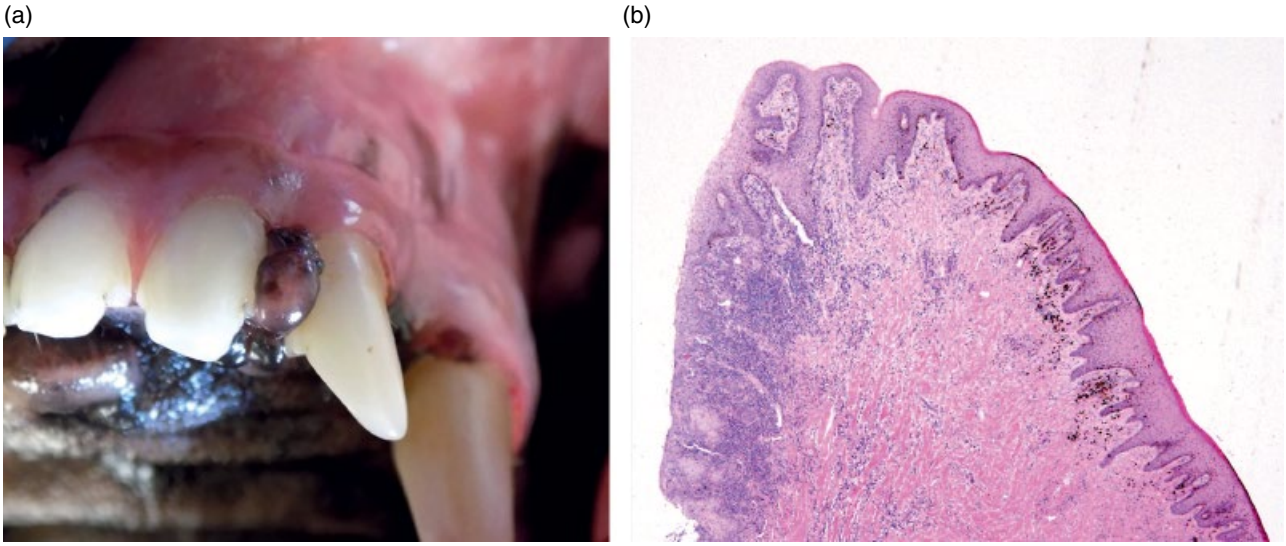


Figure 5.5 Gross and histologic images of focal fibrous gingival hyperplasia with gingivitis in a 12-year-old, spayed female, Labrador retriever. (a) and (b) Increased amounts of fibrous connective tissue cause enlargement of the free gingiva and there is asymmetrical inflammation. As a result of having opposed the plaque-covered tooth, the sulcular surface (left of b) has a lichenoid zone of densely cellular inflammation. The sulcular epithelium is eroded but not ulcerated. The outer gingival surface (right of b) has minimal inflammation with the exception of several melanophages. *Source:* M. Lommer.

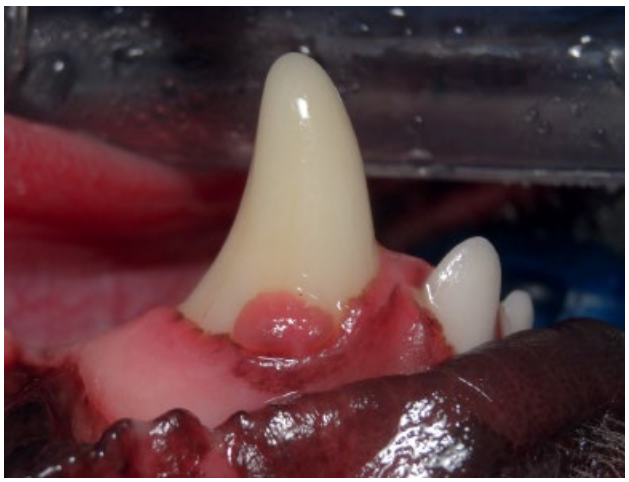


Figure 5.6 Gross image of a localized gingival mass at the right mandibular canine tooth (404) of a three-year-old, neutered male, golden retriever. Histopathology of this lesion is necessary to distinguish localized proliferative gingivitis (the diagnosis in this case) from early canine acanthomatous ameloblastoma. Particularly adjacent to a canine tooth, the two entities can look grossly identical. *Source:* B. Beckman.

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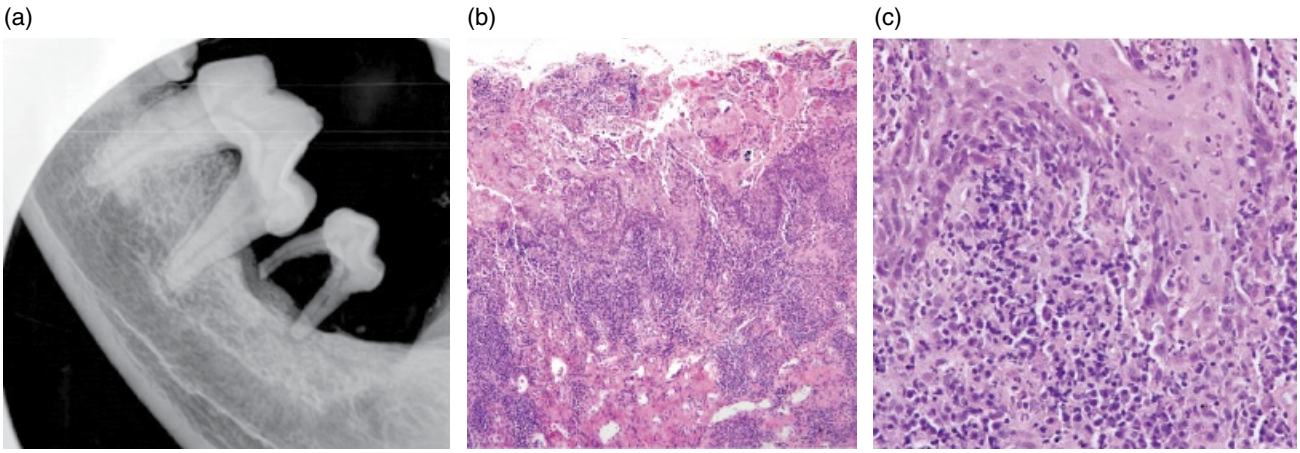


Figure 5.7 Radiographic and histologic images of localized periodontitis in a 14-year-old, spayed female, Nova Scotia retriever. (a) Significant bone loss in this localized area may be due to severe periodontitis, but aggressive neoplasia must be a concern. (b) Microscopically, concern persists at low magnification because the surface epithelium is markedly hyperplastic, and the densely cellular inflammatory infiltrates make it difficult to assess the integrity of the basement membrane. (c) At higher magnification, the epithelium demonstrates mild atypia and is not invasive. *Source:* D. Hansen.

Juvenile or aggressive periodontitis in cats is characterized by early life periodontitis that is often accompanied by proliferative gingivitis (Figure 5.8). Affected cats have gingivitis that progresses rapidly to periodontitis by about one year of age, and some breeds (Siamese and Maine coon) are considered to be predisposed [2, 10]. Rapidly progressive periodontitis also occurs in humans at or near the time of puberty, of which some cats are associated with one or more deficiencies in immune response [1]. This is unlike chronic periodontitis in which immunological function and response are generally presumed to be normal.

A periodontal abscess may form when inflammation associated with periodontitis extends apically and infection is established within the periodontium. The draining tract of a periodontal abscess may erupt (fistulate) through the skin. In dogs, cutaneous draining tracts are most likely to occur apical to the carnassial teeth, i.e. below the eye or along the caudoventral mandible. Oronasal fistula or maxillary sinusitis may occur secondary to periodontitis of the maxillary dentition when there is apical bone destruction into either the nasal passage or the maxillary sinus, respectively (Figure 5.9). A *parulis* is a lesion composed of proliferative granulation tissue that occurs at an intraoral opening to a draining tract. Osteomyelitis of the jaws (discussed in Section 5.2) occurs most frequently as an extension of chronic periodontal disease.

5.1.2 Feline Chronic Gingivostomatitis

Feline chronic gingivostomatitis (FCGS) has a poorly understood, multifactorial etiology, and clinical disease seems to occur at the intersection of dysregulated host immune response and complex antigenic stimulation. In individual cats, one or more infectious agents (viral or bacterial) might impact this relationship, exacerbating disease in some situations. Etiology and pathogenesis are discussed in more detail below.

5.1.2.1 Clinical and Gross Presentation of FCGS

Cats most often present with clinical signs of decreased appetite and signs that indicate oral pain [11]. Less frequent signs include weight loss, ptyalism, halitosis, and lethargy; mandibular lymph nodes may be enlarged on physical exam [11]. There is no sex or breed predilection, although increasing age is a risk factor for FCGS [11].

The caudal oral mucosa, including the palatoglossal arches (fauces), is the most consistently affected region of the oral cavity in cats with FCGS (Figure 5.10). The majority of cats also have similar inflammatory lesions on the alveolar and buccal mucosa of the caudal oral cavity [11, 12]. Less common sites for FCGS lesions include the soft palate and dorsal aspect of the caudal tongue [11, 12] – these regions of the oral cavity seem to be involved in the most severe cases in which inflammation seems to "spill over" to involve adjacent mucosa. The hard palate, labial mucosa, and sublingual mucosa are usually spared.

One study of cats from veterinary practices and animal shelters in North America found the prevalence of FCGS to be 3.9 %, which was 203 cases of a total group of 5179 animals [13]. The prevalence of FCGS in the United Kingdom was estimated at 0.7 %, representing 34 cases from a study of 4858 cats from first opinion practice [14]. Other studies have arrived at different prevalence values, sometimes many magnitudes of difference, but the two studies cited above are both relatively recent and

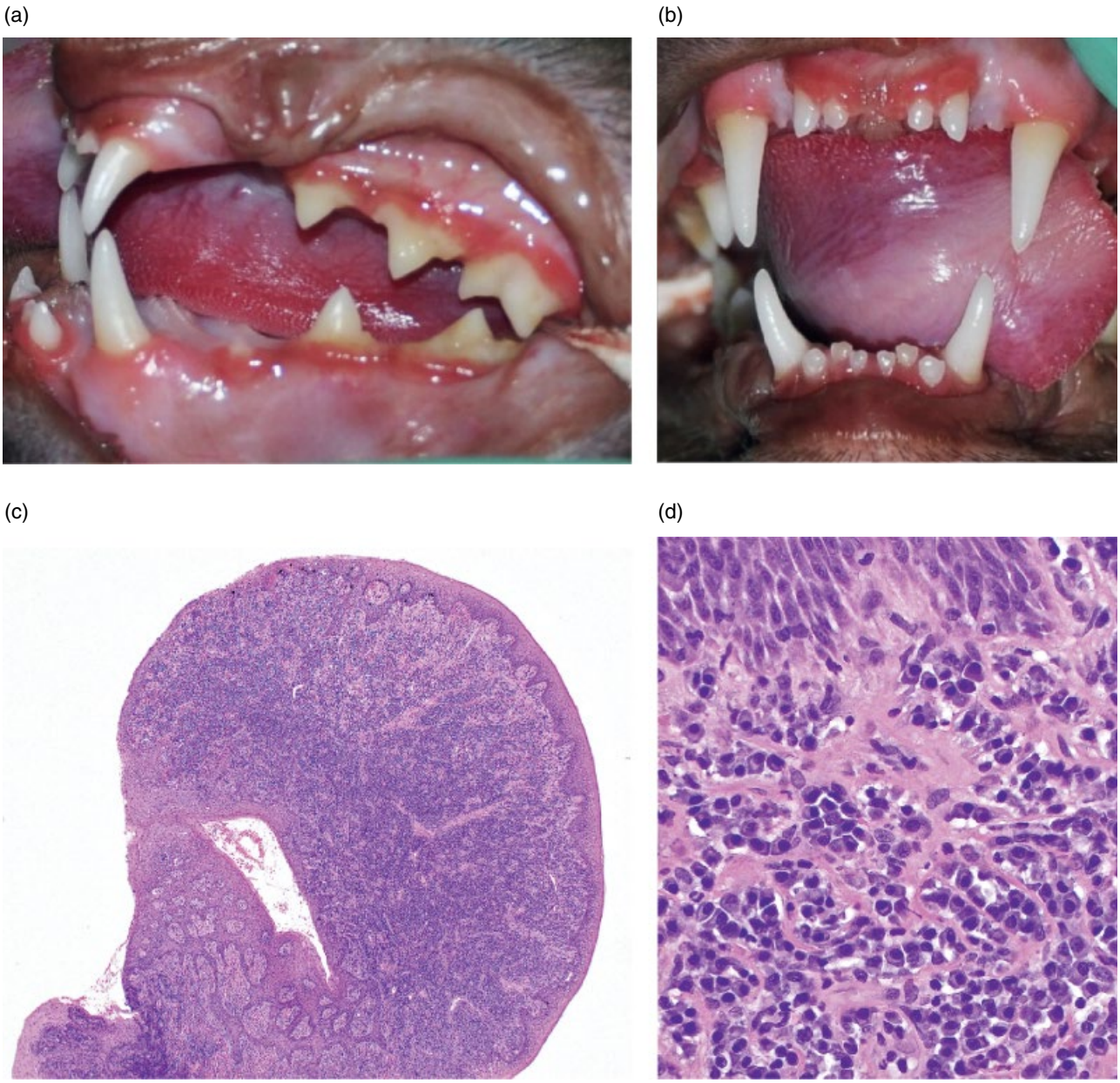


Figure 5.8 Gross and histological images of gingivitis and periodontitis in a 1.5-year-old, spayed female, Havana brown cat. (a) and (b) The gingival margin is diffusely swollen and erythematous. Despite her young age, this cat had significant periodontal disease as well as proliferative gingivitis. (c) At low magnification of the gingivectomy biopsy, the profile of the free gingiva is thickened and nodular, with cellular inflammatory infiltrates diffusely throughout the gingival stroma. (d) Plasma cells are the predominant inflammatory cell type. Cases of severe periodontitis mimic feline chronic gingivostomatitis (FCGS), so knowledge of the location of the biopsy is essential for accurate diagnosis. *Source:* D. Nossaman.

comprised large sample sizes. If FCGS is truly more prevalent in Canada and the United States, as compared to the UK, an explanation for this has yet to be determined.

5.1.2.2 Pathogenesis of FCGS

While the pathogenesis is incompletely understood, it is commonly accepted that dental plaque exacerbates FCGS. In addition, cats with FCGS are highly likely to also have moderate to severe periodontal disease and tooth resorption [11, 15]. For these reasons, tooth extraction is a common treatment approach.

Recent investigations suggest elevated plasma immunoglobulin occurs in association with FCGS. In one FCGS study, 60% of affected cats have hyperglobulinemia [11]. Another study demonstrated that cats with

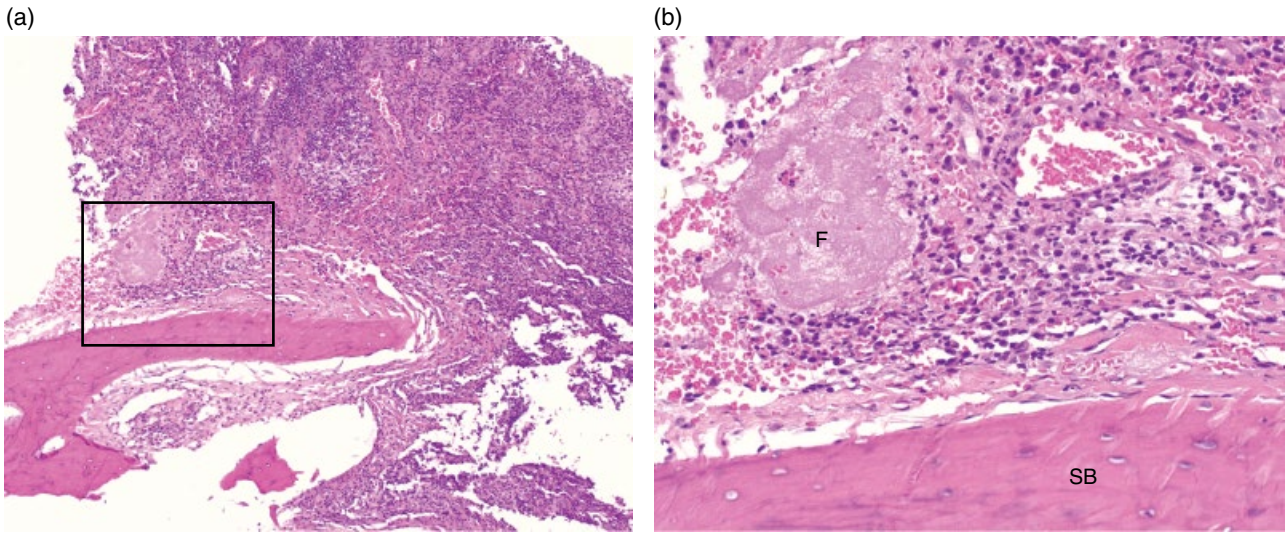


Figure 5.9 Histologic images of tissue biopsied at a site of periapical periodontitis and oronasal fistula in an eight-year-old, neutered male Boston terrier. (a) The low magnification view is of one of multiple tissue fragments submitted as the biopsy sample. An irregular fragment of bone is partially surrounded by highly cellular, inflamed granulation tissue. (b) At higher magnification, neutrophils are abundant and fibrin (F) is present. Lysis and dense remodeling of sclerotic alveolar bone (SB) is commonly seen secondary to chronic inflammation.



Figure 5.10 Gross images of Feline chronic gingivostomatitis FCGS in a 13-year-old, neutered male, DSH cat. The caudal oral mucosa is erythematous and proliferative. *Source:* M. Balke.

FCGS have elevated IgG and IgM in both serum and saliva compared to cats without oral inflammation. Levels of IgA, the immunoglobulin that is predominantly present on mucosal surfaces, in cats with FCGS is elevated in the serum but *lower* in the saliva as compared to control cats [16]. The authors of this study speculate that increased oral secretion of IgG and IgM could injure the mucosa by activating complement, and that consequent decreased oral mucosal IgA might permit adherence and growth of microorganisms [16]. These findings support the notion that cats with FCGS have measurably altered humoral immunological responses, compared to cats without oral inflammation, but additional studies are needed to address the regulatory mechanisms behind these differences. Considering the high density of salivary tissue throughout the caudal oral mucosa of cats (see Histological features of normal oral tissues), it seems logical that further investigating the role saliva plays in immunological regulation would be a good investment of research effort and might further our understanding of FCGS pathogenesis.

A study designed to screen for a broad range of bacterial pathogens in cats with FCGS, compared to control cats, provides initial evidence that points toward *Pasteurella multocida* as a possible etiology for this form of oral inflammation in cats [17]. Interestingly, this study also found that cats with FCGS may have less diverse oral flora than control cats. Regarding *Bartonella*, current thought is that there has been no proven association between this agent and FCGS [12, 18]. A number of different viral agents have also been linked to FCGS (see Section 5.1.3 on Virus-associated stomatitis in cats).

5.1.2.3 Histologic Features of FCGS

Inflammatory cell infiltrates in FCGS are usually abundant. While they are technically lymphoplasmacytic, the emphasis should be placed on *plasmacytic*. Typical cases of moderate to severe FCGS demonstrate expansion of the mucosal lamina propria by sheets of mature plasma cells in which Mott cells are usually easy to find (Figure 5.11). The inflammatory infiltrates are superficial, but may extend into the underlying submucosa, then taper to mild perivascular lymphoplasmacytic

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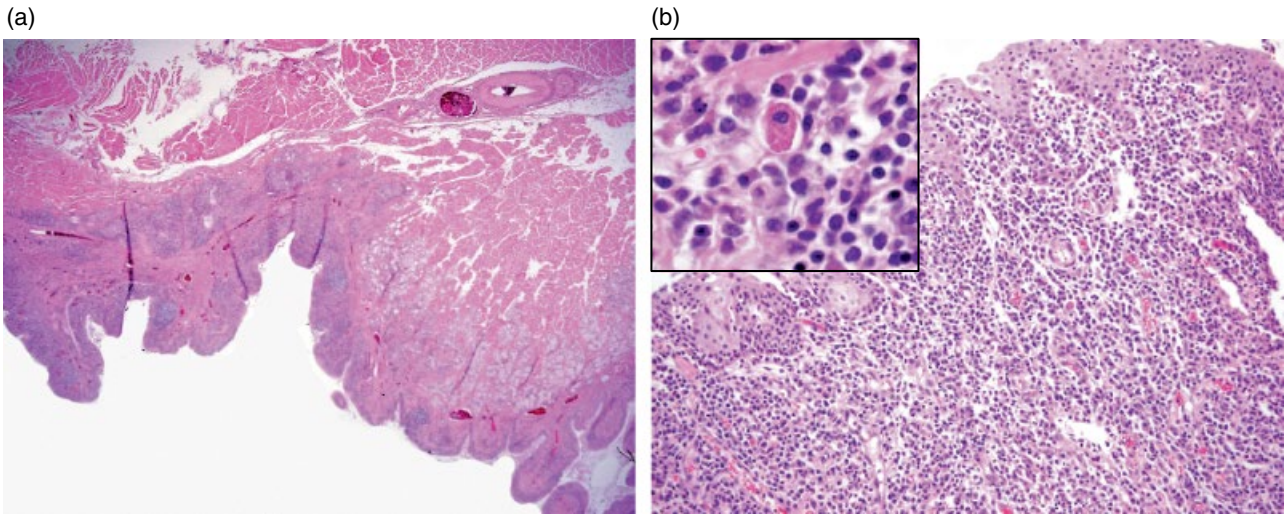


Figure 5.11 Histologic image of the caudal oral mucosa from a cat with Feline chronic gingivostomatitis FCGS. The tissue was excised during necropsy, allowing for a large tissue sample. (a) The mucosal surface is corrugated, reflecting the proliferative mucosal pattern seen grossly in Figure 5.10. The subtending tissues include mucous and mixed salivary glands and skeletal muscle, all of which can be present in surgical biopsies from cats with FCGS. (b) The mucosa propria is infiltrated by many plasma cells, including Mott cells (inset), with fewer lymphocytes and neutrophils.

inflammation. Minor salivary tissue and skeletal muscle are both commonly present within the submucosa of affected sites (i.e. the caudal oral mucosa); therefore, inflammation may "spill over" to cause adjacent lymphoplasmacytic sialadenitis and/or myositis.

At the surface, the mucosal epithelium is typically intact despite heavy infiltrates of plasma cells that are immediately deep to the basement membrane. Although not ulcerated in most cases, the epithelium is often attenuated due to erosion, yet hyperplastic with rete pegs extending deep into the underlying region of inflammation. Neutrophils may migrate from superficial vessels and into the mucosal epithelium. Epithelial hyperplasia can be quite exaggerated and demonstrate features of dysplasia. Most experienced pathologists are familiar with the problem of having small and/or superficial oral biopsies and attempting to differentiate between mucosal epithelial hyperplasia and squamous cell carcinoma. In theory, the presence of plasma cell-rich inflammation should tip one's judgment in favor of inflammation, but oral squamous cell carcinoma can be quite inflamed. In such situations, the best benchmarks for neoplasia are convincing cytological/nuclear atypia and evidence of epithelial invasion. Pathologists need to interpret histopathology based upon clinical aspects of the lesion. Unfortunately, some biopsy samples simply cannot be accurately interpreted, and it is in everyone's best interest when this diagnostic ambiguity is clearly and openly communicated.

Of course, severe FCGS lesions can be ulcerated such that the surface is covered by variable amounts of fibrin, degenerate neutrophils, necrotic debris, and occasional mats of bacteria (presumably overgrowth of oral flora). Ulceration may occur when FCGS lesions are particularly swollen and subjected to secondary occlusal trauma. This situation produces a complex histological lesion that has features of *both* pyogenic granuloma (ulcerated granulation tissue) and FCGS (superficial infiltrates of plasma cells).

Although plasma cells have taken center stage thus far in this discussion of FCGS, lymphocytes are certainly present and are probably highly involved in regulating inflammation (Figure 5.12). In FCGS lesions, elevated numbers of CD3+ T lymphocytes and higher levels of MHC class II expression have correlated with increasing severity of inflammation [19]. This study also found that CD8+ T cells are more abundant than CD4+ T cells, and that the majority of the plasma cells are of the IgG isotype [19]. Interestingly, these results are similar to those in dogs with chronic ulcerative stomatitis.

Macrophages are also present, but not usually abundant. If there are increased numbers of macrophages with foamy cytoplasm, then the pathologist should be alerted to search the tissue for disrupted salivary glands or ducts that could contribute to a histiocytic reaction. If a biopsy sample has typical features of FCGS but also pyogranulomatous inflammation (possibly due to chronic bacterial infection), then the clinician should be alerted to this fact, as it could impact his or her decision to use antimicrobial therapy in a particular case. Finally, scattered mast cells are often encountered within FCGS lesions. Compared to specific pathogen free controls, mast cells were found to be more abundant in the gingiva

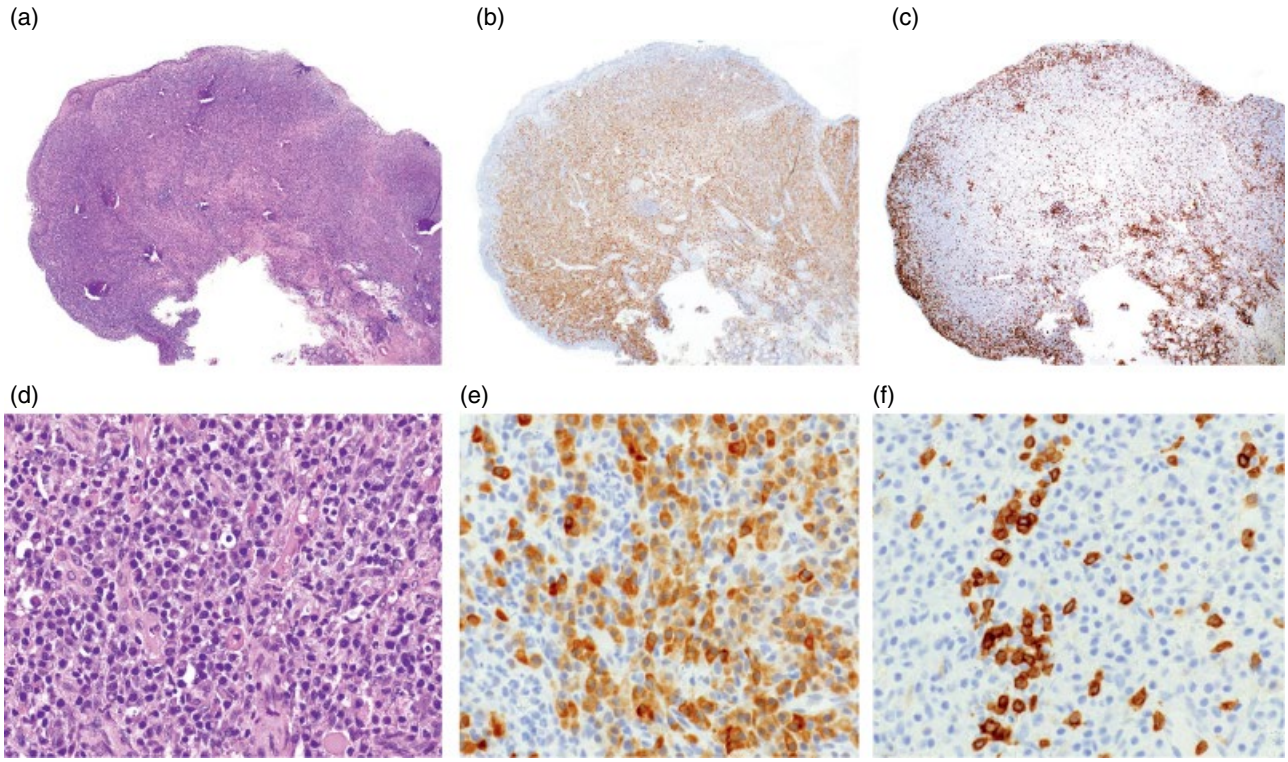


Figure 5.12 Histologic images of a Feline chronic gingivostomatitis FCGS lesion that is stained with HE (a,d) or immunolabeled with antibodies against CD79a (b,e) or CD3 (c,f). The majority of CD79a positive cells are plasma cells. The CD3 positive T cells are most abundant near the mucosal surface.

of cats with FCGS, although not specific to FCGS, since mast cells were also increased in cats with tooth resorption and periodontitis [20].

5.1.2.4 Clinical Management of FCGS

Surgical management (i.e. tooth extractions) is thought to offer the best chance for significant clinical improvement, although most cats will also require concurrent medical management for best results [11]. This type of management most often includes antimicrobial, anti-inflammatory, and analgesic medication. Interestingly, full-mouth extraction may not offer additional benefits to partial-mouth extraction (usually limited to premolar and molar teeth) – this has been demonstrated in one case series [11] and has yet to be substantiated by additional studies.

No particular antimicrobial drug therapy has been proven to be more or less effective, but those used most often include clindamycin, amoxicillin-clavulanic acid, and cefovectin [11]. According to the same study, anti-inflammatory medications used for cats with FCGS including prednisone, methylprednisolone acetate, prednisolone, and meloxicam; cyclosporine has been used rarely [11]. For analgesia, buprenorphine hydrochloride has been prescribed most often while tramadol hydrochloride and butorphenol tartrate have been used much less often [11].

According to many clinicians in practice, partial or full-mouth extractions remain the current standard of care for FCGS [21]. Even with extractions and extended medical management, complete remission rate remains relatively low at just less than 30% [11]. Therefore, additional and novel therapies are sorely needed and will no doubt emerge on the clinical scene in the coming years. For example, preliminary studies with therapy using autologous mesenchymal stem cells have had encouraging results [22]. For supplemental information, the reader is referred to Lommer's excellent summary of research performed on the etiology and treatment of FCGS [23] and a recent review of the literature regarding efficacy of treatments for FCGS [21].

5.1.3 Virus-Associated Stomatitis in Cats

Several different viral agents have been implicated in the occurrence of feline oral inflammation, ulceration, and FCGS, including feline calicivirus (FCV), feline immunodeficiency virus (FIV), feline leukemia virus (FeLV) and felid herpesvirus 1 (FHV) [24]. Whether the retroviruses FeLV and/or FIV are associated with oral disease is a bit controversial. Concurrent infections with multiple viral agents have been documented. The presence of some of these viral pathogens have been "circumstantially" linked

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to the occurrence of feline gingivostomatitis, although a causal relationship is often not clear.

FeLV infections can result in a variety of disease syndromes, one of which is ulcerative stomatitis, which can be remarkably severe, leading to tooth loss, anorexia and emaciation [25]. A large survey study in North America of over 5000 cats examined the prevalence of oral inflammation in cats with respect to age and serological status for FIV and FeLV [13]. Overall, these results established that there is about 40 % prevalence for all forms of oral inflammatory disease in cats, across all age groups. By type of oral inflammation, the total prevalence is as follows: gingivitis (~20 %), periodontitis (~10 %), and stomatitis (~4 %). In seronegative cats, increasing age was associated with higher prevalence of oral disease. Within the population of cats that are seropositive for FIV and/or FeLV, the prevalence of periodontitis (21.4 %) and stomatitis (10.0 %) were approximately twice the prevalence of seronegative cats. According to the authors, the strongest identified association was between stomatitis and increased risk of FIV seropositivity. Far from establishing a viral cause for FCGS, this and other studies have shown that the majority of cats with FCGS are seronegative for retroviruses, but both FIV and FeLV might exacerbate oral inflammatory disease [11, 13, 24].

Perhaps the strongest case for a causal link between virus and stomatitis can be made for the RNA virus FCV. FCV has been shown to be present in significantly more cats with FCGS compared to control cats [12, 24, 26, 27]. In experimental infections, FCV has been shown to be associated with acute oral inflammation, but chronic stomatitis did not develop in infected cats over a 10 month study duration [28]. FCV has a worldwide distribution. Although there is just one serotype of FCV, there is considerable antigenic and genetic variation between strains, and individual strains of calicivirus vary markedly in virulence [25]. Less virulent infections are generally confined to the upper respiratory tract, oral cavity, and conjunctiva. One of the most common and consistent gross lesions associated with FCV infections is oral ulceration. FCV infection can result in multifocal vesicle formation that rapidly progress to erosions and ulcerative stomatitis (Figure 5.13). Lesions are most often found on the rostrodorsal and lateral aspects of the tongue, and near the midline of the hard palate [29]. Viral inclusions are not identified. Diagnosis is generally confirmed by immunohistochemistry or reverse transcription polymerase chain reaction (RT-PCR).

So far, there is little evidence to suggest that FHV plays a pathogenic role in FCGS. However, FHV can infect the upper respiratory tract, and infection can result in ulcerative lesions on the tongue, pharynx, tonsil, epiglottis and larynx, most often in cats less than one year of age (Figure 5.14) [25]. Foci of cytoplasmic vacuolation in squamous epithelium can evolve into areas of necrosis and ulceration [29]. Ulcers may be covered with fibrin and necrotic debris (pseudomembrane). Cats may have concurrent infections with both FCV and FHV. FHV infection results in epithelial necrosis, and unlike FCV, infection can result in diagnostically useful intranuclear inclusions. These inclusions may be subtle and are most often identifiable within proliferative epithelial cells at the margin of the ulcer. Etiology can be confirmed using immunohistochemistry or PCR.

(a)



(b)



Figure 5.13 Gross images of feline calicivirus-associated lesions. The rostrodorsal and lateral epithelium of the tongue has discrete, multifocal (a) ulceration or (b) vesicle formation. *Source:* P. Pesavento, University of California, Davis.

5.1.4 Canine Stomatitis

The most common forms of stomatitis in dogs are focal/multifocal *contact stomatitis* and multifocal/generalized

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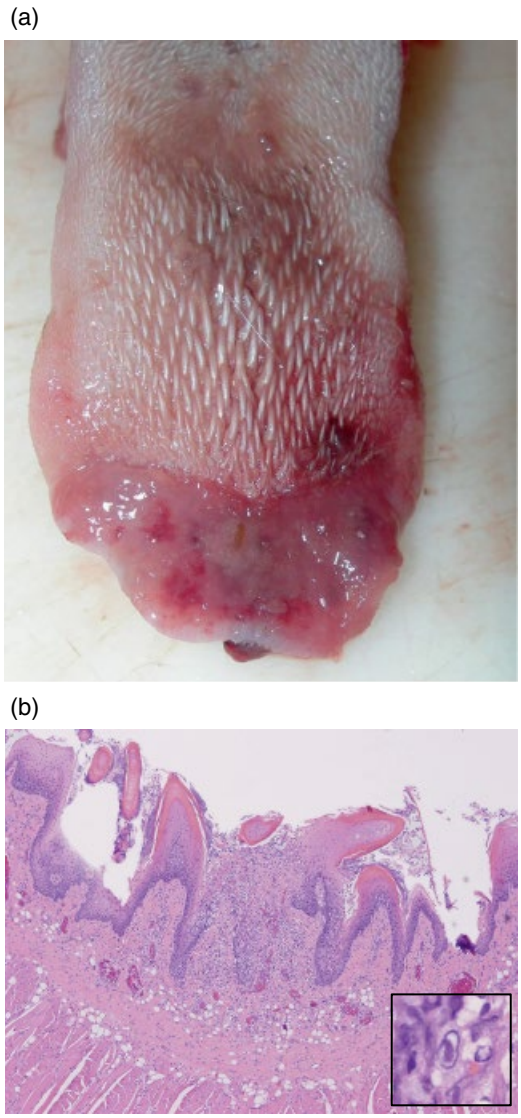


Figure 5.14 Gross and histologic images of felid herpesvirus 1-associated glossitis, cat. (a) Gross ulcerative glossitis lesion on the rostrodorsal tip of the tongue. (b) Histologic image of necroulcerative glossitis. Inset – rare intranuclear inclusion bodies are consistent with herpesvirus etiology. *Source:* P. Pesavento, University of California, Davis.

canine chronic ulcerative gingivostomatitis (CCUS). While the distribution of lesions may differ, these conditions share many overlapping clinical and pathological features. Contact stomatitis specifically refers to lesions that occur at sites of mucosa-tooth contact and generally respond well to aggressive plaque control. Discrete areas of mucosal inflammation, both with and without ulceration are common in dogs at sites of tooth contact; these have been variably referred to as "kissing lesions," contact ulcers, contact stomatitis, or chronic ulcerative paradental stomatitis (CUPS) [2]. The pathogenesis of contact stomatitis is thought to involve an inflammatory reaction to persistent plaque bacterial biofilm that damages the mucosa. Lesions most often occur on the buccal mucosa and lateral lingual mucosa, particularly mucosal regions opposite the larger tooth surfaces (i.e. canine teeth and carnassial teeth) (Figure 5.15). Often, affected buccal mucosa is depigmented and mirrors the shape of the associated tooth.

CCUS refers to widespread oral inflammation in dogs that often includes contact stomatitis lesions, but also frequently affects non-contact sites such as the gingival and palatal mucosa (Figures 5.16 and 5.17). Some dogs progress clinically from having multifocal tooth-mucosa contact lesions to having more generalized oral inflammation with ulcerations. The occurrence and severity of lesions does not necessarily associate with the amount of plaque or dental calculus; some dogs (breeds and individuals) are clearly more susceptible than others. For these animals, aggressive plaque control ceases to result in significant clinical improvement. Response to treatment with antibiotics may be transient, reflecting amelioration of a secondary infection.

The pathogenesis is currently poorly understood and presumably complex. Some evidence supports a T lymphocyte-mediated inflammatory process [30]. As has been demonstrated to occur in the skin, generalized oral inflammation in humans and dogs can be triggered by exposure to various allergens, drug administration, or other interconcurrent disease processes [31].

Mild stomatitis lesions may be found incidentally on oral examination. When symptomatic, dogs affected by stomatitis may present with drooling, halitosis, or reluctance to eat. Common histological features of canine stomatitis, both contact and CCUS, include lichenoid and perivascular infiltrates of plasma cells and lymphocytes, often in large numbers. The mucosal epithelium may be ulcerated, but is not consistently so. When intact, the epithelium may demonstrate considerable spongiosis, transmigration of neutrophils and individual T lymphocytes, vacuolar degeneration of the basal cells, and individual necrotic/apoptotic epithelial cells. If the inflammation abates but the ulcers are slow to re-epithelialize (due to size or impairment of the patient's healing response), then chronically ulcerated lesions may appear as a bed of organized granulation tissue with variable amounts of associated suppurative and mononuclear inflammation (Figure 5.17).

Some dog breeds may be predisposed to CCUS, particularly greyhounds. Some sources cite Cavalier King Charles spaniels and Maltese dogs as predisposed breeds [32]; while eosinophilic oral ulcers tend to occur in these breeds, frequent occurrence of CCUS in these breeds has not been apparent to the authors of this textbook. In a recent study focused on CCUS, none of the affected dog breeds were Maltese [30].

The task of characterizing the larger category of stomatitis in dogs lies ahead. Is it feasible and appropriate

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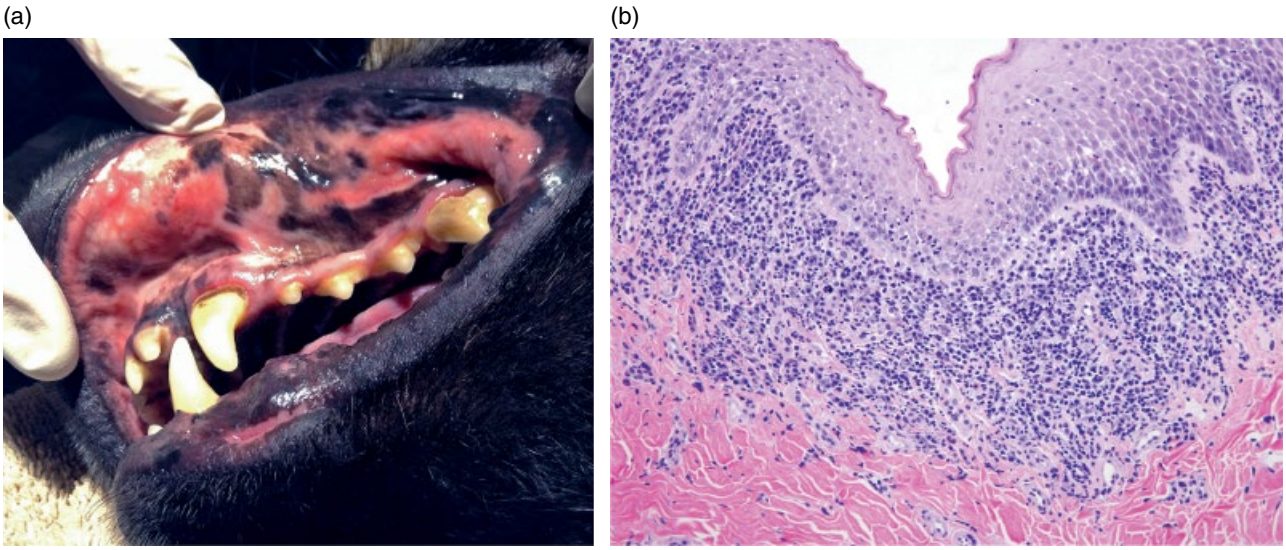


Figure 5.15 Gross and histologic images of contact stomatitis affecting the buccal mucosa of an eight-year-old, spayed female Akita dog. (a) The left upper buccal mucosa has geographic areas of depigmentation and erythema that are variably well-demarcated. The affected area corresponds with where the mucosa would lie against tooth surfaces, extending from the lateral incisor to the last premolar. (b) The histological lesion in this case is non-ulcerated and has a lichenoid band of superficial lymphoplasmacytic inflammation and thickening of the epithelial basement membrane. *Source:* S. Novak.

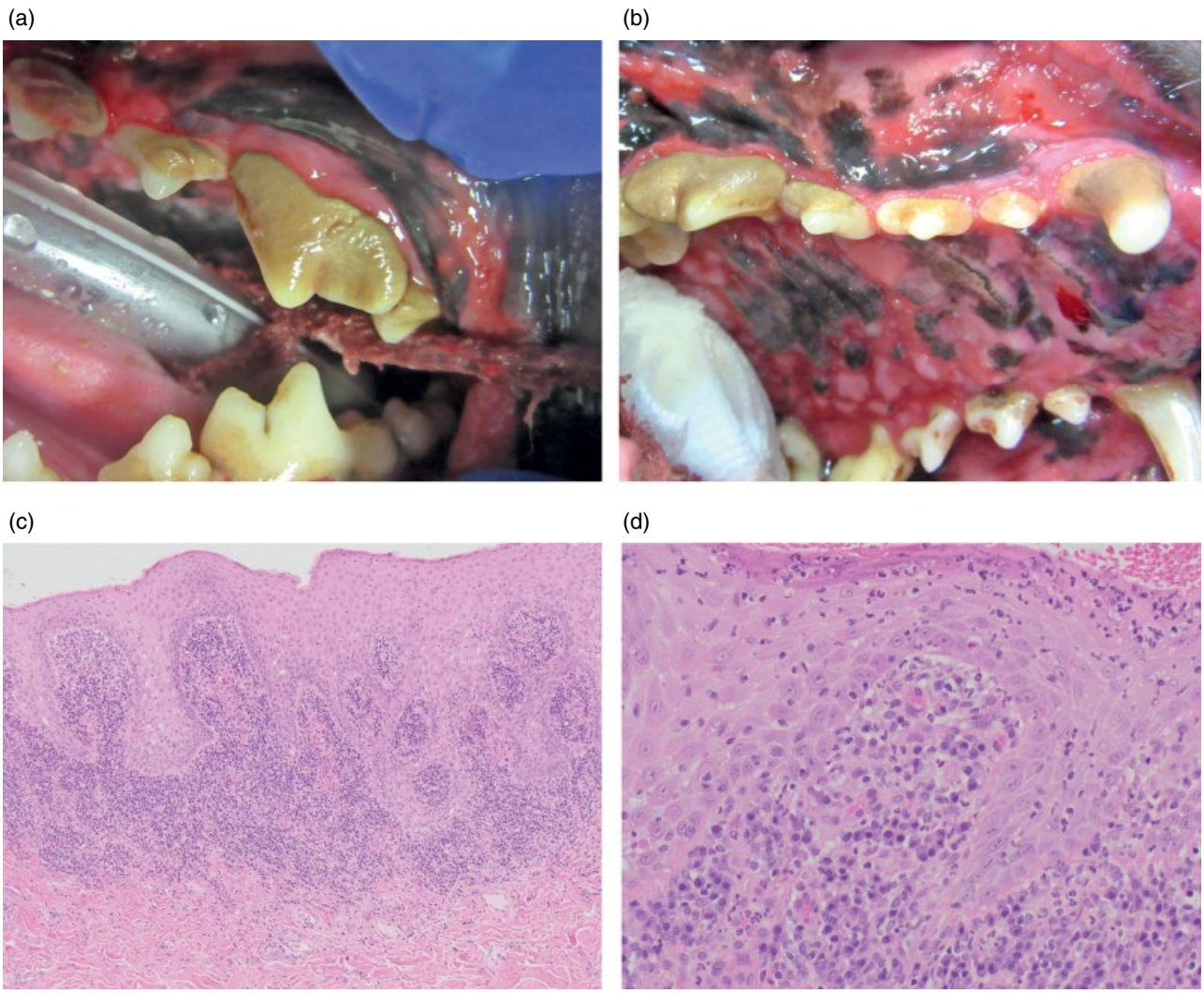


Figure 5.16 Gross and histologic images of severe CCUS in a six-year-old, neutered male, terrier cross with involvement of the (a) buccal mucosa and (b) palate. (c) The histologic legion has lichenoid infiltrates and epithelial hyperplasia in non-ulcerated areas. (d) Plasma cells and lymphocytes are predominant with intraepithelial neutrophils. *Source:* C. Waterhouse.

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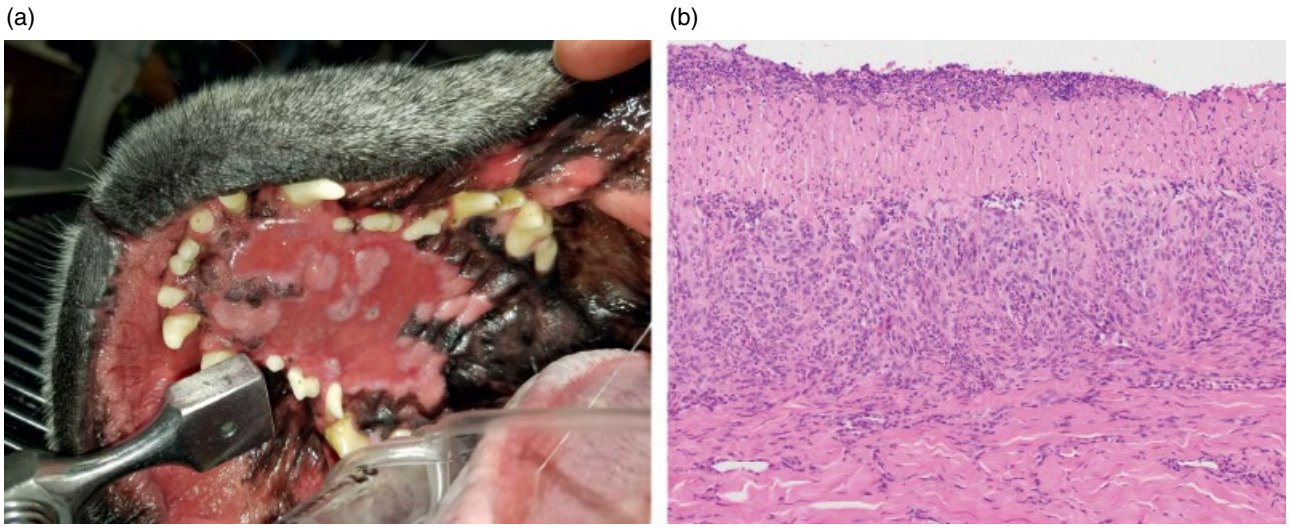


Figure 5.17 Gross and histologic images of severe CCUS in a six-year-old, spayed female Boxer dog. (a) Approximately one month after oral antibiotic treatment, palatal ulceration remains extensive and there are buccal mucosal lesions in areas of contact with the caudal premolars and molars. (b) An ulcerated area biopsied from the palate shows a fibrin-covered bed of stroma with fibroplasia and neutrophils, while plasma cells are few. Causation is not clear, but antibiotic therapy may have addressed secondary bacterial infection based on the paucity of mononuclear cells. *Source:* L. Hedemann.

to create subgroups based on etiology, pathogenesis, morphology, and/or response to treatment? In human oral pathology, several entities resemble chronic ulcerative gingivostomatitis in dogs, including oral lichen planus, lichenoid contact allergy, aphthous ulcers, chronic ulcerative stomatitis, allergic drug reactions, and graft versus host disease. Each of these conditions has an immune-mediated component, often T cell mediated, and all have similar or overlapping histological features with or without cutaneous involvement [31]. Therefore, in human patients, the full clinical picture is essential to formulate a specific diagnosis. The same is likely to apply to cases of CCUS.

Advancing our understanding of CCUS will require open communication between clinicians, pathologists and other investigators adhering to a careful, case-by-case attention to:

1) Distribution of lesions
2) Clinical appearance of lesions (vesicular, ulcerative, proliferative, etc.)
3) Rate of onset and duration of lesions
4) History with respect to concurrent diseases, drug administration, exposure to allergens (oral rinses, chew toys, etc.
5) Histological features
6) Response to therapy

5.1.5 Immune-Mediated Dermatoses with Oral Involvement

In general, immune-mediated diseases that affect the oral mucosa *also affect the skin*. When an animal has ulcerative or vesicular lesions in the oral cavity, in the absence of cutaneous lesions, other causes should be investigated before concluding that the individual has an immune-mediated disease. That said, conditions such as erythema multiforme (EM), lupus erythematosus (LE), pemphigus vulgaris (PV), and mucous membrane pemphigoid (MMP) are important differentials to consider, particularly when (i) skin or other consistent systemic lesions are present, (ii) the patient has clinical laboratory data that support an immune mediated disease (e.g. positive ANA), (iii) keratinized areas of the oral mucosa are affected preferential to non-keratinized areas, or (iv) inflammation does not improve with improved dental hygiene and antimicrobial therapy.

The immune-mediated skin diseases that are known to also affect the oral cavity of dogs are MMP, PV, paraneoplastic pemphigus, EM, and the various forms of LE. It would be rare for any of these conditions to manifest as oral lesions in the complete absence of cutaneous lesions. The pattern of involvement can be very helpful for formulating logical, ranked differential diagnoses even before the slide goes onto the microscope stage. In the oral cavity, discoid and mucocutaneous variants of LE (*discoid lupus erythematosus* (DLE) and *mucocutaneous lupus erythematosus* (MCLE)) are likely to affect keratinized oral epithelium [33] as are PV and MMP [1, 34]. This is a very handy fact to keep in mind: the keratinized oral mucosa – hard palate, gingiva, and dorsal surface of the tongue – are the oral sites most likely affected by LE, MCLE, PV or MMP. In general, MMP, PV, EM and LE have the same histological changes in the oral mucosa as in the skin. Existing veterinary dermatopathology

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references are reliable resources for diagnosing these diseases in oral tissues [29, 34].

LE occurs in systemic and cutaneous forms. The major cutaneous form in dogs is DLE. Recently, a distinctive form of MCLE was described in dogs [33]. The discoid, mucocutaneous and systemic variants of LE differ by distribution of lesions and tissue involvement (Figure 5.18). Microscopically, each is characterized by having (i) a lichenoid interface pattern of lymphocytic infiltrates with varying numbers of macrophages and plasma cells, (ii) pigmentary incontinence, and (iii) hydropic degeneration with apoptosis of basal keratinocytes. In skin lesions, plasma cells will be more abundant if there is secondary pyoderma. In oral lesions, a secondary bacterial component is almost guaranteed because of the presence of oral flora, therefore, plasma cells should be expected in LE lesions. DLE and MCLE are discussed briefly as they relate to the oral cavity, although the reader is referred to other systemic pathology or dermatopathology resources for a complete discussion of each form of LE.

Synonyms for DLE include lupus-like disease of the nasal planum [35] and photosensitive nasal dermatitis [29]. Of all the autoimmune skin diseases that may

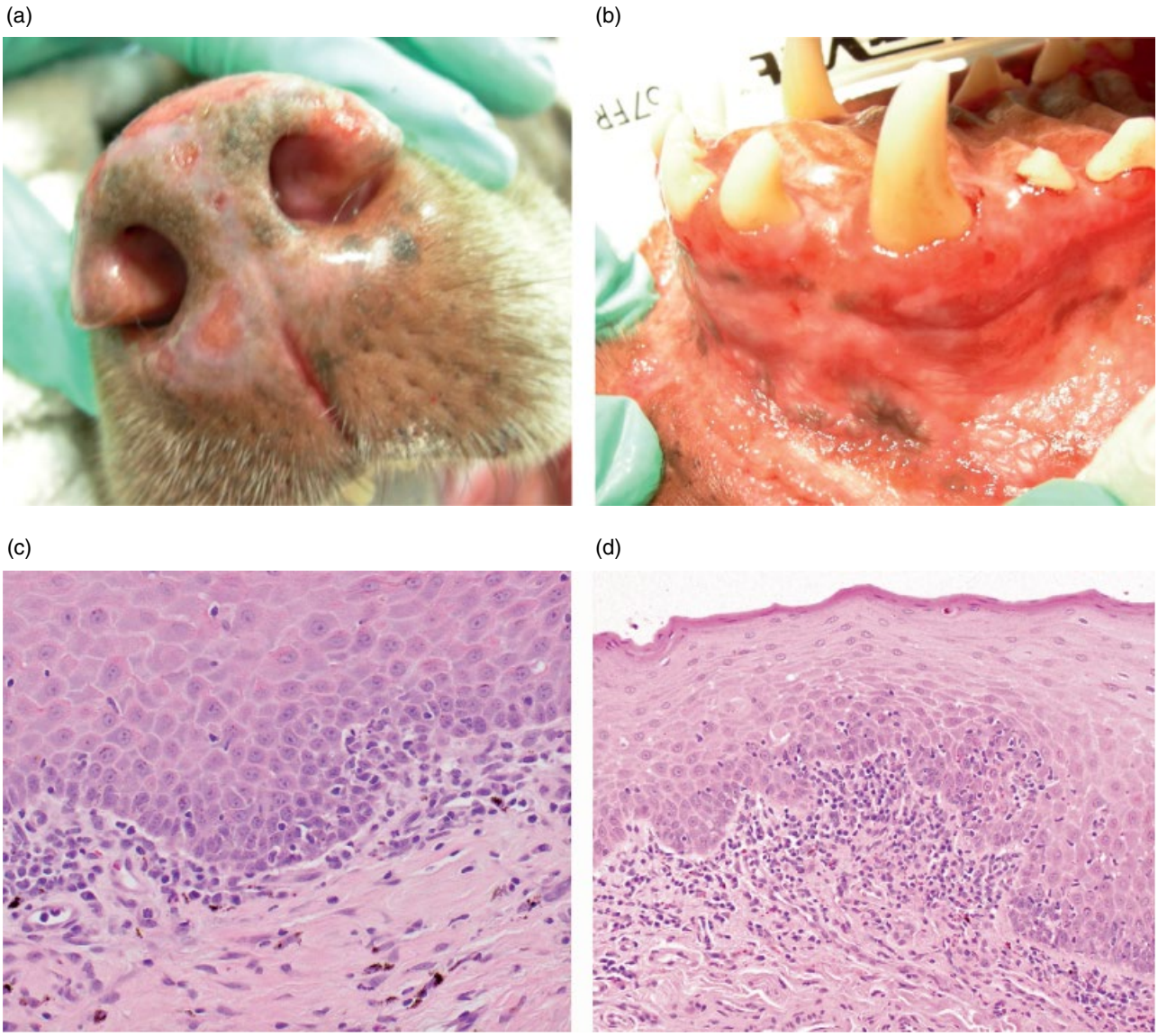


Figure 5.18 Gross and histologic images of discoid lupus erythematosus (DLE) in an eight-year-old, spayed female, Labrador retriever. (a) Clinically, the dog had multifocal ulcerations on the nose and (b) patchy erythema of the gingival and adjacent mucosa. (c) A similar histological pattern was present in both skin from the nose and (d) the labial mucosa. Microscopic features include keratinocyte degeneration and infiltration of small lymphocytes within the basal cell layers epithelium. Lymphoplasmacytic inflammation with intermixed melanophages infiltrates the subepithelium (lichenoid infiltrate). *Source:* S. Hoffman.

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involve the oral cavity of dogs, DLE occurs most frequently [34]. DLE is rare in cats and horses. DLE is aggravated by solar exposure, therefore it's pathogenesis is thought to involve antigenic alteration of keratinocytes by actinic radiation. As such, involvement of the oral cavity, which is not generally exposed to solar radiation, may occur as a result of epitope spreading, and skin involvement would be expected to precede oral involvement in cases of DLE [34]. In dogs with DLE, lichenified, crusted, depigmented, and occasionally ulcerated lesions occur most consistently on the nasal planum, while perioral, periocular, and pinnal lesions are also common. Perioral lesions are more common than lesions within the oral cavity. Shetland sheepdogs, collies, huskies and German shepherd dogs are over-represented.

MCLE has been proposed as a unique variant of cutaneous LE in dogs that has a mucocutaneous distribution that can be distinguished from the nasal dominant or generalized distribution of DLE [33]. In the original report that defined MCLE, female German shepherd dogs were over-represented. While the histopathology is indistinguishable from DLE, erosive lesions of MCLE occur most frequently at genital and perianal sites, with occasional perioral, periocular, and perinasal lesions. As in DLE, lesions within the oral cavity (gingiva and palate) should be expected less often than perioral lesion of the lips [33].

Although MMP is a rare condition of dogs, it has one of the highest rates of oral cavity involvement of the immune-mediated skin conditions [33, 34]. According to one study in dogs, the oral cavity was the most commonly affected site for MMP lesions (65% of cases) compared to any particular cutaneous site [36]. In this disease, circulating antibodies target basement membrane components, particularly collagen XVII in dogs [36].

Clinically, affected dogs have vesicles and erosions on mucous membranes and at mucocutaneous junctions of the oral cavity, as well as eyes, nose, genitals and anus. Lesions within the oral cavity occur in conjunction with lesions at the mucocutaneous junction of the lips [36]. Histologically, vesicular separation is subepidermal (or subepithelial in the case of oral mucosa). Vesicles may or may not contain inflammatory cell infiltrates including neutrophils, eosinophils, and mononuclear cells. Chronic ulcerated lesions may have significant fibrosis and lymphoplasmacytic or lymphohistiocytic inflammation of the dermis (or lamina propria in the case of oral mucosa).

PV is a clinically severe and rare immune-mediated disease that has been reported most often in middle-age dogs. In PV, autoantibodies are directed against desmoglein-3, which is expressed in the basal cell layers of the epidermis and oral mucosa. The majority of cases have oral involvement, and oral lesions occur before skin lesions in about 50% of cases [29].

The classic clinical lesions for PV are fragile vesicles, although patchy areas of ulceration, crusting and inflammation quickly follow when vesicles rupture and slough. Histologically, the key findings include suprabasilar separation/ cleft formation with separation of the individual basal cells, giving this layer a "tombstone" appearance. While inflammatory cells can be relatively sparse in uncomplicated cutaneous PV lesions, oral lesions can be expected to have at least moderate numbers of lymphoplasmacytic infiltrates secondary to ulceration and the effects of oral flora.

Paraneoplastic pemphigus has been described in humans with rare cases described in dogs. Mucosal and mucocutaneous lesions can be severe, resembling PV. The histological features of paraneoplastic pemphigus are described as a combination of EM and PV – suprabasilar acantholysis, lymphohistiocytic lichenoid infiltrates, and apoptosis of keratinocytes in various layers of the epithelium [29].

EM is perhaps the most commonly misdiagnosed immune-mediated disease in oral mucosal biopsies from dogs. Non-specific gingivitis and stomatitis (chronic or contact-associated) can mimic this disease by sharing many of the histological features that pathologists associate with EM, particularly the presence of necrotic/ apoptotic keratinocytes sprinkled throughout the epithelium. Classically, EM is a vesiculobullous and/or ulcerative skin disease with uncommon oral involvement (Figure 5.19) [37]. Common affected areas include the ventrum of the trunk, mucocutaneous junctions, footpads, and pinnae. Oral involvement, as ulcerative stomatitis and/or glossitis, has been documented in dogs more often than in cats [37, 38]. Histologically, oral lesions due to EM are expected to have the same features as skin lesions: (i) mixed inflammation (mainly lymphocytes with fewer plasma cells, macrophages and neutrophils) that obscures the interface of the mucosal epithelium and lamina propria, (ii) individual necrotic squamous cells (presumed apoptosis), and (iii) lymphocyte satelitosis of the apoptotic keratinocytes. Ulcerated lesions tend to have greater numbers of lesional plasma cells and neutrophils.

Nemec and colleagues made particularly interesting conclusions about EM and oral inflammation. First, stomatitis that is triggered by periodontitis can mimic EM in dogs that do not have a systemic immune dysregulation. Second, periodontitis exacerbates stomatitis in dogs that *do have* a systemic immune dysregulation consistent with EM [38]. But before you despair, here is the saving grace: There is *no precedent* for cases of EM that are limited to the oral cavity of dogs or cats and, in dogs, oral involvement is expected in fewer than 30% of cases [37]. As such, there is no justification for making the diagnosis of EM from an oral biopsy *unless cutaneous lesions are present.*

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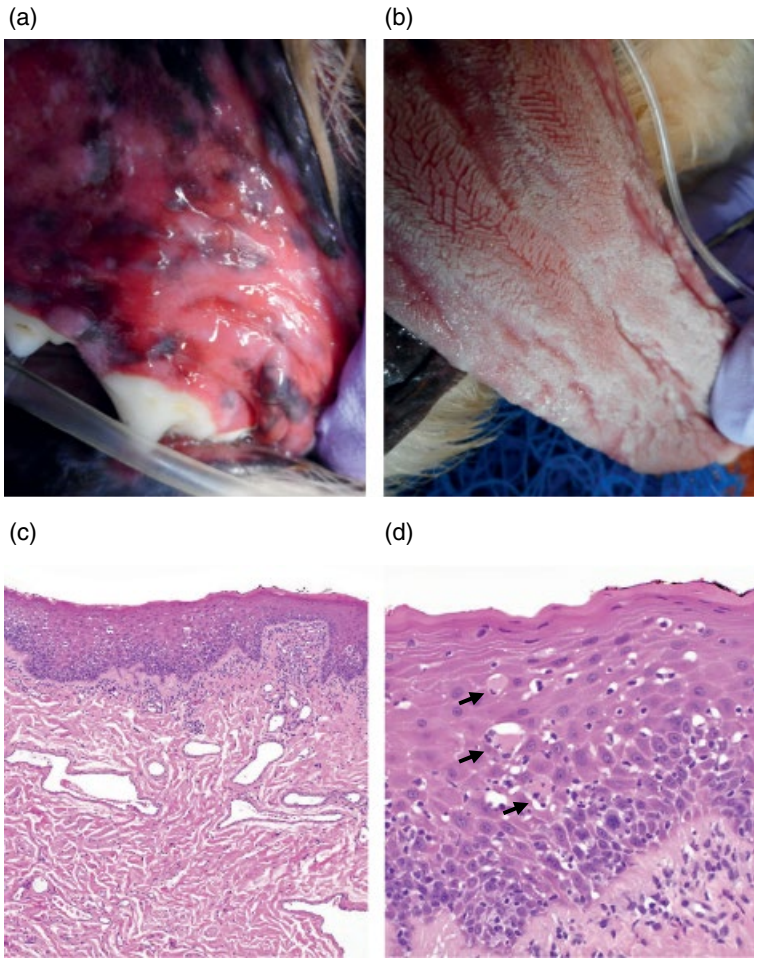


Figure 5.19 Gross and histologic images of a three-year-old, spayed female, golden retriever–poodle cross that was suspected of having erythema multiforme (EM). (a) Clinically, the dog had patchy areas of erythema, erosion and ulceration on the buccal mucosa and gingiva and (b) dorsal surface of the tongue. (c) Superficial inflammatory infiltrates were relatively mild and the most striking microscopic changes were within the epithelium. (d) Necrotic keratinocytes with lymphocytic satellitosis (arrows) were easily found. Other changes included several scattered intraepithelial small lymphocytes (but relatively few neutrophils), and degeneration and hyperplasia of the basal keratinocytes. *Source:* A. Sievers.

The most common trigger for EM, in which keratinocytes are targeted by a T cell-mediated hypersensitivity reaction, is drug therapy (particularly trimethoprim sulfa), although Staphylococcal skin infections [37] and infection with canine parvovirus [39] have also been identified as potential triggers.

Differential diagnoses for the immune-mediated skin conditions that affect the oral mucosa include chronic stomatitis in dogs, chronic gingivostomatitis in cats, mucocutaneous pyoderma (MCP), epitheliotropic lymphoma, contact stomatitis, acute viral stomatitis, and drug reactions. Some investigators insist that histopathology *cannot* distinguish between MCP and LE; thus, the only means to make a specific diagnosis is based on response to antibiotic treatment [35]. It may be fairly straightforward to differentiate bullous and acantholytic diseases (e.g. MMP and PV) from non-specific stomatitis, but chronic stomatitis in dogs can be very challenging to distinguish from the interface or lichenoid diseases (e.g. DLE and EM).

Although some of the immune-mediated skin diseases of veterinary species are known to also affect the oral

Box 5.1 Differential Diagnoses for Ulceroproliferative Diseases in Dogs

- Generalized gingivostomatitis/CCUS
- Autoimmune skin diseases
  - Erythema multiforme
  - Lupus erythematosus
  - Pemphigus vulgaris
  - Mucous membrane pemphigoid
- Uremia
- Eosinophilic granuloma complex
- Mucosal drug reaction
- Chemical or thermal injury
- Infection
  - Acute viral
  - Candidiasis
  - Other systemic infections
- Neoplasia
  - Epitheliotropic lymphoma
  - Amelanotic melanoma
  - Others

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mucosa (MMP, PV, EM and LE), autoantibodies directed toward an antigen that is unique to the oral cavity (oral flora, salivary metabolite) have not been identified. Still, chronic oral inflammatory diseases of cats and dogs are of huge clinical importance, and some of them resemble immune-mediated diseases in many ways. The majority of oral inflammatory disorders in companion animals have no apparent cause, but are thought to involve an inappropriate or dysregulated immune response. The most effective therapies are immune suppression and/or eliminating a local source of antigens (i.e. tooth extraction/periodontal care). Hopefully in the future, investigators will begin to characterize specific antigens and/or patterns of immune dysregulation that result in refractory stomatitis.

5.1.6 Mucosal Drug Reactions

A complete review of recent drug therapy is warranted for any animal that presents for acute onset of oral ulcerations, with or without cutaneous eruptions. Mucosal drug eruption is considered a hyperimmune/ allergic response to antigenic haptens on drug molecules or other xenobiotics, that may manifest as a defined syndrome (e.g. EM). Mucosal drug eruption can also manifest idiosyncratically as an unclassifiable ulcerative condition. Mucosal drug reactions have no clearly defined characteristic appearance. Rather than having a "typical" histological pattern, drug reactions can mimic various patterns of autoimmune diseases, idiopathic stomatitides, or inflammatory dental diseases. A presumptive diagnosis of a mucosal drug reaction hinges on excluding all other causes and having an appropriate history of drug exposure.

5.1.7 Mucocutaneous Pyoderma

MCP is a bacterial skin infection that most commonly occurs around the mouth, but occasionally may involve mucocutaneous junctions around the nose, eyes, genitals, or anus. As stated above, positive response to

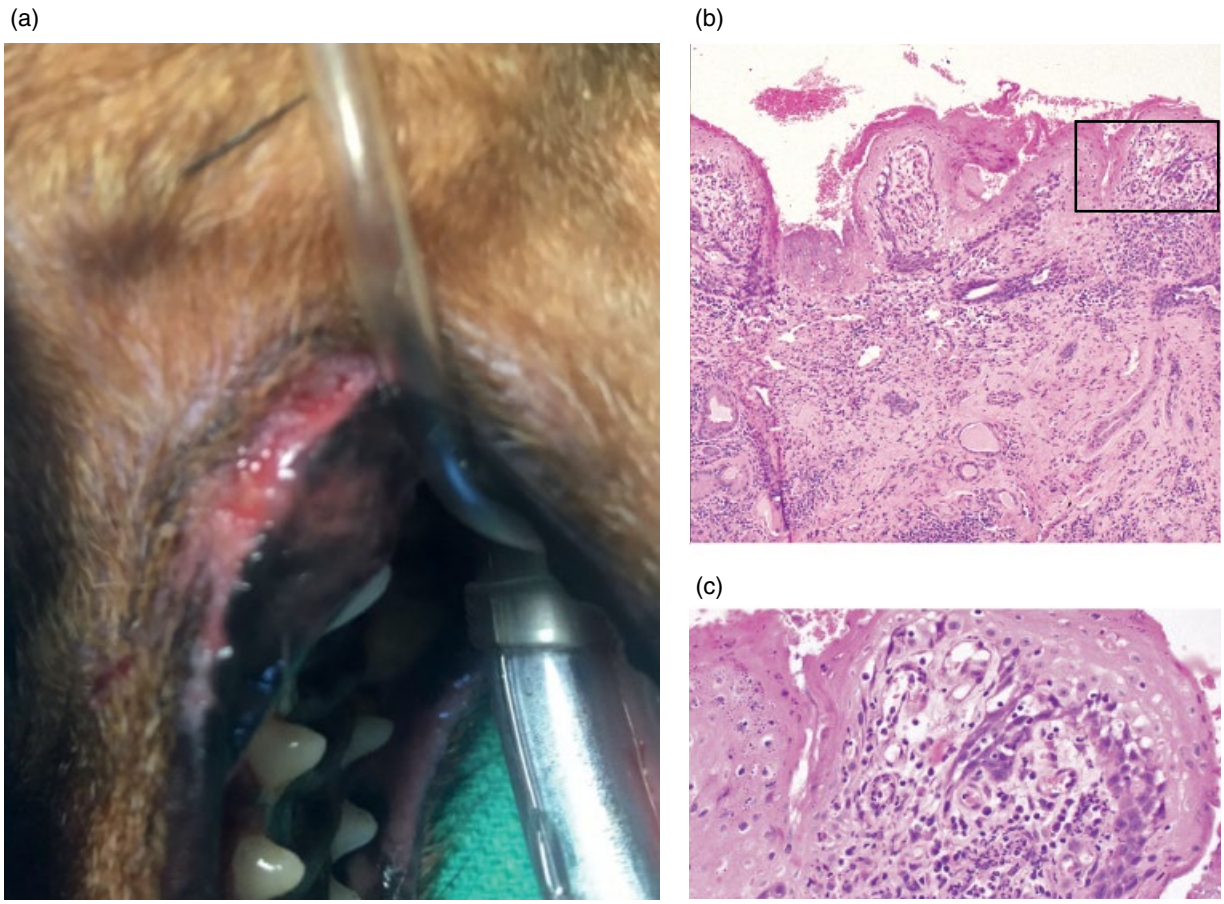


Figure 5.20 Gross and histologic images of mucocutaneous pyoderma (MCP) in a seven-year-old, neutered male miniature pinscher dog that had (a) an ulceration at the labial commissure as well as periocular lesions (not shown). (b) The microscopic lesion has superficial and deep perivascular lymphoplasmacytic inflammation and epithelial hyperplasia. (c) Other features apparent at higher magnification (area within box of b) include epithelial and subepithelial edema and areas with degeneration of the basal cell layers. This pattern is not specific, so a positive response to antimicrobial therapy would help confirm the diagnosis. *Source:* G. Thatcher.

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antibiotic therapy may be the only way to confirm a diagnosis of MCP (Figure 5.20).

Clinically and grossly, MCP lesions are often characterized by erythema, erosion, depigmentation, and/or crusting of the lips and perioral skin. Histologically, inflammation is superficial and lymphoplasmacytic with varying numbers of neutrophils and macrophages. As with pyoderma in general, the superficial inflammation may have a lichenoid interface appearance. While MCP lesions *should* have a predominance of plasma cells and *should not* have basal cell degeneration, these features are inconsistent. MCP can be particularly difficult to distinguish from DLE when there is involvement of the nasal planum or perinasal skin, when plasma cells are less pronounced than lymphocytes, or when vacuolar degeneration of basal cells occurs.

5.1.8 Eosinophilic Stomatitis

Historically, eosinophilic granuloma complex (EGC) has been split into several different entities that may involve both the skin and oral mucosa – linear granuloma, eosinophilic plaques, collagenolytic granuloma, and indolent ulcer. While some of these terms may have specific connotations and are useful when communicating with clinicians, this discussion focuses on the oral cavity only and groups all of the eosinophilic inflammatory conditions together. This complex of inflammatory diseases represents a group of similar hypersensitivity reactions to environmental, ingested material, parasitic or other antigens. While immunosuppressive therapy is commonly used, the ideal treatment involves identifying and removing exposure to the underlying cause.

Oral EGC lesions are common in cats, the most common sites are the dorsal surface of the tongue, the palate, and the mucocutaneous junction of the rostral lips. Based on cases investigated at the Center for Comparative Oral and Maxillofacial Pathology (CCOMP) at the University of Wisconsin-Madison School of Veterinary Medicine, there is a broad age and breed range among cats diagnosed with EGC lesions. In dogs, lesions tend to be palatal, with less frequent involvement of the tongue, lips or other mucosal sites. Cavalier King Charles spaniels and Siberian husky breeds are over-represented [40, 41].

Grossly, EGC lesions are well-demarcated, flat or nodular, usually ulcerated, and variable in color from bright pink to yellow. Classically, "eosinophilic ulcers" are flat, ulcerated lesions and "eosinophilic granulomas" are proliferative lesions in which there is foreign body-type response to the degenerate collagen. It is somewhat useful to discuss these histological presentations separately, although in practice, lesions often have overlapping features (Figures 5.21–5.23).

Ulcerated lesions have abrupt edges that are often slightly elevated from the ulcer bed due to hyperplasia of the bordering epithelium. The ulcerated surfaces of EGC lesions often have surprisingly little fibrin or necrotic debris, although there are exceptions when secondary bacterial infection occurs. The underlying organization of the bed of granulation tissue is characteristic, and may alert the pathologist to the diagnosis even before eosinophils are identified. This granulation tissue is more sclerotic than edematous; it features increased amounts of collagen matrix, plump fibroblasts, and blood vessels lined by hypertrophied endothelial cells. Hypertrophied fibroblasts and endothelial cells are easily mistaken for histiocytes and, although non-specific, their presence is a helpful diagnostic feature when eosinophils are sparse. Finally, intravascular and extravasated eosinophils range from few to numerous. Neutrophilic inflammation is also expected, which can be equal to or greater than the eosinophilic component of the lesion. Some lesions have perivascular lymphoplasmacytic infiltrates, particularly at the deep and lateral edges of the granulation tissue.

Proliferative or nodular EGC lesions resemble ulcerated lesions at the surface, but the underlying mass-like tissue is a mixture of granulation tissue, fibrosis, and granulomatous inflammation centered on extracellular protein. These deposits appear to be aggregates of degenerated collagen protein (collagenolysis) intermixed with degranulated eosinophil-derived proteins. This material may mineralize, giving the gross lesion a pale yellow, rough, granular appearance. Histologically, epithelioid and multinucleate giant macrophages center on the protein deposits. In addition to medical therapy, these EGC lesions may require surgical excision in order to remove the insoluble protein deposits that macrophages cannot completely eliminate.

5.1.9 Granulomatous Stomatitis

Local causes of oral granulomatous inflammatory lesions include allergy, chronic infection, and embedded foreign material. These cases can be very frustrating for pathologists, particularly in the case of an incisional biopsy, because the etiological agent is often not apparent. Successful diagnosis often requires a thorough history and careful investigation of these lesions with a battery of special stains to reveal the presence of microorganisms. We have seen granulomatous lesions in the oral cavity due to penetrating plant material with bacteria and, much less frequently, associated with Histoplasmosis and Cryptococcosis in cats.

A rare form of granulomatous disease in dogs has been compared to Wegener's granulomatosis in humans [42]. Wegener's-like disease in dogs is characterized by one or more ulcerated, proliferative, and dark red lesions that involve the gingiva and adjacent oral mucosa. Underlying bone may be lysed and replaced by the inflamed tissue. One clue to the presence

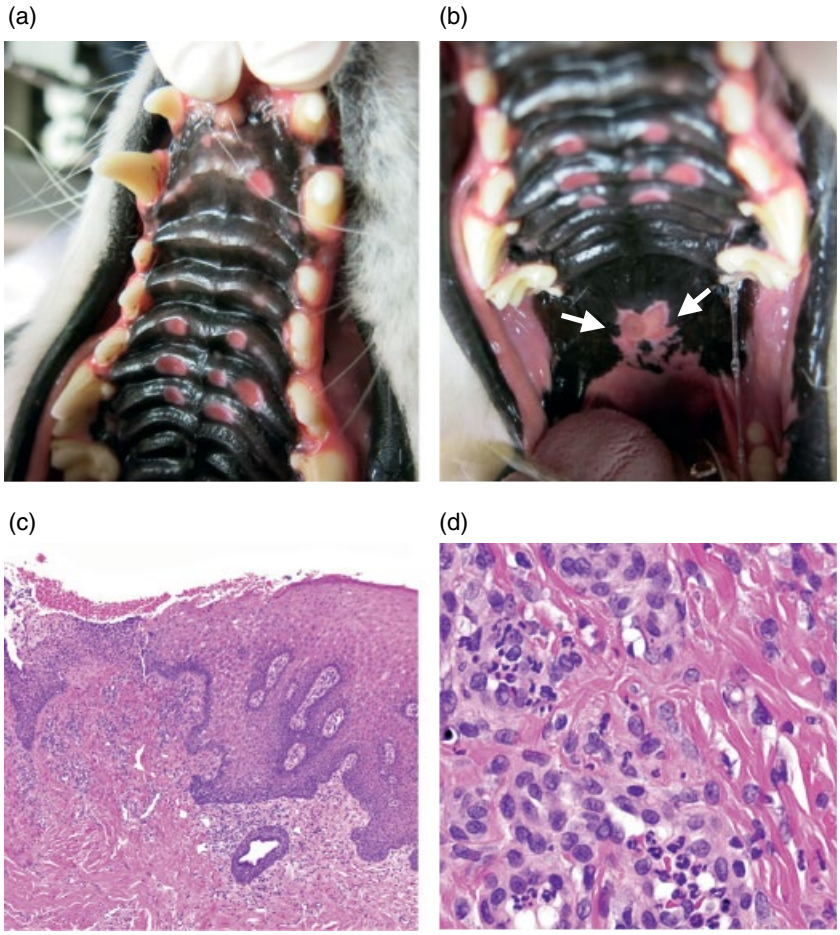


Figure 5.21 Gross and histologic images of eosinophilic granuloma complex (EGC) lesions in a three-year-old, spayed female, Samoyed dog. (a) This dog had multiple palatal ulcers that were bright pink and well demarcated. The ulcers often have a raw appearance as opposed to being covered by a dull tan membrane of fibrin. (b) A midline ulcer of the soft palate (arrows) is one of the most common clinical manifestations of oral EGC in dogs. (c) Low magnification of a histologic section of a palatal lesion features sclerotic granulation tissue underlying the ulcer and hyperplastic epithelium at the edge. (d) Proliferative vessels are lined by hypertrophied endothelial cells and, within the lumen of vessels, both neutrophils and eosinophils are present. *Source:* J. Banyard.

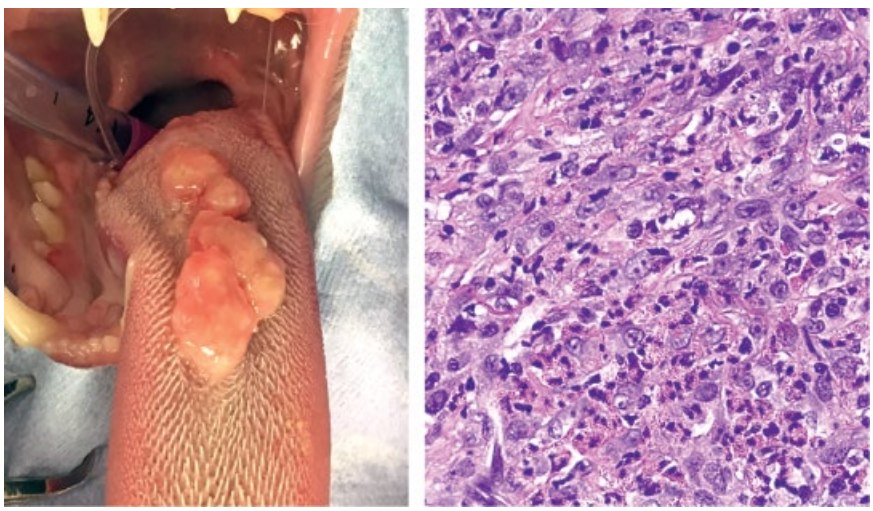


Figure 5.22 Gross and histologic images of a lingual eosinophilic granuloma complex (EGC) lesion in a 10-year-old, neutered male Maine coon cat. (a) This particularly proliferative lesion formed a broad, linear, mottled pink to yellow mass on the center of the dorsal surface of the tongue. (b) Eosinophils densely infiltrate among stromal cells that have plump euchromatic nuclei. *Source:* S. Goldschmidt.

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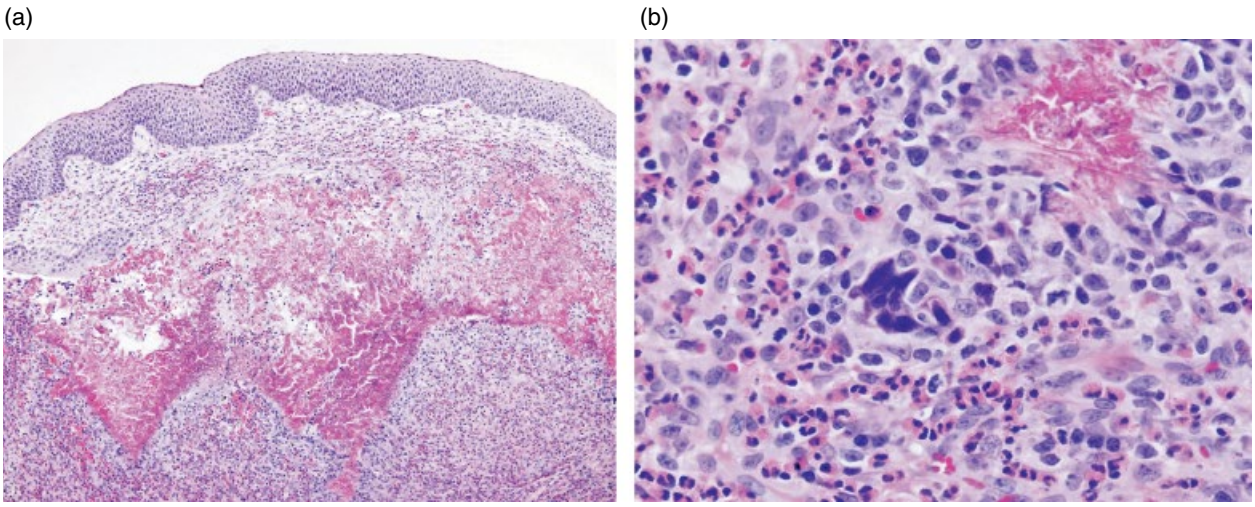


Figure 5.23 Histologic images of a proliferative eosinophilic granuloma complex (EGC) lesion from the tongue of a three-year-old, spayed female, DSH cat. The clinical appearance of this lingual mass was remarkably similar to Figure 5.22. (a) A low-magnification section from a non-ulcerated portion of the mass shows organizing inflammatory tissue (eosinophilic granuloma) with large amounts of eosinophilic protein. (b) A higher magnification images demonstrates the abundance of eosinophils, the linear to amorphous organization of the protein, and both epithelioid and multinucleate macrophages.

of this condition is when there are multifocal lesions that seem to have no relationship to one another (i.e. are not contacting sites of trauma). Histologically, Wegener's-like disease in dogs has an unstructured pattern of mixed inflammation with a predominance of histiocytes, intermixed eosinophils, and variable numbers of neutrophils, lymphocytes and plasma cells (Figure 5.24). Intralesional hemorrhage, hemosiderin within macrophages, and multinucleate macrophages may be seen. Neither necrosis nor organization as classic granulomas is expected. Wegener's granulomatosis in humans is heralded as a vascular disease, but the dense and diffuse pattern of inflammation can make it very difficult to appreciate vasocentricity. Diagnosis of Wegener's-like disease in dogs requires first eliminating other causes of granulomatous inflammation, and ultimately identifying a positive response to immunosuppressive therapy.

5.1.10 Oral Candidiasis

Oral candidiasis, or thrush, is a mycotic infection seen in dogs and foals, although it is less often diagnosed in veterinary species than in humans. Candidiasis is a

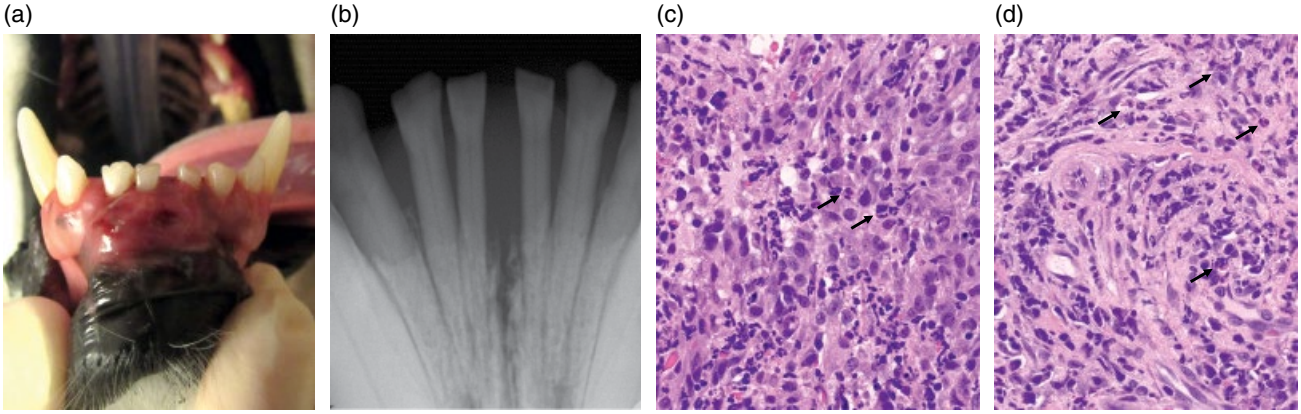


Figure 5.24 Gross, radiographic and histologic images of a Wegener's-like lesion in a seven-year-old, spayed female, husky cross dog. (a) A mildly proliferative, dark red-purple rostral mandibular lesion thickened the gingiva and labial mucosa. (b) There was horizontal alveolar bone loss around incisors at the affected site. (c) and (d) The histologic lesion features a diffuse, unstructured proliferation of inflammatory tissue with reactive fibrovascular stroma and dense inflammatory infiltrates including histiocytes and frequent eosinophils (arrows). *Source:* B. Shope.

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result of mycotic proliferation within the keratinized layer of the oral mucosae. In humans, *Candida albicans* is the most common agent, but a variety of Candida species are known to infect the human oral cavity [43].

C. albicans is a component of normal oral flora and exists in three distinct morphological forms: as a unicellular yeast measuring 1.5–5 μm in diameter, an elongated cellular form (pseudohyphae), and a "chlamydospore" form consisting of cell bodies measuring 7–17 μm in diameter with a thick refractile cell wall [43]. This mycotic agent is considered to be a relatively weak pathogen. Mycotic proliferation is thought to be the result of host immunosuppression (naturally occurring or drug-induced), or chronic antimicrobial use resulting in an oral dysbiosis. In humans, this process is called "escape from commensalism" [43], suggesting the fine line that separates and defines commensal and pathogenic microorganisms.

Lesions are characterized by patchy, pale gray pseudomembranous material on the oral mucosa and dorsocaudal aspect of the tongue [29]. Such plaques can easily be removed with a dry gauze sponge, generally without bleeding [32]. Diagnosis can be confirmed using cytology. Perhaps as result, this lesion is rarely biopsied and anatomic pathologists do not frequently diagnose it.

Histologic lesions can be relatively subtle, consisting of hyperkeratosis and epithelial hyperplasia associated with minimal suppurative inflammation. Organisms may be sparse. PAS and/or GMS stains help with highlighting the fungal agents within the epithelium.

5.1.11 Uremia-Associated Stomatitis

Multifocal oral ulceration is one of the many systemic manifestations of uremia (chronic renal disease) and is most often identified in dogs and cats. It is more common in cats and uncommonly diagnosed in human patients. The pathogenesis of uremia-associated stomatitis is thought to be related to elevated blood urea levels (azotemia). Oral bacteria capable of producing urease generate cytotoxic levels of ammonia from urea excreted in the saliva. Fibrinoid necrosis of arterioles within the oral mucosae also seems to be a feature of this disease, which could cause necrosis and ulceration by infarction [29].

The lesions have a particular anatomic location and somewhat pathognomonic gross appearance (Figure 5.25). Grossly, the lesions are necroulcerative and typically occur along the ventral aspect of the tongue and buccal mucosa. Why uremia-associated stomatitis predictably occurs in these anatomic sites has not been determined. Lesions are characterized as a foul-smelling film coating the ulcerated surface (necrotic tissue); a uremic odor may be detectable from the mouth. Uremia-associated stomatitis should be high on the differential list for cats with the appropriate signalment – thin, older, anorexic cats with polyuria/polydipsia [32].

Histologically, uremic stomatitis is characterized by ulceration with an attached necrotic pseudomembrane (Figure 5.26). Depending on chronicity, the lamina propria may demonstrate some degree of reparative tissue (granulation tissue/fibrosis) and moderate, mixed inflammation. Scattered mineralized deposits



Figure 5.25 Gross images of the rostroventral aspect of the tongue from two cats with chronic renal failure-associated uremic glossitis. Ventral tongue from (a) a 15-year-old DSH cat, and (b) 13-year-old DLH cat. *Source:* (a) M.J. Keating, University of California, Davis and (b) A. Koehne, University of California, Davis.

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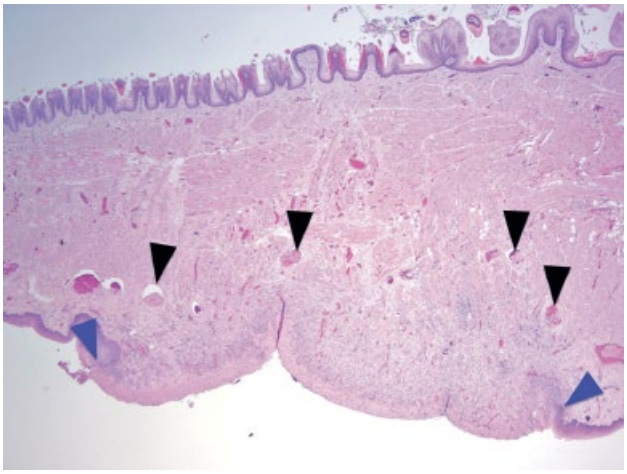


Figure 5.26 Histologic image of a uremic ulcer along the ventral surface of the tongue, 13-year-old DLH cat with chronic renal failure. The sharply delineated lesion margins (blue arrowheads) are bordered by proliferative epithelium. Multiple vessels contain fibrin thrombi (black arrowheads). This is the same lesion as Figure 5.25b.

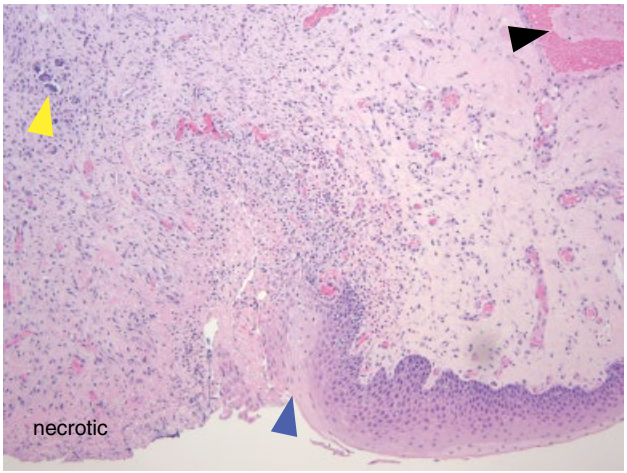


Figure 5.27 High-magnification image of a uremic ulcer along the ventral surface of the tongue, 13-year-old DLH cat (same lesion as Figures 5.25b and 5.26). The ulcerated lesion is covered with an eosinophilic necrotic pseudomembrane (necrotic), and has subepithelial inflammation, granulation tissue, and mineralized debris (yellow arrowhead). A vessel contains an aggregate of fibrin (black arrowhead).

within the lesion may be the result of either dystrophic mineralization or metastatic mineralization (resulting from hyperphosphatemia). Scattered vessels adjacent to the lesion may contain fibrin thrombi (Figure 5.27).

5.1.12 Oral inflammation Due to Chronic or Systemic Disease

Lingual thrombosis, infarction, and necrosis is a rare condition in dogs, and underlying risk factors have not been identified. A full medical work-up is indicated for animals diagnosed with ischemic lesions. The pattern of distribution is very helpful, as the affected area is often wedge-shaped or involves the entire rostral tongue. The histological features present in a lingual infarct depend greatly on the precise location within the lesion, ranging from coagulative necrosis to granulation tissue (Figure 5.28). One of the authors (CB) has seen cases of necroulcerative glossitis resulting from soft tissue mineralization in dogs with iatrogenic hyperadrenocorticism (Figure 5.29). Some studies suggest that dogs with hypothyroidism and diabetes mellitus are more prone to stomatitis, gingivitis and/or periodontal disease [44].

Figure 5.28 Gross image of lingual infarction in a 13-year-old, male, Pomeranian dog that had a history of hyperparathyroidism secondary to chronic renal disease. The tip of the tongue was reported to have become discolored, then fell off. Biopsy taken at the time of this photo was consistent with fibrosis. *Source:* M. Buelow.



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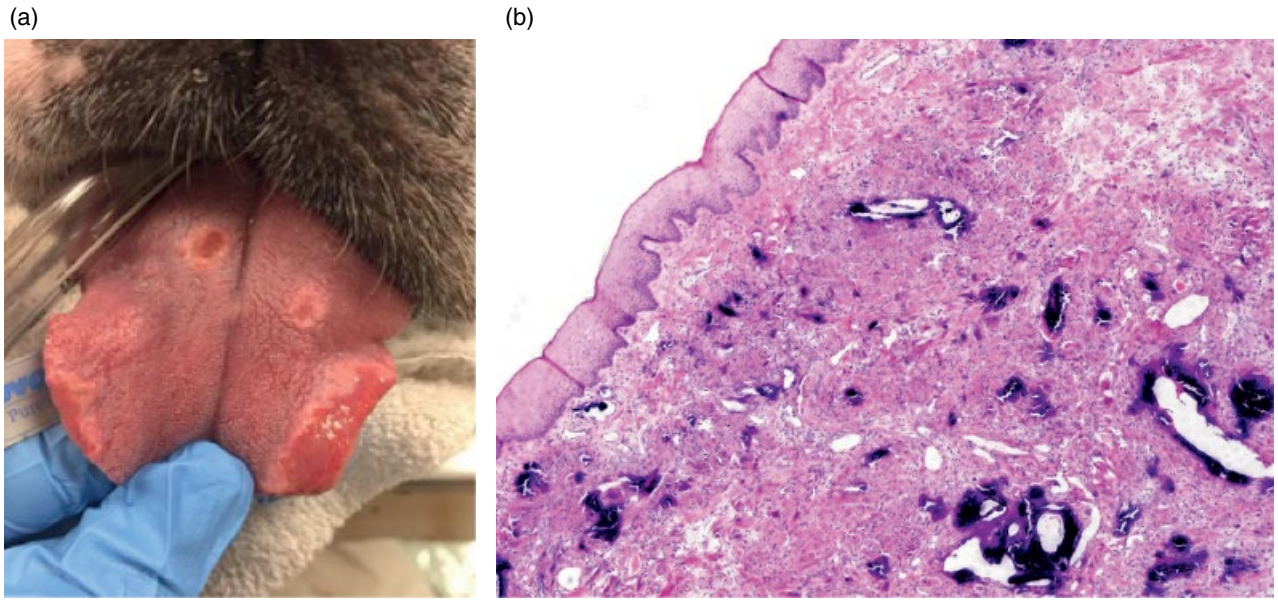


Figure 5.29 Gross and histologic images of lingual mineralization in a five-year-old, spayed female, English bulldog with iatrogenic hyperadrenocorticism. (a) Multifocal lingual lesions are swollen and ulcerated with a rim of pallor. (b) Affected areas had extensive mineralization of stromal collagen and blood vessels. This dog had similar dermal lesions consistent with calcinosis cutis. *Source:* S. Teichner.

References

1 Neville, B.W., Damm, D.D., Allen, C.M., and Chi, A.C. (2016). *Oral and Maxillofacial Pathology*, 4e. St. Louis, Missouri: Elsevier.

2 Wiggs, R.B. and Lobprise, H.B. (1997). *Veterinary Dentistry: Principles and Practice*. Philadelphia: Lippincott-Raven Publishers.

3 Elliott, D.R., Wilson, M., Buckley, C.M., and Spratt, D.A. (2005). Cultivable oral microbiota of domestic dogs. *J. Clin. Microbiol.* 43: 5470–5476.

4 Holcombe, L.J., Patel, N., Colyer, A. et al. (2014). Early canine plaque biofilms: characterization of key bacterial interactions involved in initial colonization of enamel. *PLoS One* 9: e113744.

5 Sturgeon, A., Pinder, S.L., Costa, M.C., and Weese, J.S. (2014). Characterization of the oral microbiota of healthy cats using next-generation sequencing. *Vet. J.* 201: 223–229.

6 Sturgeon, A., Stull, J.W., Costa, M.C., and Weese, J.S. (2013). Metagenomic analysis of the canine oral cavity as revealed by high-throughput pyrosequencing of the 16S rRNA gene. *Vet. Microbiol.* 162: 891–898.

7 Davis, I.J., Wallis, C., Deusch, O. et al. (2013). A cross-sectional survey of bacterial species in plaque from client owned dogs with healthy gingiva, gingivitis or mild periodontitis. *PLoS One* 8: –e83158.

8 Harris, S., Croft, J., O'Flynn, C. et al. (2015). A pyrosequencing investigation of differences in the feline subgingival microbiota in health, gingivitis and mild periodontitis. *PLoS One* 10: e0136986.

9 Kyllar, M., Doskarova, B., and Paral, V. (2013). Morphometric assessment of periodontal tissues in relation to periodontal disease in dogs. *J. Vet. Dent.* 30: 146–149.

10 Perry, R. and Tutt, C. (2015). Periodontal disease in cats: back to basics--with an eye on the future. *J. Feline Med. Surg.* 17: 45–65.

11 Jennings, M.W., Lewis, J.R., Soltero-Rivera, M.M. et al. (2015). Effect of tooth extraction on stomatitis in cats: 95 cases (2000–2013). *J. Am. Vet. Med. Assoc.* 246: 654–660.

12 Dowers, K.L., Hawley, J.R., Brewer, M.M. et al. (2010). Association of Bartonella species, feline calicivirus, and feline herpesvirus 1 infection with gingivostomatitis in cats. *J. Feline Med. Surg.* 12: 314–321.

13 Kornya, M.R., Little, S.E., Scherk, M.A. et al. (2014). Association between oral health status and retrovirus test results in cats. *J. Am. Vet. Med. Assoc.* 245: 916–922.

14 Healey, K.A., Dawson, S., Burrow, R. et al. (2007). Prevalence of feline chronic gingivo-stomatitis in first opinion veterinary practice. *J. Feline Med. Surg.* 9: 373–381.

15 Farcas, N., Lommer, M.J., Kass, P.H., and Verstraete, F.J. (2014). Dental radiographic findings in cats with chronic gingivostomatitis (2002–2012). *J. Am. Vet. Med. Assoc.* 244: 339–345.

VetBooks.ir

16 Harley, R., Gruffydd-Jones, T.J., and Day, M.J. (2003). Salivary and serum immunoglobulin levels in cats with chronic gingivostomatitis. *Vet. Rec.* 152: 125–129.

17 Dolieslager, S.M., Riggio, M.P., Lennon, A. et al. (2011). Identification of bacteria associated with feline chronic gingivostomatitis using culture-dependent and culture-independent methods. *Vet. Microbiol.* 148: 93–98.

18 Quimby, J.M., Elston, T., Hawley, J. et al. (2008). Evaluation of the association of Bartonella species, feline herpesvirus 1, feline calicivirus, feline leukemia virus and feline immunodeficiency virus with chronic feline gingivostomatitis. *J. Feline Med. Surg.* 10: 66–72.

19 Harley, R., Gruffydd-Jones, T.J., and Day, M.J. (2011). Immunohistochemical characterization of oral mucosal lesions in cats with chronic gingivostomatitis. *J. Comp. Pathol.* 144: 239–250.

20 Arzi, B., Murphy, B., Cox, D.P. et al. (2010). Presence and quantification of mast cells in the gingiva of cats with tooth resorption, periodontitis and chronic stomatitis. *Arch. Oral Biol.* 55: 148–154.

21 Winer, J.N., Arzi, B., and Verstraete, F.J. (2016). Therapeutic management of Feline chronic gingivostomatitis: a systematic review of the literature. *Front. Vet. Sci.* 3: 54.

22 Arzi, B., Mills-Ko, E., Verstraete, F.J. et al. (2016). Therapeutic efficacy of fresh, autologous mesenchymal stem cells for severe refractory gingivostomatitis in cats. *Stem Cells Transl. Med.* 5: 75–86.

23 Lommer, M.J. (2013). Clinical veterinary dentistry. *Vet. Clin. North Am. Small Animal Pract.* 43: 555–571.

24 Tenorio, A.P., Franti, C.E., Madewell, B.R., and Pedersen, N.C. (1991). Chronic oral infections of cats and their relationship to persistent oral carriage of feline calici-, immunodeficiency, or leukemia viruses. *Vet. Immunol. Immunopathol.* 29: 1–14.

25 Maclachlan, N. (2016). *Fenner's Veterinary Virology*. Boston, MA: Elsevier.

26 Thomas, S., Lappin, D.F., Spears, J. et al. (2017). Prevalence of feline calicivirus in cats with odontoclastic resorptive lesions and chronic gingivostomatitis. *Res. Vet. Sci.* 111: 124–126.

27 Fernandez, M., Manzanilla, E.G., Lloret, A. et al. (2017). Prevalence of feline herpesvirus-1, feline calicivirus, Chlamydophila felis and Mycoplasma felis DNA and associated risk factors in cats in Spain with upper respiratory tract disease, conjunctivitis and/or gingivostomatitis. *J. Feline Med. Surg.* 19: 461–469.

28 Knowles, J.O., McArdle, F., Dawson, S. et al. (1991). Studies on the role of feline calicivirus in chronic stomatitis in cats. *Vet. Microbiol.* 27: 205–219.

29 Maxie, M.G. (2016). *Jubb, Kennedy, and Palmer's Pathology of Domestic Animals*, 6e. St. Louis, Missouri: Elsevier.

30 Anderson, J.G., Peralta, S., Kol, A. et al. (2017). Clinical and histopathologic characterization of canine chronic ulcerative stomatitis. *Vet. Pathol.* 54: 511–519.

31 Neville, B.W. (2009). *Oral and Maxillofacial Pathology*, 3e. St. Louis, Mo: Saunders/Elsevier.

32 Niemiec, B.A. (2010). *Small Animal Dental, Oral & Maxillofacial Disease: A Color Handbook*. London: Manson/Veterinary Press.

33 Olivry, T., Rossi, M.A., Banovic, F., and Linder, K.E. (2015). Mucocutaneous lupus erythematosus in dogs (21 cases). *Vet. Dermatol.* 26: 256–e255.

34 Gross, T.L.,.I.,.P., Walder, E.J., and Affolter, V.K. (2005). *Skin Diseases of the Dog and Cat: Clinical and Histopathologic Diagnosis*, 2e. Wiley.

35 Wiemelt, S.P., Goldschmidt, M.H., Greek, J.S. et al. (2004). A retrospective study comparing the histopathological features and response to treatment in two canine nasal dermatoses, DLE and MCP. *Vet. Dermatol.* 15: 341–348.

36 Olivry, T., Dunston, S.M., Schachter, M. et al. (2001). A spontaneous canine model of mucous membrane (cicatricial) pemphigoid, an autoimmune blistering disease affecting mucosae and mucocutaneous junctions. *J. Autoimmun.* 16: 411–421.

37 Scott, M. Jr. (1999). Erythema multiforme in dogs and cats: literature review and case material from the Cornell University College of Veterinary Medicine (1988–96). *Vet. Dermatol.* 10: 297–309.

38 Nemec, A., Zavodovskaya, R., Affolter, V.K., and Verstraete, F.J. (2012). Erythema multiforme and epitheliotropic T-cell lymphoma in the oral cavity of dogs: 1989 to 2009. *J. Small Anim. Pract.* 53: 445–452.

39 Favrot, C., Olivry, T., Dunston, S.M. et al. (2000). Parvovirus infection of keratinocytes as a cause of canine erythema multiforme. *Vet. Pathol.* 37: 647–649.

40 Madewell, B.R., Stannard, A.A., Pulley, L.T., and Nelson, V.G. (1980). Oral eosinophilic granuloma in Siberian husky dogs. *J. Am. Vet. Med. Assoc.* 177: 701–703.

41 Bredal, W.P., Gunnes, G., Vollset, I., and Ulstein, T.L. (1996). Oral eosinophilic granuloma in three cavalier King Charles spaniels. *J. Small Anim. Pract.* 37: 499–504.

42 Krug, W., Marretta, S.M., de Lorimier, L.P. et al. (2006). Diagnosis and management of Wegener's granulomatosis in a dog. *J. Vet. Dent.* 23: 231–236.

43 Regezi, J.A., Sciubba, J.J., and Jordan, R.C.K. (2012). *Oral Pathology: Clinical Pathologic Correlations*, 6e. St. Louis, Mo: Elsevier/Saunders.

44 Arzi, B.A., Anderson, J.G., and Verstraete, F.J.M. (2008). Oral manifestations of systemic disorders in dogs and cats. *J. Vet. Clin. Sci.* 1: 112–124.

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5.2 Inflammation of the Jaw

Inflammation of the jaws (mandibular/ maxillary osteitis, or osteomyelitis if the marrow is involved) is a relatively common lesion in veterinary species. Although hematopoietic tissue (bone marrow) is present within the bones of the jaw, it is generally less abundant than it is in other bones of the skeleton (sternum, vertebrae, pelvis, and appendicular bones). Inflammation of the mandible or maxilla is typically the result of a bacterial infection, but other microbial agents like fungi can also be responsible.

Bone infections can result from three possible routes of inoculation – *hematogenous, implantation,* or *local extension*. Infectious agents include: *Actinomyces bovis* (in cattle), *Staphylococcus* spp., *Streptococcus* sp., *Fusobacterium necrophorum*, *Truperella pyogenes*, *Nocardia* spp., and several different fungal agents including *Coccidioides immitis* (horses, llamas, cats, and dogs), *Cryptococcus neoformans* (cats and llamas), *Aspergillus* spp., *Candida* spp. *and* occasionally *Pythium insidiosum*.

The least common route of inoculation for the bones of the jaw is hematogenous. Osteomyelitis resulting from hematogenous inoculation is caused by bloodborne bacterial agents like *Escherichia coli*, *Streptococcus* spp., *Salmonella* spp., *Klebsiella* spp. and *T. pyogenes*. Hematogenous infection is the result of bacteremia and occurs most commonly in young horses and young ruminants as a result of inadequate humoral immunity (failure of passive antibody transfer shortly after birth). Bacteremia most commonly results in the inoculation of the metaphyses of bones formed through endochondral ossification (appendicular bones/vertebrae), and less often those bones formed through intramembranous ossification (mandible and maxilla). Nevertheless, bacteremia in foals and young ruminants can result in mandibular or maxillary abscesses (Figure 5.30).

Implantation occurs in all species as a result of open jaw fractures (traumatic, pathologic, or iatrogenic), contamination of surgical sites, bite wounds, or gunshot wounds. The most common form of bacterial inoculation of the mandible and/or maxilla is via *local extension* from an infection of the tooth or periodontal tissues (pulpitis/ periodontitis/ alveolitis). Periodontitis can be associated with extensive and progressive plaque/ calculus accumulation on the tooth crown and/or root (common in carnivores), or traumatic inoculation of foreign material into the periodontal ligament/ alveolus (a form of implantation that is relatively common in ruminants and rodents). Four overlapping syndromes of jaw inflammation are recognized in veterinary species – (i) periodontal osteomyelitis, (ii) *lumpy jaw* of ruminant species (actinomycosis), (iii) mandibulofacial/maxillofacial abscesses of mice, and (iv) periostitis ossificans. Mandibular or maxillary osteomyelitis can resolve spontaneously but generally requires appropriate antimicrobial and/or surgical treatment. It can also progress, resulting in pain, disfigurement, draining tracts, pathologic fractures, jaw dysfunction (anorexia), and death.

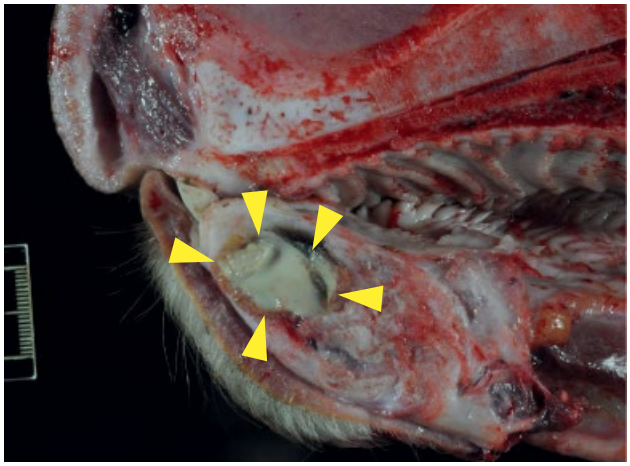


Figure 5.30 Gross image of abscessing osteomyelitis of the rostral mandible, one-year-old heifer calf. This lesion (abscess, yellow arrowheads) is associated with the incisor teeth and is the result of an infection with *Truperella pyogenes*. Contrast this sepsis-associated lesion with the lesion of lumpy jaw in adult cattle (Figures 5.36 and 5.37). *Source:* M. F. Sheley, University of California, Davis.

5.2.1 Periodontal Osteomyelitis

Periodontal osteomyelitis, often identified in carnivores, can be associated with extensive accumulation of plaque/ calculus and is defined by alveolar bone loss and loss of adhesion of the gingival epithelium at the tooth cemento-enamel junction (Figure 5.31). Periodontal osteomyelitis is also known as periapical periodontitis and is described under Degenerative and inflammatory disorders of teeth. This loss of epithelial adhesion (attachment loss) exposes the periodontal apparatus to the plaque-associated microflora, resulting in bacterial periodontitis. Food debris may also be impacted into the exposed periodontal space, providing a persistent nidus of infection. Local extension of bacteria and inflammatory cells into the adjacent bone results in alveolar osteomyelitis. The presence of microorganisms stimulates osteoblasts and inflammatory cells to produce inflammatory cytokines like TNF alpha, IL1, and IL6. These mediators stimulate osteoclasts, resulting in bone and tooth root resorption. Osteoclast-mediated bone resorption can result in cavitation and abscess formation (periodontal abscess), which is often localized to the root apex. Exudate drainage occurs through the path of least resistance, which

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Figure 5.31 Gross image of a dog with advanced periodontal disease, 11-year-old Greyhound dog. Generalized and severe dental calculus formation, tooth loss, gingival recession, and furcation exposure are grossly evident; periodontal inflammation and alveolar bone loss are presumed. The mandibular canine tooth has evidence of attrition and exposed tertiary dentin. *Source:* D. A. Tokarz, University of California, Davis.

may be the periodontal ligament, the adjacent oral mucosa (parulis), or skin (fistula).

In dogs, a periapical abscess associated with pulpal necrosis secondary to a crown fracture of the maxillary carnassial tooth (fourth maxillary premolar) is often associated with a characteristic maxillary sinusitis and fistulation through the skin ventral to the orbit. It is also possible to have appreciable loss of alveolar marginal bone prior to the loss of epithelial attachment, suggesting that the host systemic inflammatory response may affect bone physiology to promote bone loss.

Histologically, acute tooth-associated osteomyelitis is characterized by an influx of neutrophils, edema, necrotic debris and fibrin deposition. Once the cementoenamel-epithelial seal is breached, a biofilm of intermixed bacteria, basophilic material and birefringent food debris may be deposited on the tooth root or adjacent alveolar bone (Figure 5.32). The periodontal ligament may become necrotic or may be replaced by granulation tissue, aggregates of degenerate neutrophils, and fragments of bone. Islands of odontogenic epithelium (rests of Malassez) may proliferate in response to the inflammatory milieu. Smaller numbers of mononuclear inflammatory cells (lymphocytes and macrophages) extend peripherally into the intertrabecular space of the alveolar bone. The affected tooth may demonstrate histological evidence of inflammation or necrosis of the pulp. In severe bacterial periodontitis, the sulcular epithelium may become markedly hyperplastic and must be differentiated from neoplastic disorders like oral squamous cell carcinoma.

Although periodontal osteomyelitis is initially a localized infection, with chronicity, it may extend to involve

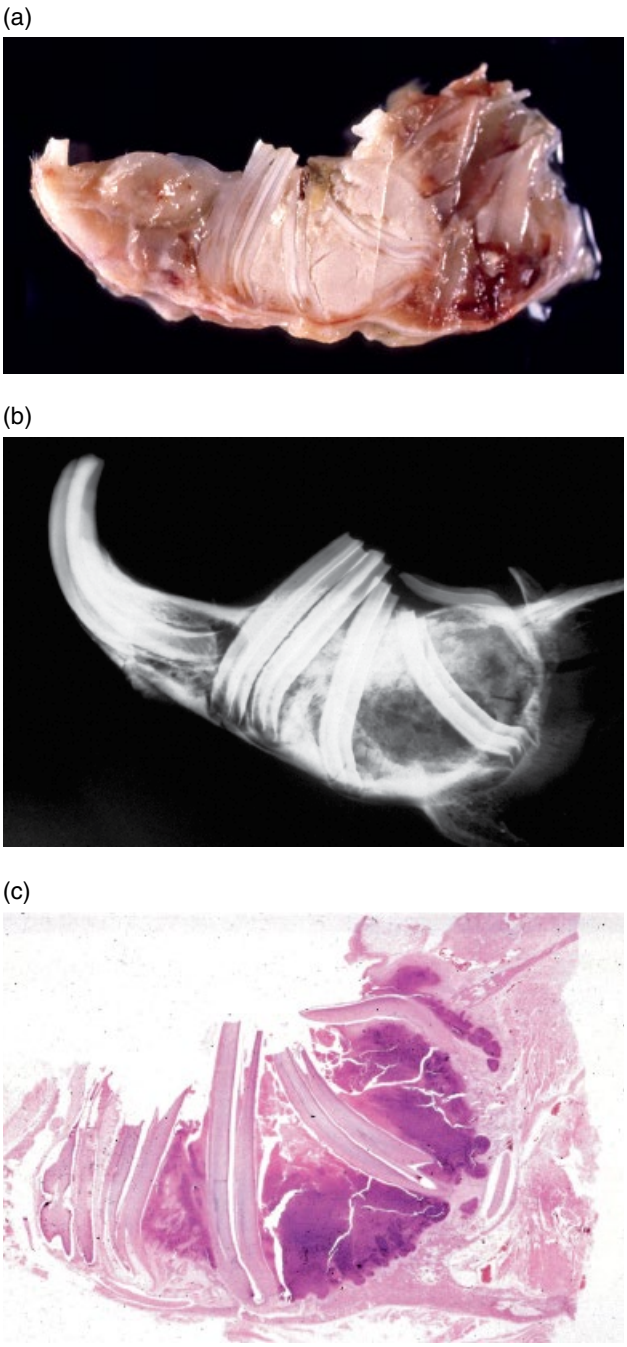


Figure 5.32 Gross, radiographic, and histologic images of abscessing mandibular osteomyelitis, rabbit. A mandibular abscess replaces the alveolar bone and distorts multiple cheek teeth – (a) gross image, (b) radiograph, (c) histologic image. *Source:* R. R. Dubielzig, University of Wisconsin.

the bone of adjacent teeth, the mandibular canal, and even the maxillary sinuses. The suppurative exudate is progressively replaced by granulation tissue, fibrous connective tissue, and reduced numbers of mononuclear inflammatory cells (although some neutrophils may persist within the lesion, Figure 5.33). A combination of

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Figure 5.33 Histologic image of tooth root and bone resorption associated with periodontitis, maxilla, 10-year-old cat. Black arrowheads denote intralesional calculus and food debris while red arrowheads denote granulation tissue and inflammatory infiltrates replacing the alveolar bone. Note the extensive loss of the tooth roots.

osteoclast-mediated bone resorption and osteoblast-mediated bone formation (so called *reactive bone*) is often present at the margins of the lesion. This results in a proliferative/lytic pattern which may be appreciated on dental radiographs. Tooth root resorption may extend through the outer cemental matrix and into the dentinal matrix, or even into the pulp cavity. With chronicity, this process may result in the focal/multifocal loss of the periodontal ligament with ankylosis into the alveolar bone. Isolated fragments of necrotic bone (sequestra) may be embedded and isolated within a collar of fibrous connective tissue (involucrum).

In small biopsy samples, the paucity of inflammatory cells and presence of fibrous connective tissue in chronic osteomyelitis of the jaw may serve to confound the diagnosis of inflammatory bone disease. In such cases, patient signalment, history, radiographic findings, and the opinion of the submitting clinician should all be considered. Although a reliance on histological features alone is not advised, *small numbers of infiltrating neutrophils and plasma cells in concert with reactive bone and fibrous connective tissue support a diagnosis of chronic osteomyelitis* (Figure 5.34).

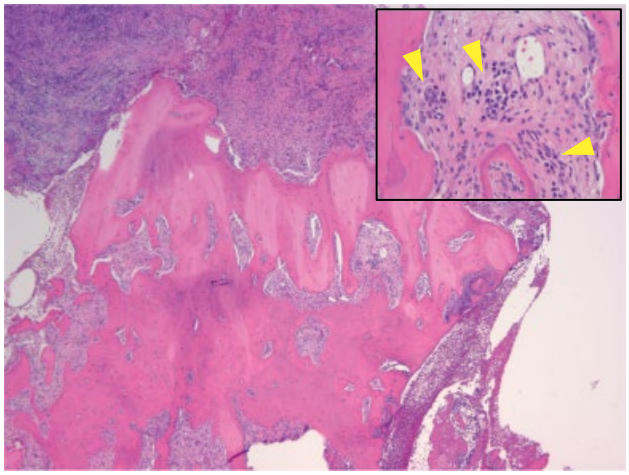


Figure 5.34 Histologic image of maxillary osteomyelitis, Scottish terrier dog. Mixed inflammation is present in the periodontal ligament and adjacent alveolar bone (intraosseous spaces). The affected bone is both lamellar and woven. Inset – interosseous regions have fibrous connective tissue and multiple clusters of plasma cells, a feature of chronic osteomyelitis (yellow arrowheads).

In cats, periodontal osteomyelitis involving the maxillary canine teeth, or less often, the premolar and/or molar teeth, can result in a lesion referred to as *feline alveolar bone expansion and osteomyelitis* [45]. Synonyms for this syndrome include peripheral osteitis, alveolar osteitis, peripheral buttressing, or feline buccal bone expansion. Grossly, this lesion is characterized as a smooth proliferation of the buccal aspect of the alveolar bone. Histologically, the lesion is comprised of compressed trabeculae of mature remodeled bone and loose fibrous stroma associated with inflammation (leukocytes may be sparse) and proliferative spicules of woven bone. In cats in particular, the intratrabecular stroma of these lesions may be largely comprised of basophilic-staining myxomatous tissue (Figure 5.35). Clinicians may recognize this "jelly-like" stroma during surgical procedures. This feline lesion often occurs in conjunction with periodontitis and/or tooth resorption.

Periodontal osteomyelitis involving the roots of hypsodont teeth, like the incisor teeth of rabbits, the cheek teeth of guinea pigs and chinchillas, or the canine teeth (tusks) of pigs, has an additional and potentially important sequela. In such teeth, the enamel organ persists into adulthood. Periodontal inflammation involving the root-associated enamel organ can induce a proliferative and dysplastic lesion referred to as *odontogenic dysplasia* (Figure 5.36). To a degree, this lesion can be a mimic of odontoma. Interested readers are referred to the section on odontogenic dysplasia (Degenerative and inflammatory disorders of teeth). In addition, periodontal osteomyelitis in guinea pigs and chinchillas often has evidence

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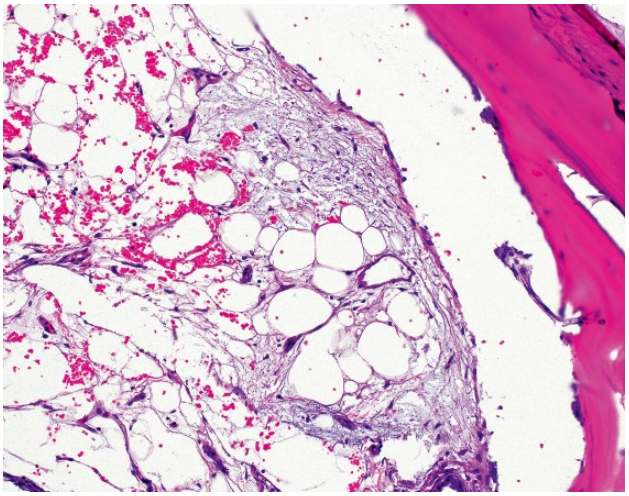


Figure 5.35 Histologic image of feline alveolar bone expansion and osteomyelitis demonstrating the myxoid appearance of the lesion-associated stroma. *Source:* C. Bell.

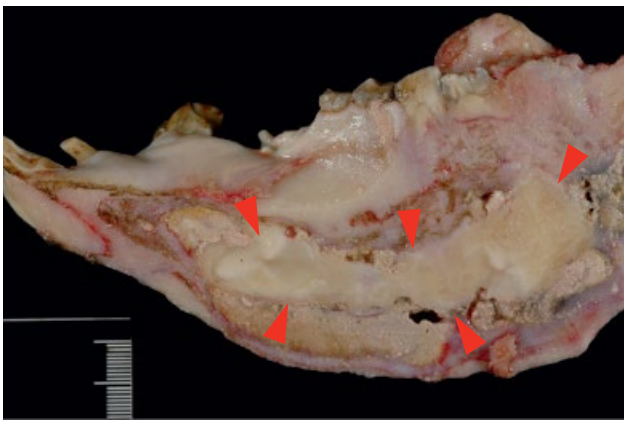


Figure 5.36 Gross image of mandibular osteomyelitis and odontogenic dysplasia of the tusk (canine tooth), 14-year-old pot-belly pig. The irregularly shaped tusk (red arrowheads) is partially surrounded by an inflammatory exudate. *Source:* S. Siso, University of California, Davis.

of resorption of the mineralized dental matrices with replacement by bone or fibrous tissue.

5.2.2 Lumpy Jaw (Actinomycosis)

Mandibular osteomyelitis, colloquially known as *lumpy jaw*, is a well-recognized and important disease syndrome that occurs most often in cattle, but is also recognized in other species like horses, deer, sheep, goats, cats, and dogs. The maxilla is rarely involved. In cattle, this proliferative mandibular lesion is generally the result of an infection with *A. bovis*, and as a result, is also known as actinomycosis. Other species of *Actinomyces*, *Nocardia*, or *Fusobacterium* may be the cause of "lumpy jaw" in mammals other than cattle. The mechanism of microbial

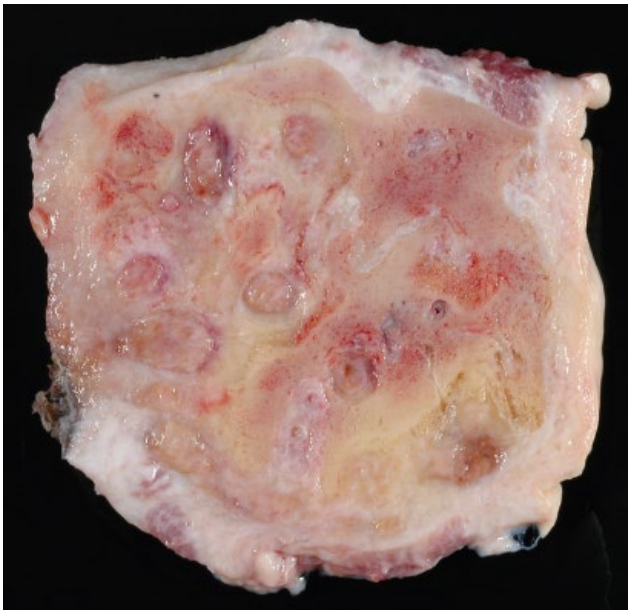


Figure 5.37 Gross image of the mandible from a bovine with lumpy jaw, seven-year-old Angus cow. In this transverse section of the mandible, the cortical bone has been replaced by a sieve-like network of fibrosis, proliferative bone and interspersed granulation tissue. (*Source:* D. A. Tokarz, University of California, Davis.)

inoculation likely varies, but is thought to primarily involve traumatic inoculation of bacteria-contaminated plant material into the periodontal ligament.

Lumpy jaw is characterized by massive expansion and deformation of the mandible. Fistulous draining tracts (oral mucosa or skin) are common. On section, the mandible is focally to diffusely replaced by a cribriform structure of proliferative/reactive bone and interspersed pockets of inflamed granulation tissue (Figure 5.37). The alveolar bone, cortex, and mandibular canal are often obliterated, resulting in loosening and loss of associated teeth.

Histologically, the lesion is characterized by linking bony trabeculae embedded within a proliferative stroma with abundant pyogranulomatous inflammation. The stroma varies from immature, highly proliferative granulation tissue to mature fibrovascular tissue. Neurovascular structures are often entrapped by the abundant fibrous stroma. Bone formation (especially periosteal bone) and bone destruction are concurrently present. Osteoclast-mediated bone resorption can be impressive, with continuous rows of attached osteoclasts associated with wavelike scalloped bone margins. Discrete regions of hemorrhage and necrosis may be interspersed throughout the lesion.

Distributed throughout the granulation/fibrous tissue are moderate numbers of 1–2 mm diameter "sulfur granules" (Figure 5.38). These discrete structures are bacterial

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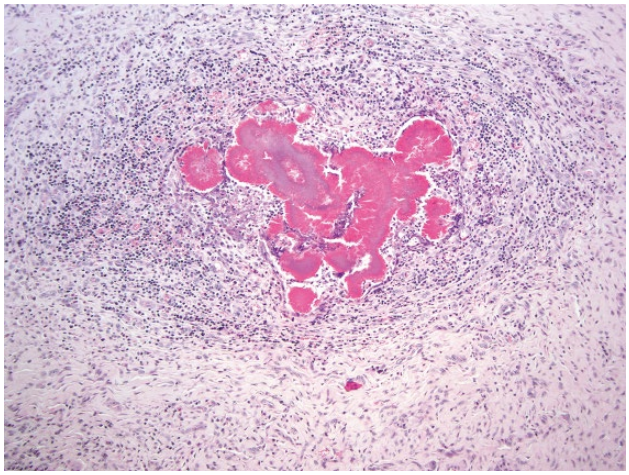


Figure 5.38 Histologic image of a "sulfur granule" (bacterial biofilm), mandible, seven-year-old Angus cow. Pyogranulomatous inflammation surrounds an eosinophilic, botryoid aggregate of bacteria and Splendore-Hoeppli material. This histologic image is from the gross lesion depicted in Figure 5.37.

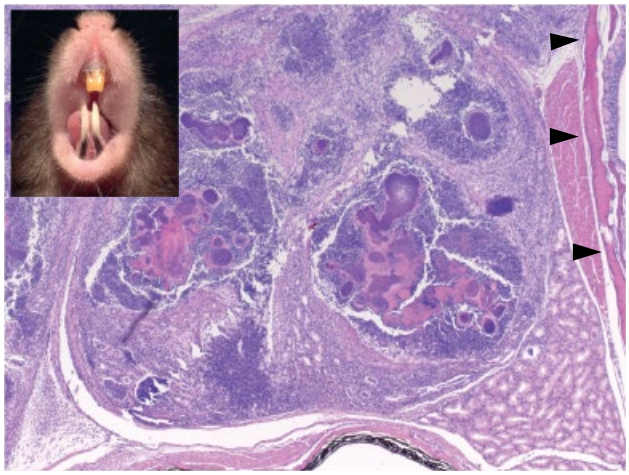


Figure 5.39 Gross and histologic images of murine maxillofacial abscess (botryomycosis). Note the multiple aggregates of bacteria and Splendore-Hoeppli material. Black arrowheads delineate remnant maxillary bone. Inset – Gross image of "hair tooth" or foreign body periodontitis; often a precursor lesion to maxillofacial abscesses. *Source:* D. Imai-Leonard, M. Hurrath, Comparative Pathology Laboratory, University of California, Davis.

biofilms comprised of a tangled core of basophilic, Gram-positive pleomorphic bacterial filaments, rods, and coccoid forms surrounded by an irregular club-shaped rim of eosinophilic matrix (Splendore-Hoeppli material). Although bony sequestra are generally not thought to be a feature of lumpy jaw, small fragments of bone, lacking osteocytes, can occasionally be identified. The clinical management of this lesion can be difficult as the mandibular inflammation and tissue disruption at the time of diagnosis are often extensive.

5.2.3 Mandibulofacial/Maxillofacial Abscesses of Mice

These remarkable lesions are the result of a common murine behavior, barbering. As a result of barbering, self and communal grooming of the pelage and vibrissae, variable numbers of clipped hair shafts become multifocally implanted into the periodontal ligament, inoculating the alveolar bone with *Staphylococcus aureus,* and initiating an abscessing osteomyelitis of the jaw bones. The hair-associated lesions have focal lysis of the jaw bone and can extend into the adjacent tissues of the face and nasal passages (cellulitis), referred to as mandibulofacial/maxillofacial abscesses [46]. The abscesses may eventually fistulate and drain through the skin. Histologically, the lesions are characterized by sheets of neutrophils and interspersed globular aggregates of bacterial Splendore-Hoeppli material (Figure 5.39). An older (and technically incorrect) term for *S. aureus*-associated facial abscesses in rodents is *botryomycosis* (staphylococcal cellulitis). The term botryomycosis is a misnomer as it inappropriately implies a fungal etiology.

(a)



(b)

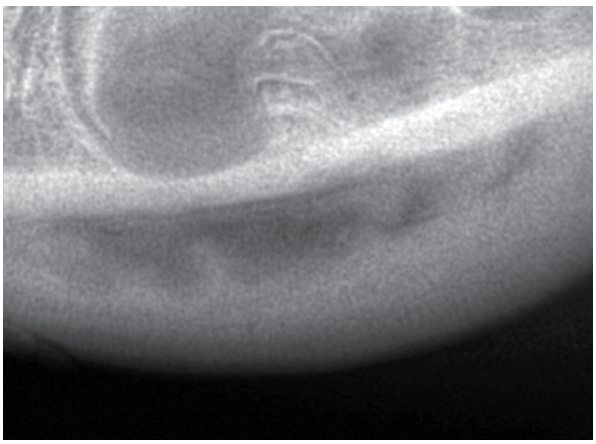


Figure 5.40 Gross and radiographic images of the mandible of a 13-week-old, male, mixed-breed dog. Periostitis ossificans presents as a non-painful bone swelling with a "double cortex" on radiographs. *Source:* A. Mees.

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5.2.4 Periostitis Ossificans

Periostitis ossificans occurs infrequently in young, large-breed dogs. The condition presents as a unilateral, firm, non-painful swelling of the caudal body of the mandible and affects dogs with a median age of approximately four months [47]. Radiographically, the lesion has a distinctive double cortex (Figure 5.40).

Histologically, samples from the outer radiopaque proliferation show organized plates of woven bone, consistent with new periosteal bone [48]. Inflammation within the bone may be underwhelming or absent. However, samples taken from the radiolucent center of the lesion have been shown to include fibrin, neutrophils and/or necrotic bone [47].

The pathogenesis of periostitis ossificans is likely to be multifactorial and the mandibular bone of young, large breed dogs appears to be intrinsically predisposed. One theory proposes that pericoronitis (gingivitis surrounding the crown of an incompletely erupted tooth) progresses to periostitis when inflammation extends along the subperiosteum [47]. In humans, caries-associated osteomyelitis is the most common cause of periostitis ossificans [48]. Trauma, occlusal forces and foreign bodies are considered risk factors. Spontaneous resolution of the condition was observed in most reported cases in dogs [47].

References

45 Bell, C.M. and Soukup, J.W. (2015). Histologic, clinical, and radiologic findings of alveolar bone expansion and osteomyelitis of the jaws in cats. *Vet. Pathol.* 52: 910–918.

46 Lawson, G.W. (2010). Etiopathogenesis of mandibulofacial and maxillofacial abscesses in mice. *Com. Med.* 60: 200–204.

47 Blazejewski, S.W. 3rd, Lewis, J.R., Gracis, M. et al. (2010). Mandibular periostitis ossificans in immature large breed dogs: 5 cases (1999–2006). *J. Vet. Dent.* 27: 148–159.

48 Neville, B.W. (2009). *Oral and Maxillofacial Pathology*, 3e. St. Louis, Mo: Saunders/Elsevier.

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6

Trauma and Physical Injury

6.1 Soft Tissue Injury

Traumatic lesions to the tissues of the oral cavity are bound to be more common than is apparent to veterinarians or pet owners. Such lesions are more likely to be noticed on the externally visible lips. Many are noted incidentally during an anesthetized oral exam. The most common sites of oral soft tissue injury are the lip margins, buccal mucosa, lateral margins of the tongue, and sublingual mucosa. Morphologically, trauma-induced lesions of the oral soft tissues range from flat, hyperkeratotic plaques to deep ulcerations to exophytic masses.

Causes

- Traumatic lesions are often secondary to masticatory trauma or malocclusion, which includes misalignment of teeth as well as abnormalities in tooth shape or surface.
- Fractured teeth typically have rough or sharp surfaces that may traumatize opposing soft tissues. Fractured incisors may rub against the lip margins or against the sublingual mucosa when a dog is panting.
- In cats, supereruption of teeth (i.e. displacement in the occlusal direction so that the tooth emerges further from the socket) may contribute to the etiology of traumatic soft tissue lesions when the affected tooth contacts the opposing mucosa [1].
- Oral mucosa is at greater risk of masticatory or occlusal trauma when it is swollen for any reason (e.g. inflammation, edema, sialocele, and neoplasia). Furthermore, mucosal swelling is more likely to be exaggerated where there are redundant folds of mucosa and loose submucosa. This may partially explain why traumatic lesions are so commonly located on the buccal vestibular mucosa and sublingual mucosa.

6.1.1 Abrasions and Lacerations

Rubbing, friction, and abrasion tend to cause non-ulcerated thickened plaques where the mucosal epithelium is hyperplastic and hyperkeratinized. These lesions are unlikely to be associated with significant inflammation or other changes in the submucosa (Figure 6.1).

Laceration, puncture, or other forms of sharp trauma are more damaging to the oral mucosa than lesions resulting from abrasion. Contact with teeth is a common cause for mucosal trauma. Malocclusion often affects the labial mucosa (Figures 6.2 and 6.3). The sublingual frenulum may be traumatized, usually against the mandibular incisors; this injury can be iatrogenic when the tongue of anesthetized animals is exteriorized during intubation or manipulated during oral exam (Figure 6.4). The lateral and ventral surfaces of the tongue are sites most likely to be injured by sharp points, due to crown fracture or abnormal attrition, along the mandibular arcades (Figure 6.5). When discovered long after the initial injury, traumatic wounds are likely have healed with significant fibrosis (Figures 6.6 and 6.7). If a cause of trauma is no longer apparent, it may be difficult to histologically distinguish trauma-associated fibrosis from low-grade fibrosarcoma. For this reason, it is useful to know which sites in the oral cavity are predisposed to trauma versus common sites and breeds of animals with a predisposition for fibrosarcoma.

6.1.2 Traumatic "Granuloma"

The vestibular buccal mucosa and lateral lingual/sublingual mucosa are typical sites of "chewing" trauma. When denuded of epithelium, an acute inflammatory response in the submucosa will result in edema, vasodilation and congestion, and influx of neutrophils. There is also a fibrovascular proliferative response that may form exophytic, lobular nodules of exuberant granulation tissue (Figure 6.8). Robust proliferation of granulation tissue may occur when the area of injury is too large to quickly re-epithelialize or when the site is subjected to persistent/repetitive injury. These benign proliferative mass lesions have historically been called "granuloma," the term referring to *granulation tissue* and not granulomatous inflammation.

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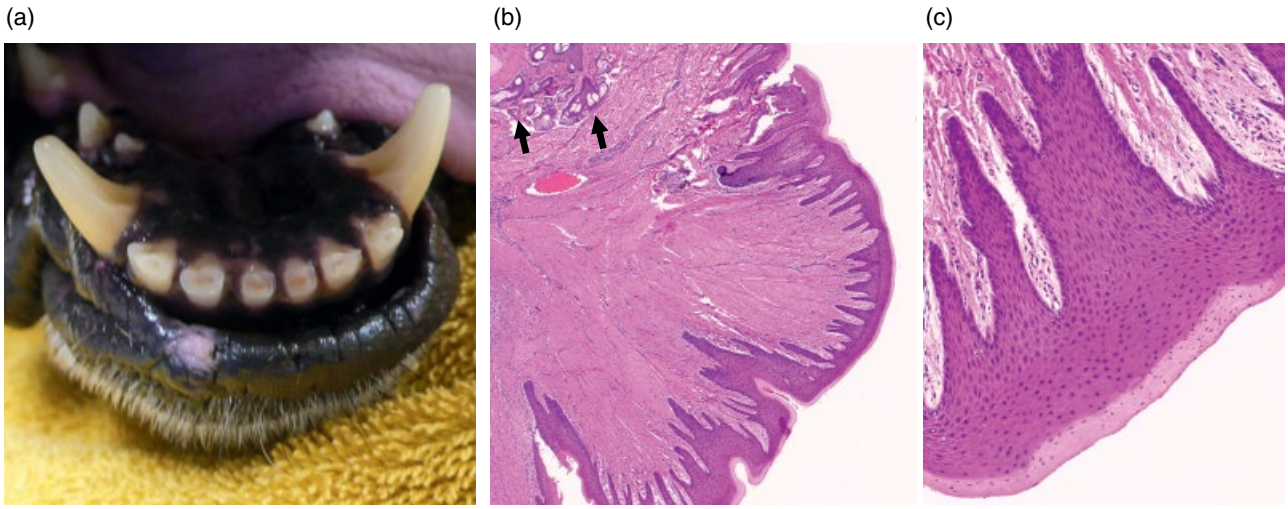


Figure 6.1 Gross and histologic images of chronic abrasive trauma, six-year-old, spayed female mixed breed dog. (a) Grossly, this lesion appears as a thickened depigmented area at the mucocutaneous junction of the lower lip. (b) Histologically, the affected area has abundant, homogeneous fibrous connective tissue and sebaceous glands (arrows) at one edge of the lesion, consistent with mucocutaneous location. (c) Like a "lick granuloma" in the skin, chronic abrasive lesions on the lip have hyperplastic epithelium with variably sized rete pegs that interdigitate with the papillary fibrous stroma. The epithelium lacks pigment and has a thick parakeratotic layer at the surface. *Source:* D. Hoover.

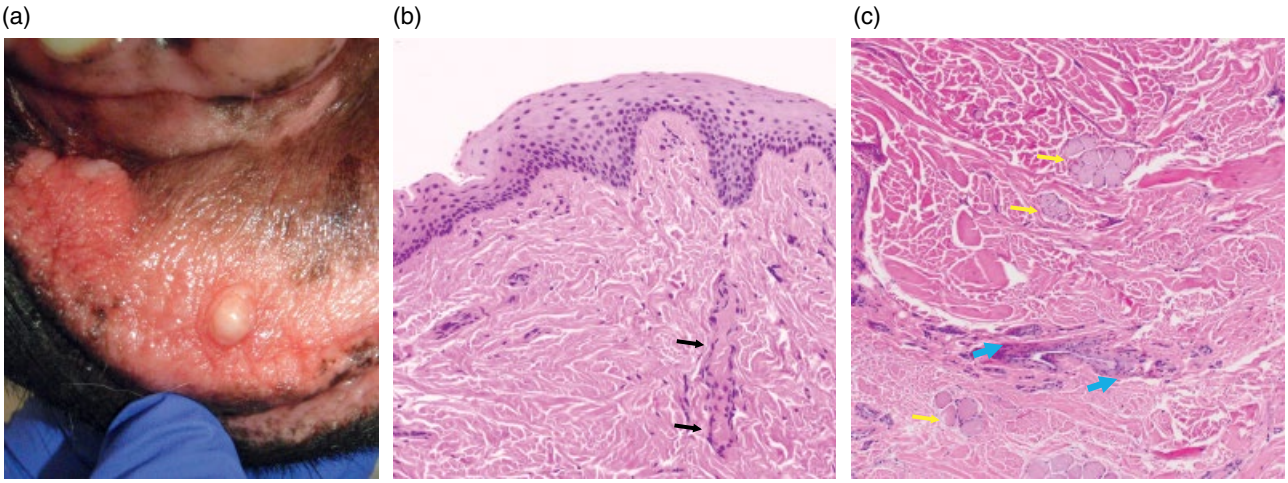


Figure 6.2 Gross and histologic images of a chronic mucosal lesion associated with sharp trauma (traumatic fibroma), two-year-old, neutered male, mixed breed dog. (a) An area of labial mucosa near the mucocutaneous junction has a discrete, palpably firm/fibrous nodule. This area was adjacent to a maxillary canine tooth and traumatic contact with the cusp of the opposing mandibular canine was the most likely cause of focal fibrosis or "traumatic fibroma." (b) Intact mucosal epithelium covers a homogeneous area of poorly cellular fibrous tissue with abundant collagen arranged in thick bundles. The increased thickness of the fibrous tissue and a vessel perpendicular to the surface (arrow) are evidence that the tissue represents mature granulation tissue as opposed to normal lamina propria. (c) At higher magnification, the fibrous tissue includes small proliferative vessels (blue arrows) and entraps atrophied skeletal muscle fascicles (yellow arrows). *Source:* R. MacLellan.

Oral microbial flora may colonize the surface of ulcerated lesions and can delay healing. Opportunistic pathogens also have the opportunity to proliferate; as such, traumatic injury of oral soft tissues contributes significantly to oral candidiasis, fusobacteriosis (necrobacillosis), and actinomycosis (discussed elsewhere in this textbook).

The term *pyogenic granuloma* has become a common synonym for chewing granuloma or traumatic granuloma, particularly in reference to cats [2,3]. The clinicopathological features of pyogenic granuloma in cats are fairly predictable. These lesions most often occur on the mucosa that is buccal (sometimes distal and/or lingual)

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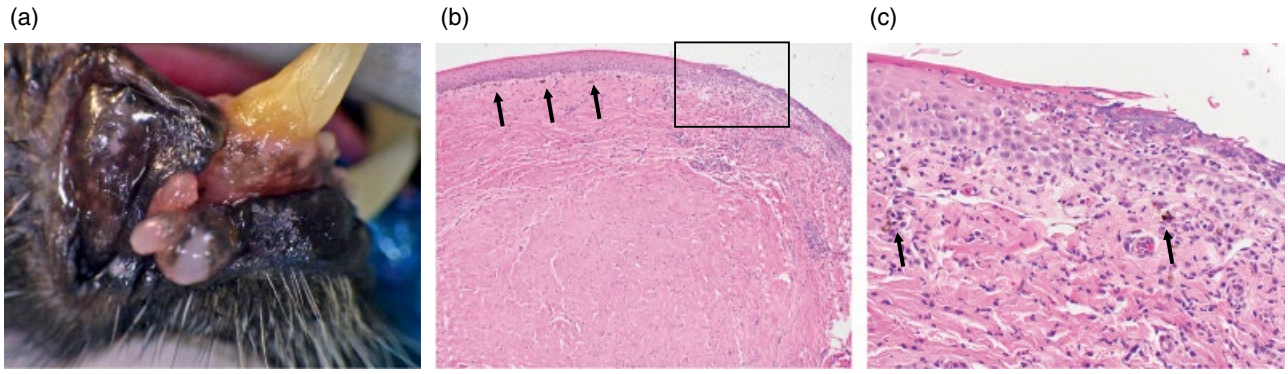


Figure 6.3 Gross and histologic images of a traumatic mucosal lesion, 11-year-old, neutered male, DSH cat. (a) This proliferative mucosal lesion near the right mandibular canine tooth on the lower lip margin had been traumatized by the opposing right maxillary canine tooth. (b) Histologically, the subgingiva/ submucosa is expanded by a nodule of dense, poorly cellular fibrous tissue, and epithelium disappears at a site of ulceration. Within the nodule, the collagen is glassy (hyalinized). Melanophages (arrows) suggest previous injury of the pigmented epithelium. (c) The ulcerated area has proliferative small vessels and neutrophils. *Source:* E. Rachwitz.

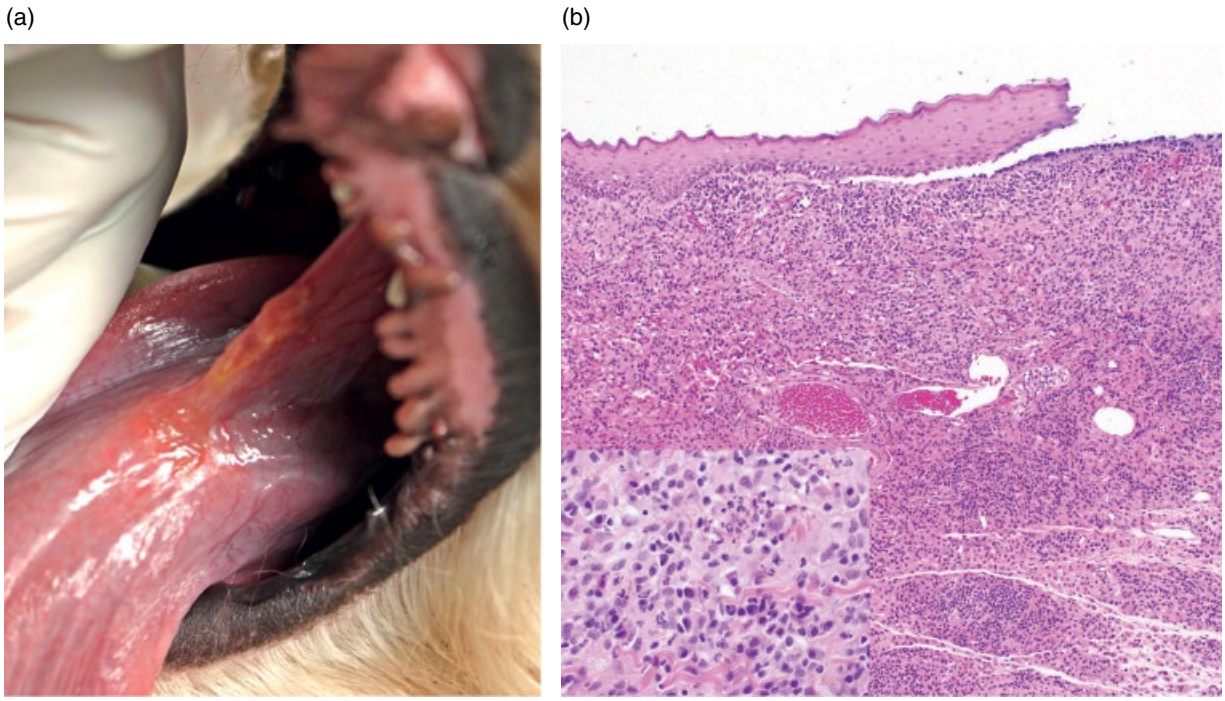


Figure 6.4 Gross and histologic images of the lingual frenulum in a dog. The lingual frenulum is a common site of oral mucosal trauma in dogs. (a) In this case, the orange discoloration of the lesion is due to hemosiderin deposits, indicative of previous intra-lesional hemorrhage. (b) At the edge of the ulceration, there are densely cellular inflammatory infiltrates that extend from superficial to deep within the submucosa. The inflammatory cell population is mixed with neutrophils, macrophages, lymphocytes, and plasma cells (inset). *Source:* D. Hoover.

to a mandibular molar tooth or, much less often, the lateral aspect of the tongue can be affected (Figure 6.9). Grossly, pyogenic granuloma in cats is a red, glistening, exophytic mass with a nodular to lobular shape. The most consistent histological presentation is of a broadly ulcerated proliferation of granulation tissue with vessels and collagen fibers showing oblique or perpendicular orientation with respect to the surface. Proliferative vessels may be the most striking change; this lesion may mimic hemangioma, grossly and histologically (Figures 6.9 and 6.10).

While usually ulcerated, lesions have inflammation with few neutrophils nearest the ulcerated surface. Remember, the primary cause is trauma. That noted, many feline lesions have clinical and histological features of pyogenic granuloma plus significant lymphoplasmacytic

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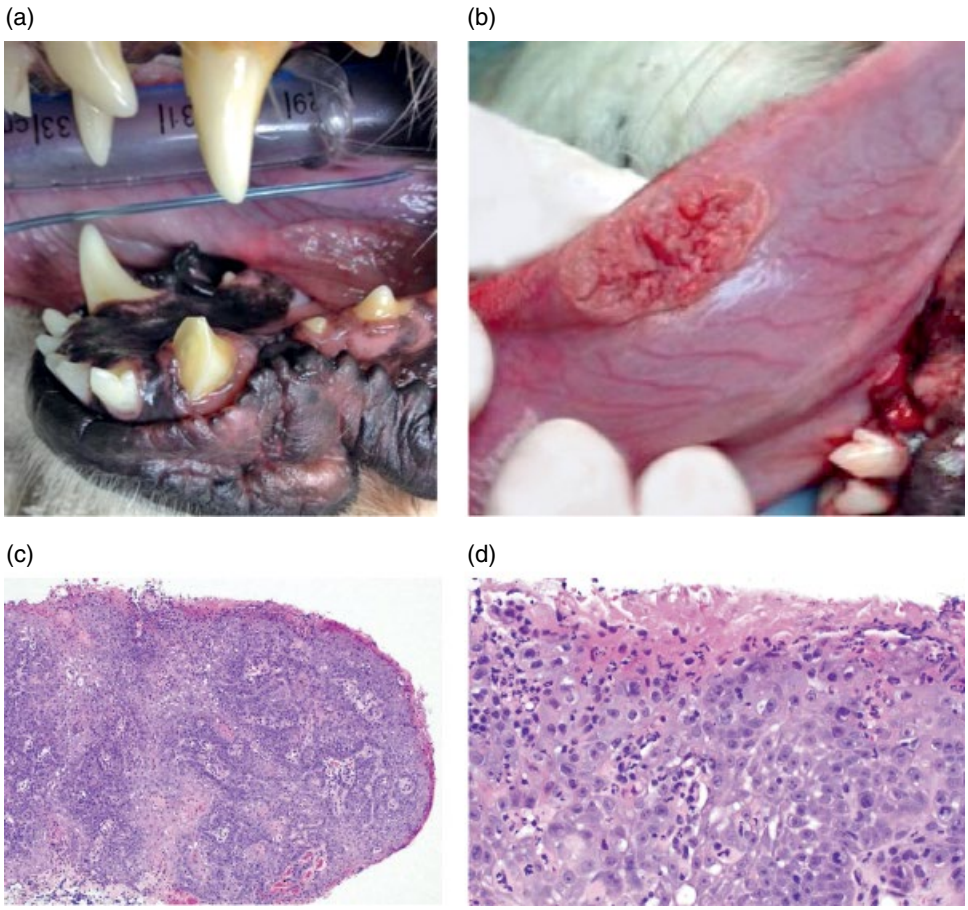


Figure 6.5 Gross and histologic images of a sublingual lesion associated with chronic sharp trauma, eight-year-old, spayed female, great Pyrenees. (a) and (b) The sharp cusp of a fractured left mandibular canine tooth lacerated the sublingual mucosa and, with persistent/repetitive injury, resulted in a linear proliferative lesion with a micronodular surface. (c) Histologically, the tissue demonstrates marked hyperplasia of the sublingual mucosal epithelium. (d) While the basal and prickle cell layers are proliferative, the superficial layers are eroded and feature many intraepithelial neutrophils. *Source:* B. Greenfield.

inflammation. In these cases, it is often difficult to distinguish between pyogenic granuloma and chronic caudal stomatitis. Sometimes, both processes are present, especially when the caudal mucosa is markedly swollen and predisposed to secondary traumatic injury. Useful indications that a cat may have underlying chronic stomatitis are an abundance of plasma cells and erosion within the lesion but no evidence of ulceration. Squamous cell carcinoma is another important differential for pyogenic granuloma (Box 6.1).

Box 6.1 Differential Diagnoses for Pyogenic Granuloma in Cats

Feline chronic gingivostomatitis
Squamous cell carcinoma
Eosinophilic granuloma
Inflamed molar gland

6.1.2.1 Clinical Features

Treating the traumatic lesions must be accompanied by resolving the underlying cause of trauma. Clinicians are encouraged to evaluate the entire oral cavity. In cats, lesions that occur buccal to a first mandibular molar are most often caused by chronic masticatory trauma as a result of the opposing maxillary premolar contacting the mucosa. There is anecdotal evidence that previous extraction or loss of the mandibular molar is a predisposing factor. Without this opposing tooth, supereruption of the fourth premolar would be more likely to occur. The recommended treatment is conservative excision of the lesion with either crown reduction (odontoplasty) or extraction of the opposing maxillary fourth premolar tooth.

A primary reason for soft tissue swelling may not be apparent in a surgical biopsy sample when proliferative

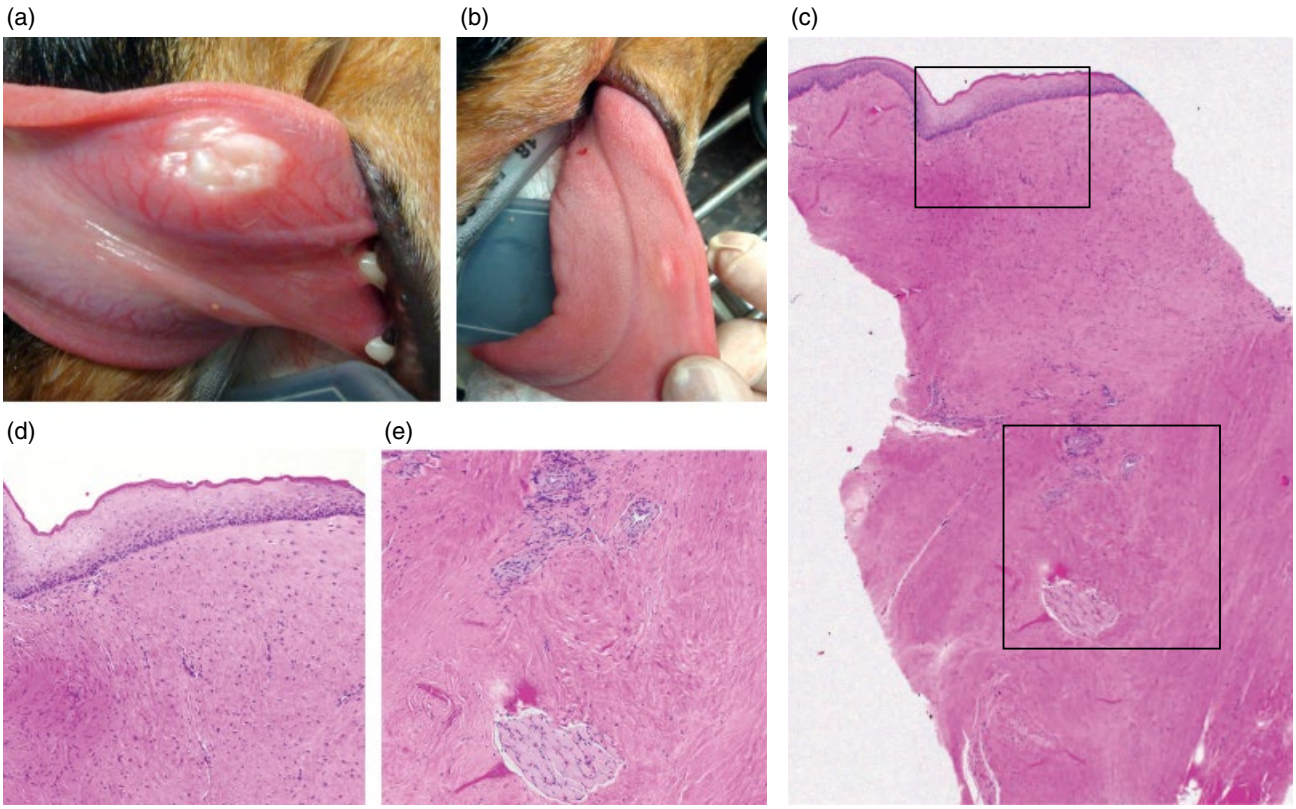


Figure 6.6 Gross and histologic images of a lingual lesion associated with chronic trauma, spayed female Dachshund dog. (a) A firm, white lesion is evident on the ventral surface of the tongue. (b) The same lesion is hardly noticeable on the dorsal lingual surface. (c) Histologically, dense fibrous scar tissue extends deep into the tongue, replacing skeletal muscle. (d) The surface has re-epithelialized while (e) rare myofibers are isolated within the scar tissue and perivascular inflammation is minimal. It is easy to imagine that this case represents the outcome of lesions, as in Figure 6.5b, which are left to heal without surgical intervention. *Source:* C. Durand.



Figure 6.7 Gross image of an incidental finding at necropsy in an aged horse. Multiple sites of fissured proliferative scar tissue in the sublingual mucosa and lateral surface of the tongue. The largest lesion in the mid-body of the tongue approached midline. These lesions healed by granulation and fibrosis; they were likely caused by traumatic laceration due to sharp points on the adjacent cheek teeth. *Source:* B. Njaa.

granulation tissue ("granuloma") is excised at its base. Any gross abnormality of the underlying mucosa is an indication to take an incisional biopsy in addition to excising the traumatic lesion. It may be necessary to query the pet owner regarding history of observed trauma or atypical chewing habits when occlusion, dentition and oral mucosa appear normal. The clinician should bear in mind that they are serving as the "eyes" of the pathologist, astute clinicians *are gross pathologists*!

6.1.3 Thermal and Chemical Burns

Burns are a form of direct tissue damage caused by caustic substances (e.g. chemicals) or energy (e.g. direct heat, ionizing radiation, and electricity). Burn lesions are the result of acute soft tissue necrosis with or without underlying osteonecrosis. Most burns are focal/localized or regionally extensive.

Hydrophilic chemicals tend to cause superficial burns, having necrotizing effects on the tissues that directly contact the caustic agent. Direct thermal heat may conduct to deeper tissues, but in a conscious animal, withdrawal responses will usually prevent contact for any significant amount of time. In contrast, radiation and

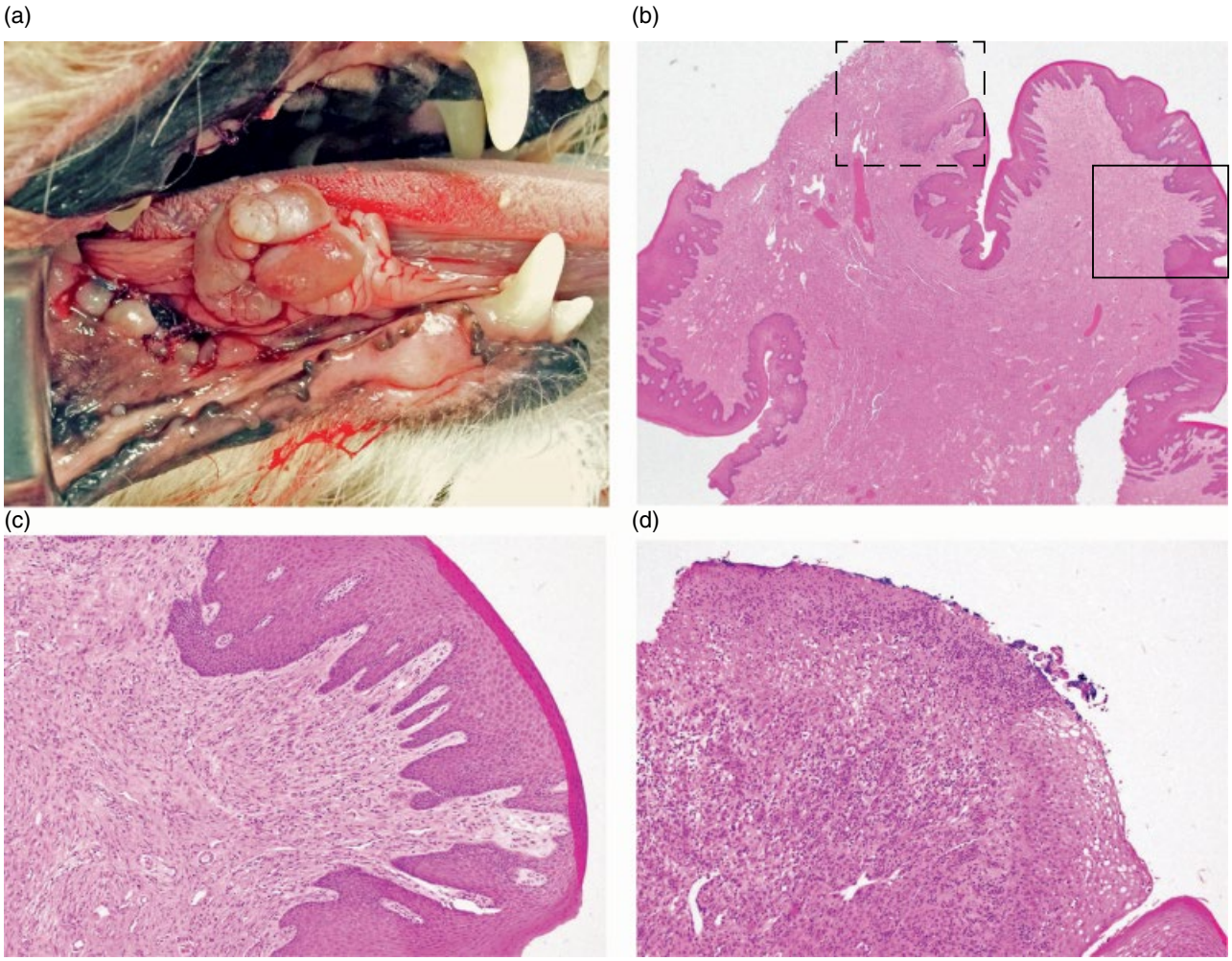


Figure 6.8 Gross and histologic images of a sublingual "chewing granuloma," 13-year-old, spayed female Maltese dog. (a) This "chewing granuloma" was bilateral but reported to be more severe on the right. (b) The low-power histologic image of the lesion demonstrates a polypoid, multilobular mass. (c) The non-ulcerated portion of the mass resembles organizing granulation tissue with mild inflammatory infiltrates (solid line box from b). (d) The ulcerated portion is notably more cellular due to immature granulation tissue and neutrophilic inflammation (dashed box from b). *Source:* M. Buelow.

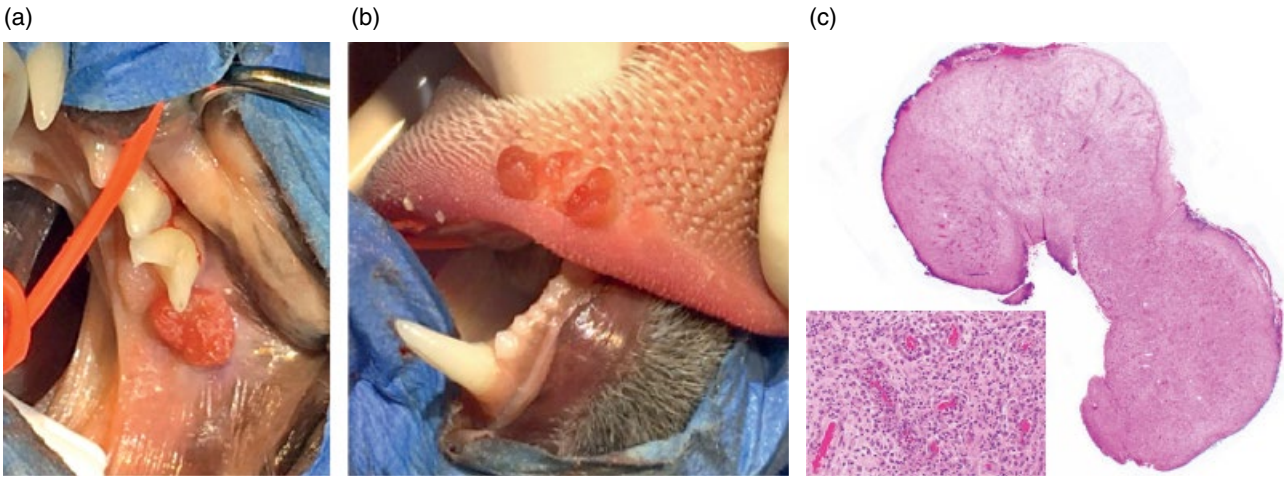


Figure 6.9 Gross and histologic images of pyogenic granulomas in a cat. (a) A bright red, raised mass is buccodistal to the mandibular molar (b) and similar lesions are on the lateral surface of the tongue. (c) The broad-based, exophytic mass is ulcerated and composed of granulation tissue with neutrophilic inflammation (C). *Source:* C. Miles.

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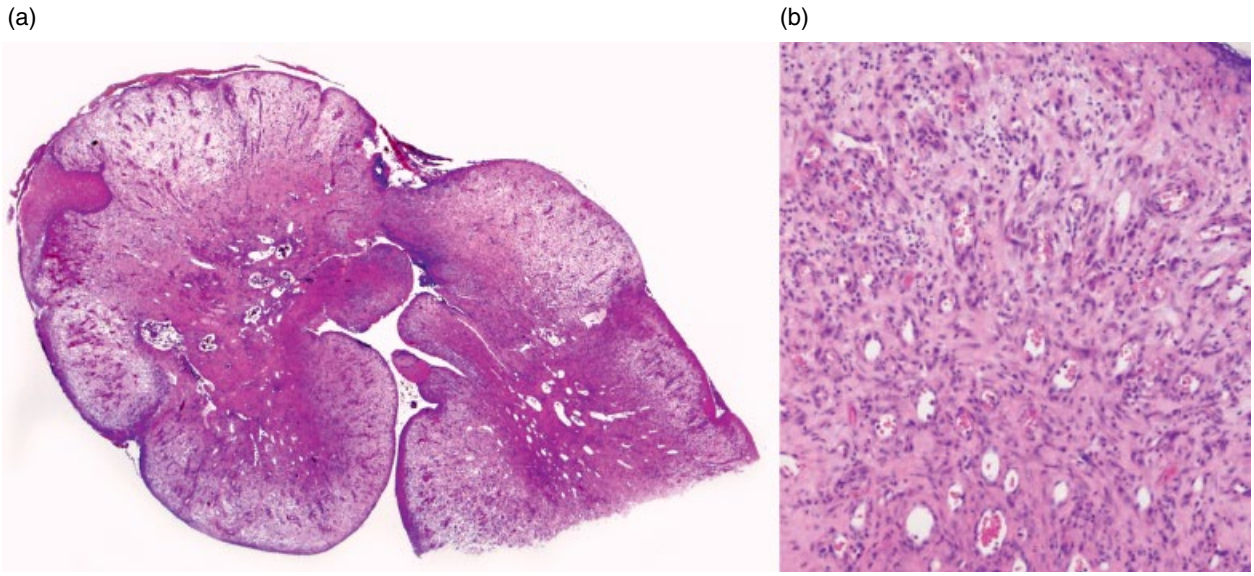


Figure 6.10 Additional histologic images of pyogenic granulomas in cats. (a) A polypoid mucosal mass has a central core of organized fibrovascular stroma and peripheral immature granulation tissue. (b) When inflammation is mild, the pattern of "hemangiomatous" hyperplasia of fibrovascular tissue can mimic a vascular neoplasm.

electrical energy conduct into the deep tissues almost instantaneously. Radiation energy may "burn" soft tissues by having a necrotizing effect. Therapeutic levels of radiation may cause fibrinous mucositis and sloughing of oral mucosa, which quickly regenerates [4]. When not fatal, high voltage electrical injuries are highly damaging to the oral tissues – these are perhaps the most likely type of oral burn to be brought to the attention of a veterinarian.

In the authors' experience, most oral electrical injuries are the result of an animal chewing an electrical cord. Dogs, cats, and rabbits seem to be the most likely culprits. Dogs and cats tend to gnaw with their caudal dentition, which are designed for shearing. If there is a "typical" location for an electrical cord chewing injury in dogs and cats, it is within the region of the mandibular caudal premolars to first molar. Sometimes, the opposing maxillary region (caudal premolars) is also affected. The lesions that result from electrical cord burns are characterized by soft tissue necrosis/loss, often more buccal than lingual, and osteonecrosis. In severe cases, the gingiva and alveolar mucosa may be completely absent (having combusted!) with exposure of the jawbone (Figure 6.11). The mucosa of the lip is often affected as well.

The electrical injury is not always fatal and the incident is not always observed. The immediate signs can be nonspecific and transient, including drooling, mouth shyness, anorexia, or behavioral changes. In these situations, the pet may be presented several days post-injury with the complaint of halitosis. Electrical burn sites fail to heal when the underlying bone is necrotic and exposed bone is often heavily colonized by a bacterial biofilm (Figure 6.11).

6.2 Traumatic Lesions of the Teeth and Jaws

If injured during development, certain tissues, particularly bone and developing teeth, seem to have an extraordinary potential to give rise to proliferative, often bizarre lesions in response to physical disruption. Some of the conditions presented in this section are presented in greater detail elsewhere. Here, however, the goal is to highlight the role trauma plays in lesion pathogenesis. Because they are the result of disrupted tooth development, trauma-associated odontogenic cysts, hamartomas, and tooth dysplasia do not occur in mature animals (although an individual may be mature at the time the lesion is first diagnosed). Similarly, periostitis ossificans and aneurysmal bone cysts seem to be aberrant responses of physiologically active bone that are simply not observed in mature bone.

6.2.1 Disrupted Tooth Development

Traumatic jaw injury in young animals may result in the formation of one or more dysplastic teeth. For pathologists who are not familiar with such lesions they can be quite confusing and may be inappropriately categorized as neoplastic. When the dysplastic tooth is unable to erupt normally, there is the potential for hyperplasia/dysplasia of the dental follicle, formation of a dentigerous cyst, or periostitis ossificans. Trauma may be iatrogenic as well as accidental; for example, premature extraction of a deciduous tooth may impair normal development of the permanent tooth [5].

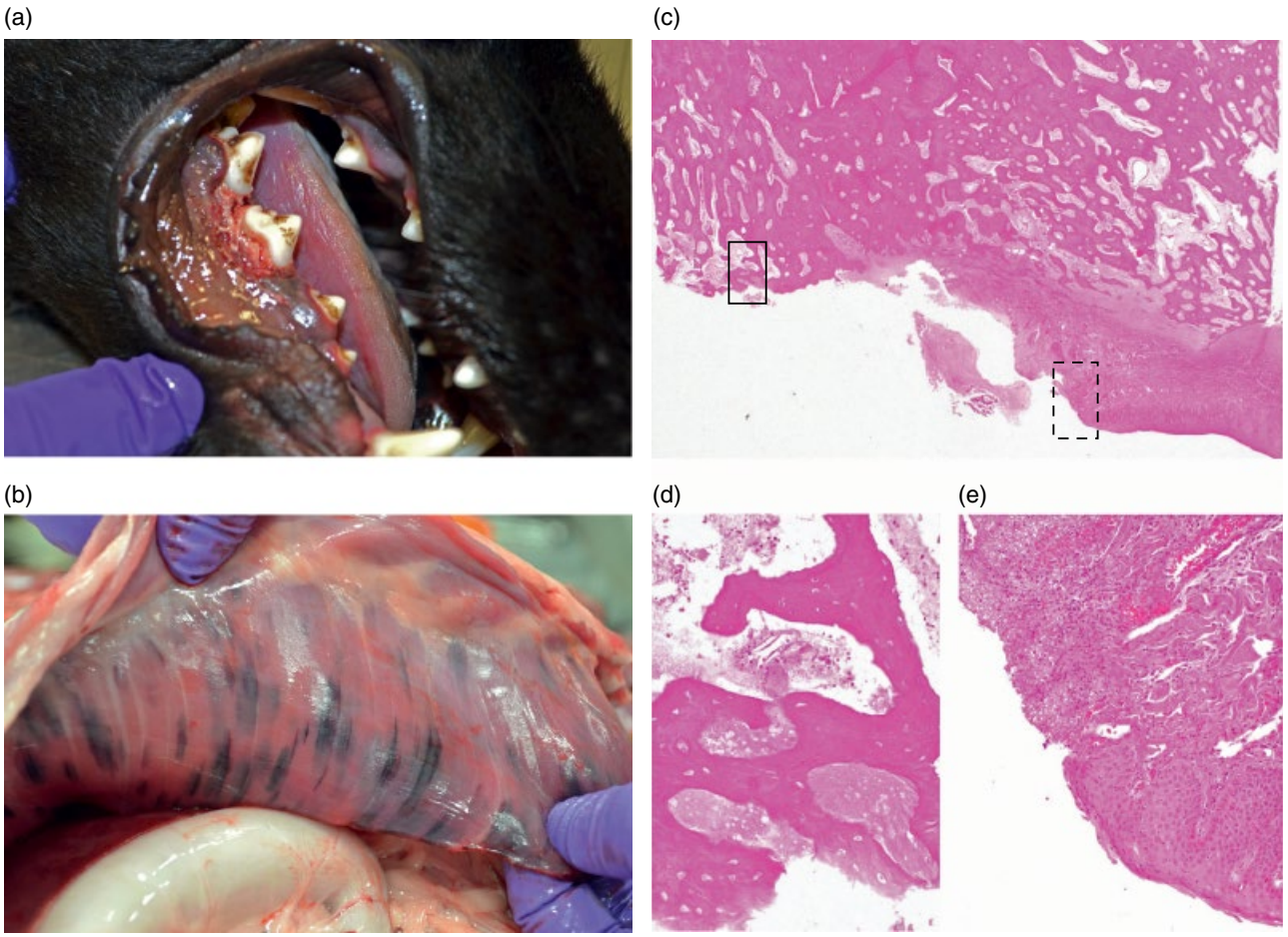


Figure 6.11 Gross and histologic images of lesions associated with sudden death due to electrocution (chewing on an electrical cord), young German shepherd dog. (a) The right mandible has an area, buccal to 407, where there is loss/necrosis of gingiva and alveolar mucosa with exposure of the underlying bone. (b) Linearly arranged hemorrhages were seen in other tissues, including linear hemorrhages in the diaphragm. (c) A histological section from the buccal surface of the mandible has attached gingiva over bone (lower right) adjacent to exposed bone (left). (d) The exposed bone lacks osteocytes within lacunae and the intertrabecular tissue has no differential staining, consistent with necrosis (solid line box from c). (e) The gingival epithelium is abruptly ulcerated at a site of necrosis (dashed box from c).

Trauma-associated cysts and *trauma-associated odontodysplasia* may result in a clinically obvious swelling of the jaw or may be detected incidentally upon evaluation of dental radiographs (Figures 6.12 and 6.13). Radiographs are indicated in a young dog when a tooth is absent or showing abnormally delayed/partial eruption. The affected dog may have a localized, non-painful swelling of the jaw. As is true for any odontogenic cyst, the swelling may be fluctuant.

Because dysplastic teeth can occur for reasons other than physical disruption, a history of trauma is required to make a firm etiological association. Trauma to a particular area of the jaw may cause dysplasia of more than one tooth. In these situations, the term "focal" or "segmental" odontodysplasia is preferred over "regional" since the latter implies a specific entity (discussed previously in Chapter 4 on developmental diseases).

6.2.2 Aneurysmal Bone Cyst (Pseudocyst)

Aneurysmal bone cyst is a rare lesion that is most likely to occur in young animals, presumably due to the effects of trauma on their immature and actively modeling bone. Since there is no epithelial lining, this lesion is more appropriately referred to as a pseudocyst. Intraosseous or subperiosteal hemorrhage, frequently secondary to trauma, contributes to formation of an expansile, fluid-filled lesion that eventually is encased within immature, proliferative bone. Aneurysmal bone pseudocyst has a distinctive histological appearance of the tissue that surrounds the blood-filled void. The granulation tissue that borders the lumen includes multinucleate giant cells and amorphous to globular material of unknown origin (Figure 6.14). Due to the

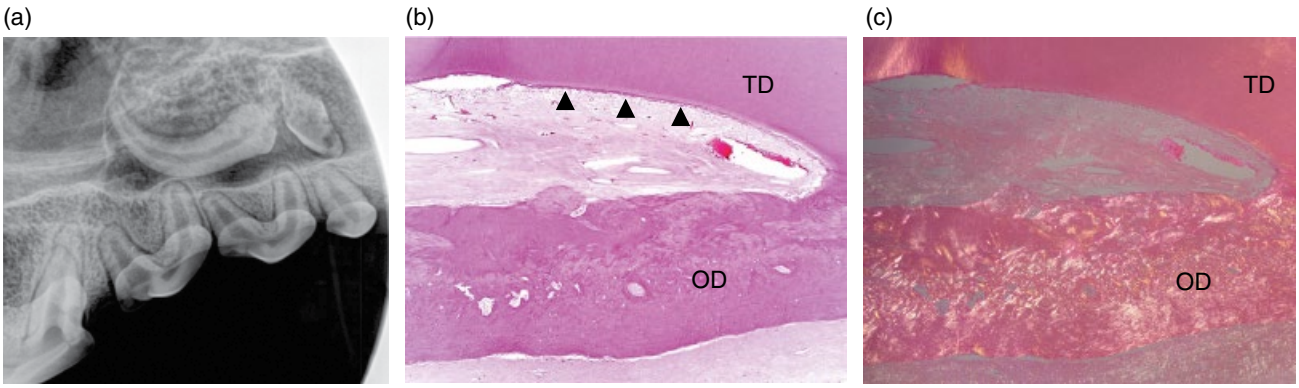


Figure 6.12 Radiographic and histologic images of dental trauma in a young dog. At approximately three to four month age, this puppy was bitten on the face by another dog but recovered and was visually normal at the time of adoption. (a) At eight months of age, dental radiographs were taken due to failed eruption of the right maxillary canine tooth (104). Radiographs revealed a malformed and impacted 104 that was located apical to the first through third maxillary premolars. (b) and (c) Histologically, one wall of the tooth is composed of organized tubular dentin (TD) with a row of odontoblasts (black arrowheads), while the other wall of the tooth is comprised of osteodentin (OD) with amorphous, fiber-rich matrix (polarized in c). Osteodentin in a young animal is usually a reparative response secondary to physical disruption of dentinogenesis, which was segmental in this tooth. *Source:* D. Hansen.

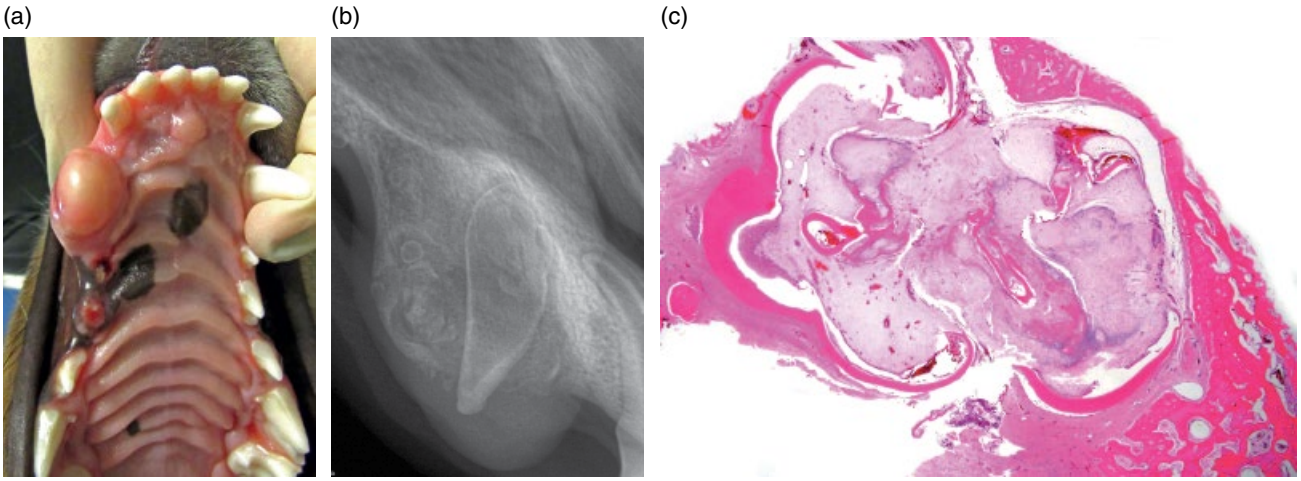


Figure 6.13 Gross, radiographic, and histologic images of dental trauma in a young dog. A six month old dog that had a traumatic injury when 12 weeks of age. (a) This clinical image shows a gingival mass at the site of absent 104 and incompletely erupted 105 and 106. (b) The radiograph demonstrates that the canine tooth is impacted, dysplastic, and associated with several adjacent smaller tooth-like structures (denticles). (c) An H&E photomicrograph shows a mass of disorganized dental pulp with dysplastic, coalescing denticles that is partially confined within the disrupted dental wall of a larger tooth, presumed original 104. The term "traumatic odontoma" could apply to this dysplastic lesion. *Source:* K. Feigin.

hemorrhagic content of the cavitated lesion, hemosiderin and cholesterol deposits may be seen.

6.2.3 Dentoalveolar Trauma

Trauma is an important cause of crown fracture and tooth avulsion. The largest study of dentoalveolar injuries in companion animals showed that young animals are at the greatest risk and that the most common type of trauma is altercation with another animal [6]. Root and crown fractures occurred at approximately the same frequency and maxillary teeth are more likely to be avulsed than mandibular teeth, possibly due to the lower density of maxillary bone [6]. The pathologies associated with tooth fracture are likely to be those that occur as secondary complications such as pulp exposure, pulpitis, and periapical periodontitis – each of these topics is discussed elsewhere in this textbook.

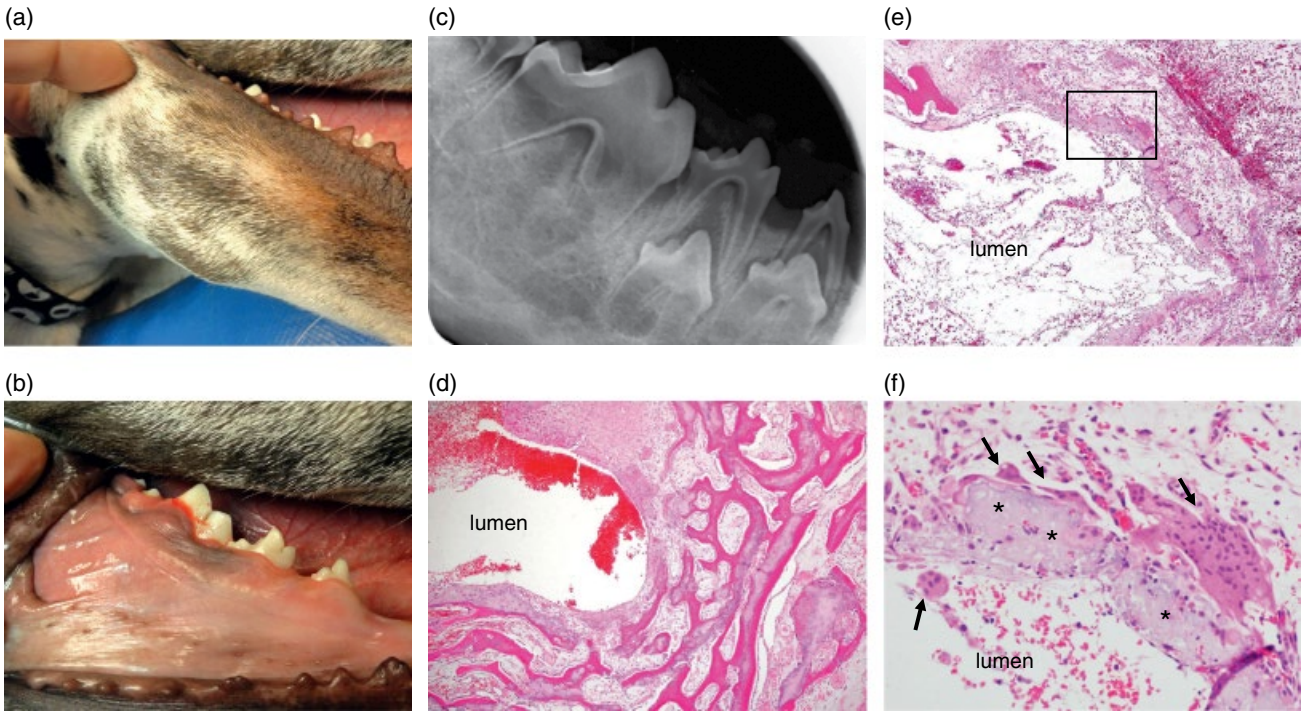


Figure 6.14 Gross, radiographic, and histologic images of an aneurysmal bone cyst, four month old, male great Dane puppy. (a) An aneurysmal bone "cyst" causes swelling of the caudal body of the right mandible that is centered on the 1st molar tooth (409) and bulges along the ventral rim of the mandible. (b) The overlying mucosa is intact and unaltered. (c) Radiograph shows a cyst-like lucency and defect in the apical mesial root of the 1st molar. (d) Histologically, the lumen of the intraosseous cavity contains blood and lesser amounts of protein and cellular debris. Some areas of the pseudocyst are surrounded by trabeculae of immature bone. (e) and (f) The inner surface has no epithelial lining; instead there is lightly basophilic, amorphous material (asterisks) with several multinucleated foreign body macrophages (arrows). *Source:* D. Hansen.

6.2.4 Fractures of the Jaw

A retrospective study of mandibular fractures in dogs showed that automobile trauma accounted for more than 50% of cases, while approximately 10% were iatrogenic occurring during dental extraction [7]. Malocclusion and osteomyelitis are frequent complications secondary to mandibular trauma in dogs [7].

Mandibular fractures in cats frequently affect the symphysis, with automobile trauma, falls and fights as the most common causes [8]. Cats that fall from a significant height generally land in such a way that there is impact of the face and this results in a triad of injuries that was named "high rise syndrome." While the triad of epistaxis, split hard palate, and pneumothorax is considered distinctive for this syndrome, affected cats often have other oral injuries including fractured canine teeth, fractured mandibular symphysis, and luxated mandible [9,10]. A study of rostral mandibular and maxillary fractures in horses found that soft tissue infection was one of the most common complications and draining tracts were associated with sequestration of necrotic bone (Figure 6.15) [11].

Callus formation and eventual modeling of new bone characterize the pathology of bone fractures. Radiographically and histologically, the initial proliferative phase features deposition of woven bone, fibrous tissue and cartilage (callus) that is centered on the fracture site. The amount of bone deposited and the deposition pattern is governed by stress forces, stability of the fracture, blood supply, and presence of infection and/or necrotic bone. Pathologists in diagnostic practice rarely have the opportunity to evaluate bone from a traumatic fracture. Bone from a suspected pathological fracture is much more likely to be biopsied for histopathology and/or culture. In these cases, evaluation for evidence of metabolic bone disease, infection/inflammation, or neoplasia is at least as important as characterizing the bony changes. Clinical history and radiographic features of a jaw fracture must be considered when interpreting the histopathology of these lesions since reactive bone can be very difficult to distinguish from well-differentiated neoplastic bone.

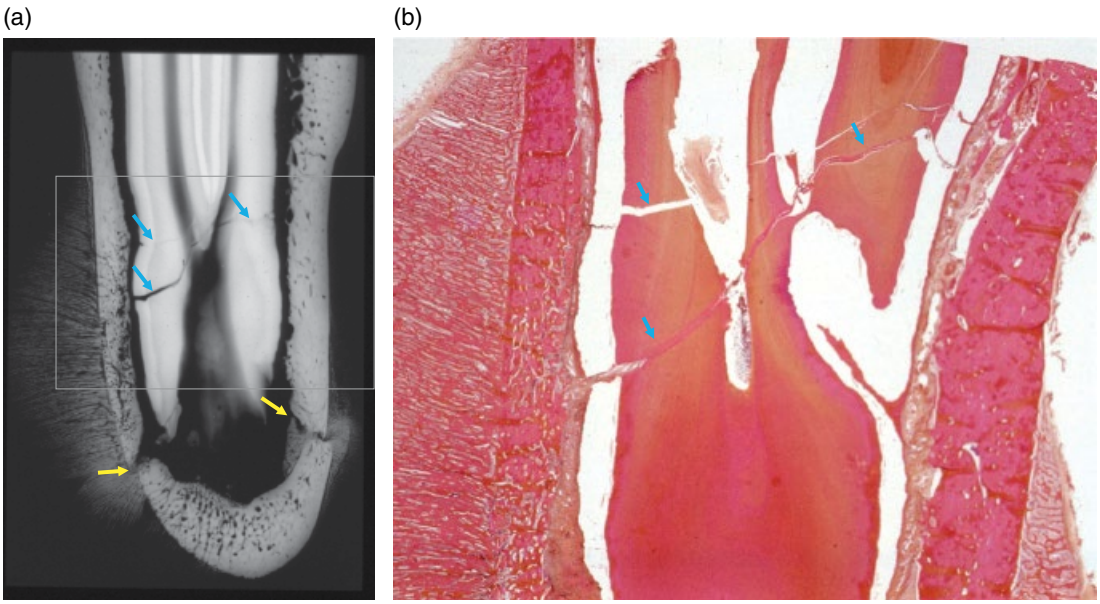


Figure 6.15 Mandibular radiograph and histologic image of dental and alveolar trauma in a horse. (a) Multiple complete fractures of the ventral cortex (yellow arrows) and apical cheek tooth (blue arrows) are present. (b) There is an organized peripheral periosteal reaction but minimal endosteal or alveolar bone proliferation. Where the tooth is fractured, there are thin seams of fibrovascular connective tissue (blue arrows). *Source:* R.R. Dubielzig, University of Wisconsin-Madison.

References

1 Lewis, J.R., Okuda, A., Shofer, F.S. et al. (2008). Significant association between tooth extrusion and tooth resorption in domestic cats. *J. Vet. Dent.* 25: 86–95.

2 Riehl, J., Bell, C.M., Constantaras, M.E. et al. (2014). Clinicopathologic characterization of oral pyogenic granuloma in 8 cats. *J. Vet. Dent.* 31: 80–86.

3 Gracis, M., Molinari, E., and Ferro, S. (2015). Caudal mucogingival lesions secondary to traumatic dental occlusion in 27 cats: macroscopic and microscopic description, treatment and follow-up. *J. Feline Med. Surg.* 17: 318–328.

4 Collen, E.B. and Mayer, M.N. (2008). Acute oropharyngeal effects of full-course radiation treatment of tumors of the head. *Can. Vet. J.* 49: 509–512.

5 Menzies, R.A., Reiter, A.M., and Lewis, J.R. (2012). Developmental tooth anomaly in a cat. *J. Vet. Dent.* 29: 112–113.

6 Soukup, J.W., Mulherin, B.L., and Snyder, C.J. (2013). Prevalence and nature of dentoalveolar injuries among patients with maxillofacial fractures. *J. Small Anim. Pract.* 54: 9–14.

7 Umphlet, R.C. and Johnson, A.L. (1990). Mandibular fractures in the dog. A retrospective study of 157 cases. *Vet. Surg.* 19: 272–275.

8 Umphlet, R.C. and Johnson, A.L. (1988). Mandibular fractures in the cat. A retrospective study. *Vet. Surg.* 17: 333–337.

9 Bonner, S.E., Reiter, A.M., and Lewis, J.R. (2012). Orofacial manifestations of high-rise syndrome in cats: a retrospective study of 84 cases. *J. Vet. Dent.* 29: 10–18.

10 Robinson, G.W. (1976). The high rise trauma syndrome in cats. *Feline Pract.* 6: 40–43.

11 Henninger, R.W., Beard, W.L., Schneider, R.K. et al. (1999). Fractures of the rostral portion of the mandible and maxilla in horses: 89 cases (1979-1997). *J. Am. Vet. Med. Assoc.* 214: 648–1652.

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7

Odontogenic Tumors

7.1 Approach to Odontogenic Neoplasms

As a result of their embryologic connection to tooth germ, odontogenic neoplasms are unique to the oral cavity, arising centrally from the jawbones or peripherally within the gingiva. These tumors can arise at any stage in the animal's life. For some, the diagnosis of odontogenic neoplasms is one of the most fascinating and exciting aspects of oral pathology. While it is true that the complex histologic patterns of odontogenic tumors can be exquisite, it is also true that many find these lesions to be frustrating. Individual odontogenic tumors can share substantial morphologic overlap with one another and the precise diagnosis often hinges upon the identification of key histologic features like the presence or absence of the mineralized dental matrices (dentin and/or enamel). Sometimes, the key diagnostic feature can be like a "a needle in a haystack"; as a result, the pathologist must have an index of suspicion and the perseverance to hunt for it.

Essentially all of the odontogenic tumor classification schemes devised over the past 150 years or so are structured around the process of tooth embryogenesis. As might be expected, these classification schemes originated with human lesions. For veterinary species, the classification of odontogenic lesions is still relatively young. It is only in the past 40 years that classification schemes were adapted to veterinary species (reviewed by Soukup and Bell) [1, 2]. In order to assign a correct diagnosis, it is imperative for the pathologist to have a reasonable understanding of the process of odontogenesis (see Box 7.1). Definitions of Odontogenesis; a review of Chapter 3 on odontogenesis may be in order.

As is true for any diagnostic process, odontogenic lesion classification depends upon the positive identification of *a collection of specific features*. In the diagnostic strategy described here, these specific features have been clustered into four tissue groups; each group is based upon the process of odontogenesis. These odontogenic tissue groups include: (i) odontogenic epithelium, (ii) mineralized dental matrices, (iii) dental papilla, and (iv) dental follicle (Figure 7.1). The goal of this diagnostic process is to determine if the lesion in question exhibits features consistent with one or more of these odontogenic tissue groups, which should inform the final diagnosis in a relatively straightforward manner. The devil, of course, is in the details.

7.1.1 Odontogenic Epithelium

As virtually all odontogenic tumors include proliferative odontogenic epithelium, the diagnostic process often begins with a single critical histologic observation: *is the proliferative epithelium within the lesion odontogenic in origin*? In certain situations, this seemingly simple question may be difficult to answer. What exactly *is* odontogenic epithelium? Pathologic odontogenic epithelium may appear as primitive, thin branching cords reminiscent of the dental lamina or may demonstrate some degree of enamel organ differentiation. Odontogenic epithelium will generally demonstrate *at least some* characteristic histologic/cytologic features that can be helpful in the diagnostic process [3]. The cardinal features of odontogenic epithelium include – (i) *palisading* of the basilar epithelium, (ii) the palisading epithelial cells have *antibasilar nuclei* (nuclei located at the apical pole) and (iii) the palisading cells can have a *basilar clear zone* within the cytoplasm. A fourth cardinal feature of odontogenic epithelium refers not to the palisading ameloblasts, but to the centrally located cells of the differentiated enamel organ – (iv) centrally, the odontogenic islands are (should be, may be …) comprised of polygonal cells with long intercellular desmosomal bridges *reminiscent of the stellate reticulum* (Box 7.2). Importantly, this fourth cardinal feature, the presence of stellate reticulum-like cells, *is not present* in the common canine acanthomatous ameloblastoma (CAA) lesion.

The pathologist should realize that *pathologic* odontogenic epithelium may not demonstrate all (or even

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Box 7.1 Definitions of Odontogenesis

Enamel organ – A complex structure of odontogenic epithelium that produces enamel. It includes the outer enamel epithelium, stellate reticulum and inner enamel epithelium. The enamel organ arises from the leading edge of the dental lamina.
Stellate reticulum – Enamel organ epithelial cells that occupy the central region between the inner and outer enamel epithelium. The stellate shape of these cells is due to exaggerated extracellular space and prominent intercytoplasmic processes.
Dental lamina – A specialized segment of the embryologic gingival epithelium that invaginates into the developing jaw and gives rise to the enamel organ.
Dental follicle – Ectomesenchymal tissue that immediately surrounds the enamel organ and dental papilla; this tissue gives rise to cementum, periodontal ligament and alveolar bone.
Dental papilla – Ectomesenchyme of the jaw that is *induced* by odontogenic epithelium and gives rise to dental pulp and odontoblasts.

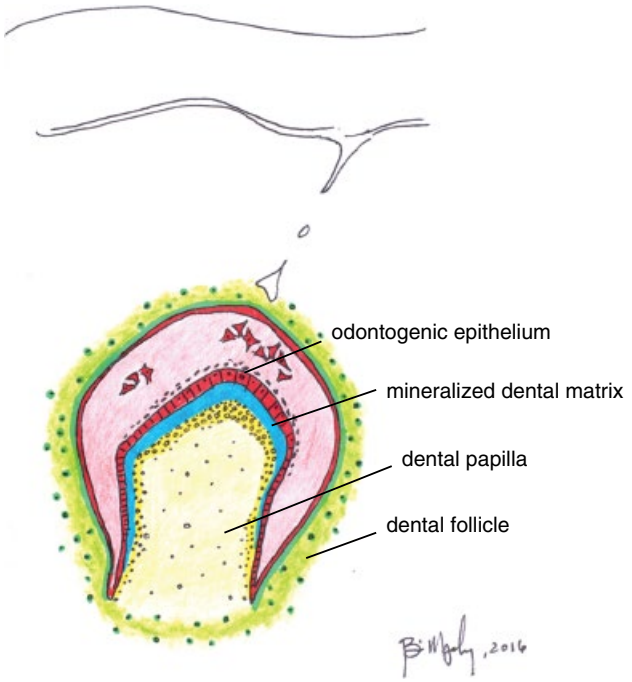


Figure 7.1 Diagram of the late bell stage of odontogenesis/tooth germs.

Box 7.2 Cardinal Histologic Features of Odontogenic Epithelium

i) Palisading of the basilar epithelium
ii) Palisading epithelial cells have *antibasilar nuclei*
iii) The palisading cells have a *basilar clear zone* within the cytoplasm
iv) Centrally, the odontogenic islands are comprised of polygonal cells with long intercellular desmosomal bridges *reminiscent of the stellate reticulum*

Box 7.3 Architectural Arrangement of Odontogenic Epithelium

i) Plexiform ribbons
ii) Round follicles
iii) Anastomosing trabeculae
iv) "Ink drop" structures

any) of the cardinal features. As a result, the rigid reliance on these cardinal features of odontogenic epithelium as one's only diagnostic criteria for identification is unwise. The definitive identification of odontogenic epithelium through immunohistochemical (IHC) means would be a useful tool for pathologists. Unfortunately, in veterinary species, IHC studies designed to specifically identify epithelium of odontogenic origin have been disappointing [4, 5].

As another diagnostic tool, some pathologists have found that the *architectural arrangement* of the epithelium itself can provide a useful clue to its odontogenic origin. Odontogenic epithelium typically adopts one of four architectural arrangements: thin plexiform ribbons, round follicles, broad anastomosing trabeculae or arranged as unique "ink drop" structures (Box 7.3 and Figure 7.2). Although some of these epithelial architectures can be found in other pathologic lesions (e.g. plexiform ribbons in squamous cell carcinoma) others are essentially pathognomonic for odontogenic epithelium ("ink drop" structures). Odontogenic epithelium arranged as plexiform ribbons (dental lamina-like) or spherical follicles (odontogenic rest-like) often lack some or all of the cardinal odontogenic features, while anastomosing trabeculae and "ink drop" structures generally exhibit most or all of the cardinal features. It is also true that odontogenic proliferative lesions often demonstrate multiple architectural arrangements of the epithelium within a *single lesion*. As for nomenclature, lesions comprised of proliferative odontogenic epithelium often (but not always) are named with the prefix "amelo-" (as in *ameloblastoma*).

One other general feature of pathologic odontogenic epithelium that the pathologist should be aware of is a tendency for central degeneration with subsequent cyst formation. In odontogenic cysts, the bordering epithelium often undergoes a metaplastic change to a stratified squamous epithelium that bears little or no

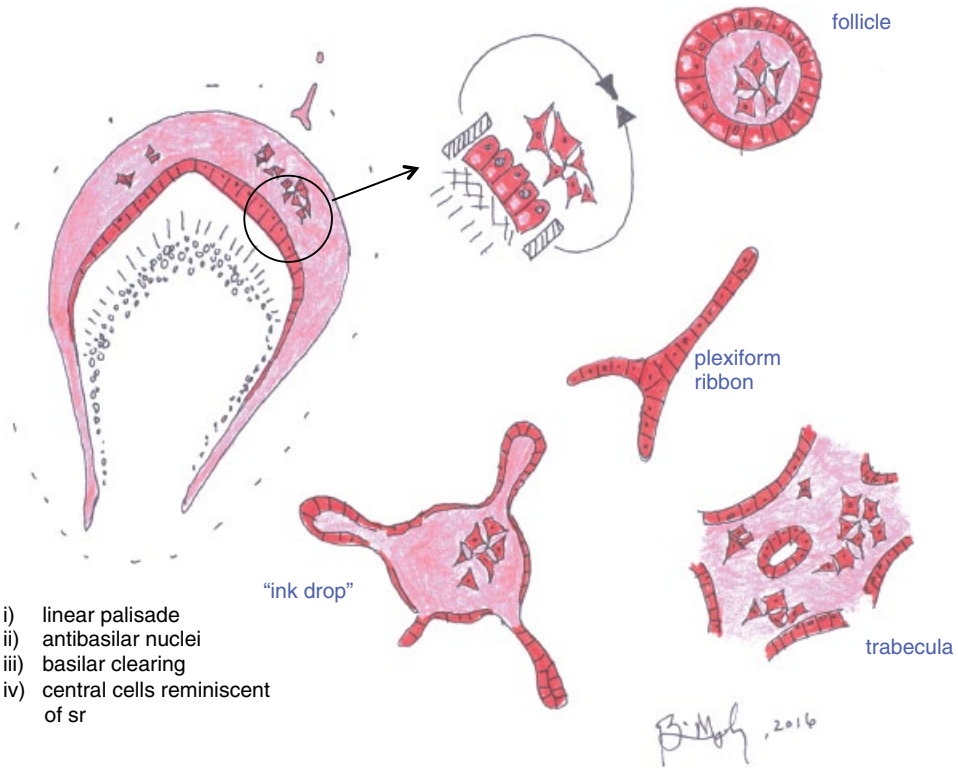


Figure 7.2 Diagram of the cardinal histologic features and architectural shapes of odontogenic epithelium.

resemblance to the parent odontogenic tissue. Cyst formation occurs in many odontogenic tumor types and can be a helpful "separating criterion" from confounding non-odontogenic epithelial tumors, such as squamous cell carcinoma. Epithelial lesions lacking odontogenic features that arise centrally within the tooth-bearing aspect of the jaws are presumed to have an odontogenic origin.

7.1.2 Mineralized Dental Matrices

The odontogenic mineralized matrices (aka dental or odontogenic matrix) can be derived from either the ectoderm (ameloblasts producing enamel) and/or ectomesenchyme (odontoblasts producing dentin). It is important to note that when we speak of these odontogenic matrices we are *not* referring to cementum or woven bone, which are associated with the dental follicle. In odontogenic proliferative lesions, dentin is identified much more frequently than enamel. Recall that the process of *reciprocal induction* necessitates ameloblasts to signal odontoblasts to make dentin which in turn signal ameloblasts to make enamel (there must be dentin for there to be enamel). As a result, pathologic lesions featuring ameloblasts alone are incapable of producing enamel. Lesions featuring odontogenic matrix production *must have* an odontoblastic component, and often the matrix that is produced is dentin. Proliferative lesions characterized by the production of the mineralized dental matrices often have the term "odonto-" within the lesion name. If only one type of dental matrix is produced, it will be dentin; enamel will not be present without dentin due to the process of reciprocal induction. It is also true that enamel-based matrix, being of high mineral content, is less likely to persist in histologic preparations due to the demineralization step during tissue processing.

In order to appropriately cut sections, mineralized dental matrix generally must be decalcified. The resulting odontogenic matrix is typically pink (dentin-based), although it may be intermixed with purple-staining matrix (enamel-based) or even amphophilic-gray staining material (intermingled dentin/enamel). The pathologist needs to be able to histologically differentiate odontogenic matrix from other eosinophilic staining substances such as amyloid, fibrin, keratin, cementum, or the osteoid of woven bone. The odontogenic matrices also may be difficult to distinguish from matrix components of tissue derived from the dental papilla and dental follicle (discussed below). Fortunately, the odontogenic matrix within pathologic lesions is often arranged in characteristic *linear, serpentine, or ring-shaped structures* that partially recapitulate odontogenesis. Frequently, the odontogenic matrix will be palisaded by a row of epithelial cells

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(ameloblasts) or aggregating polygonal shaped mesenchymal cells (odontoblasts, see *reciprocal induction* in Odontogenesis).

One other note of caution, do not expect that the lesional dentinal matrix will necessarily demonstrate characteristic dentinal tubule formation (most often it does not). Atubular dentin has been referred to as *osteodentin* – a rapidly formed type of tertiary dentin that is present in some pathologic lesions. As the name suggests, osteodentin may entrap odontoblasts, resulting in a histologic appearance that mimics bone or cementum.

7.1.3 Dental Papilla

Differentiation of the tissues of the dental papilla (aka dental pulp or odontogenic pulp) is induced by the presence of the enamel organ (palisading ameloblasts) during odontogenesis. In neoplastic lesions, odontogenic pulp often appears as a loose, relatively homogeneous conglomerate of variably dense spindle-shaped mesenchymal cells with bland cytologic features embedded within a basophilic myxoid stroma (due to the production and extracellular deposition of hygroscopic proteoglycan molecules). In some lesions, the extracellular matrix of the dental papilla is not basophilic and stains poorly or has a "clear" histologic appearance. Again, this is likely the result of hygroscopic proteoglycan molecules creating the impression of relatively edematous extracellular matrix. Embedded mesenchymal cells of the dental papilla are often widely spaced but the density and arrangement of these cells is variable.

In some pathologic lesions, it is also possible for the pulp ectomesenchyme to lose its basophilic (or clear) myxomatous matrix, adopting a more fibrous, dense, collagen-rich appearance. When the term "fibro-"is used in odontogenic lesions, the pathologist should think *dental papilla-derived*, as in the lesion ameloblastic *fibro*-odontoma. The ectomesenchyme of the dental papilla must be histologically differentiated from the periodontal ligament and simple fibrovascular connective tissue. As a result of this morphologic plasticity, the histologic identification of dental pulp tissue in oral lesions can be challenging. In some odontogenic lesions, the only evidence of pulp ectomesenchyme is a jumbled aggregate of polygonal cells forming a loose palisade-like structure organized along mineralized dental matrix. The presence of the dentinal matrix allows the inference that these cells are odontoblasts.

Cytokeratin (panCK AE1/AE2) and vimentin-based IHC assays can be helpful in distinguishing between these various tissues. All of the ectomesenchymal derived odontogenic pulp tissue is vimentin positive. Although the embryonic enamel organ (stellate reticulum and palisading ameloblasts) has been characterized as expressing *both* cytokeratin and vimentin, many lesions comprised of odontogenic epithelium are CK positive and vimentin negative. In the authors' experience with pathologic tissues from dogs, cats, horses, cattle, and rabbits, the use of panCK and vimentin IHC assays generally allow one to accurately distinguish between odontogenic epithelium and the induced ectomesenchyme of the dental papilla.

7.1.4 Dental Follicle

The ectomesenchymal mantle of the odontogenic follicle gives rise to the periodontal ligament, cementum, and encasing alveolar bone. Multipotent mesenchymal cells of the follicle are capable of producing three different extracellular matrices – (i) cementum (produced by cementoblasts), (ii) osteoid (produced by osteoblasts) and (iii) collagen I-rich connective tissue (along with other biomolecules produced by fibroblasts). The bone, cementum and the periodontal ligament sandwiched between them comprise the gomphosis, which anchors the tooth into the adjacent alveolar bone or socket.

The periodontal ligament has characteristic histologic features – variably cellular angular fibroblast-like cells amidst a dense finely fibrillar collagen background, elastin fibers, other specialized fiber types and regularly positioned empty blood vessels. The collagen-based extracellular matrix of the periodontal ligament *does not* form large robust matrical bundles. Periodontal ligament must be distinguished from the connective tissues of the gingival lamina propria and dental papilla, reparative fibrous tissue (fibrosis), and neoplastic fibroblasts of the oral cavity (fibroma and fibrosarcoma). Distinguishing between these various mesenchymal tissues can be challenging.

7.1.5 Induction

Neoplasia occurs as the result of genetic perturbations within a particular tissue, likely initiating within the genome of a single cell. How then, do fantastically complex odontogenic tumors, comprised of a dizzying array of tissue types, arise? Do multiple tissues of the developing tooth germ simultaneously become neoplastic? Although there is a chance that such an event could take place (e.g. collision tumor), the more likely etiopathogenesis of complicated multilineage odontogenic tumors is through the process of *induction*.

Induction is a physiologic process of tissue and organ formation whereby the development of one tissue influences the fate of another (Figure 7.3). This influence is mediated through cell-to-cell signaling. Induction plays a critical role in tooth formation as the presence of odontogenic epithelium-derived ameloblasts *induces* the aggregation, proliferation, and differentiation of the

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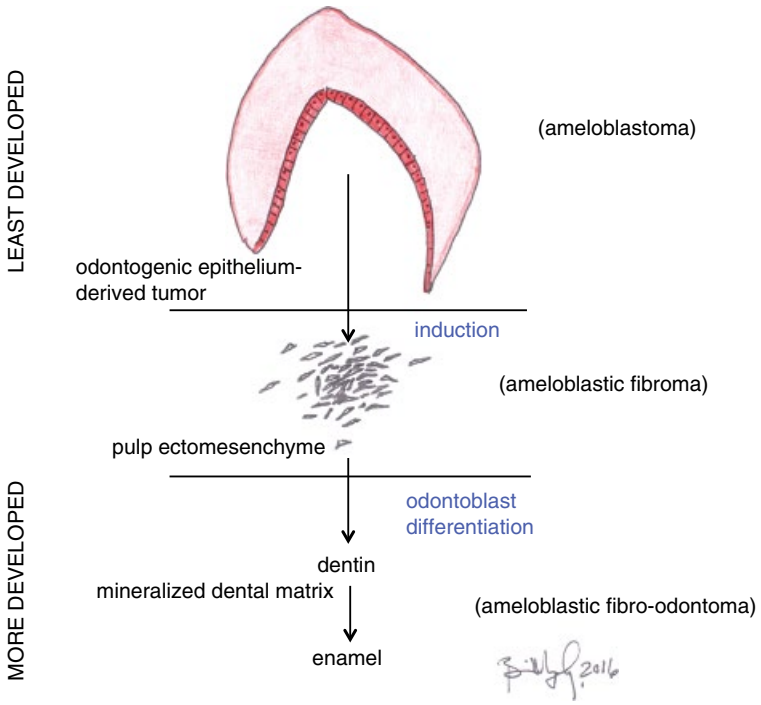


Figure 7.3 Diagram of the process of odontogenic induction.

subjacent ectomesenchymal cells to become the dental pulp/papilla. Nomenclature wise, the general class of odontogenic tumor is determined by *whether or not induction is present*.

This inductive process is similar to what takes place in a scirrhous (desmoplastic) carcinoma. In scirrhous carcinoma, neoplastic epithelium *induces* the neighboring mesenchyme to proliferate into a scar-like stroma, which provides a blood supply and support to the epithelial (neoplastic) component of the tumor. There is evidence that this inductive process results in epigenetic changes in the genome of the mesenchymal cells (fibroblasts), resulting in their proliferation and stroma formation. However, in odontogenic neoplasms, the tumor-associated mesenchyme is capable of becoming so much more than simple fibrous tissue!

Most (but not all) odontogenic tumors involve a component of odontogenic epithelium. In some lesions, the neoplastic odontogenic epithelium *may not* be capable of inducing the differentiation of the ectomesenchyme of the dental papilla. Instead, the epithelium may induce the formation of a simple fibrovascular stroma lacking the histological features of odontogenic pulp ectomesenchyme. Such is the case for ameloblastoma. However, if the neoplastic odontogenic epithelium *is capable* of inducing the development of dental papilla-like ectomesenchyme, the resulting lesion is called a *mixed tumor,* such as ameloblastic fibroma (AF). If the differentiated dental papilla further develops into odontoblasts that are capable of synthesizing and secreting mineralized dental matrix, the odontogenic lesion includes the term *odontoma* in its name. Once dental matrix is formed, it can influence the neoplastic ameloblasts to produce enamel through the process of reciprocal induction. It is by this winding chain of events that the various odontogenic tumors are derived.

7.1.6 Diagnosing Odontogenic Neoplasms – the Process

The classification systems for both human and veterinary odontogenic lesions are ever in revision. For veterinary species, two of the most widely utilized classification systems are the 2003 WHO Histological Classification of Tumours of Odontogenic Origin in Domestic Animals, and the 2005 and 2017 WHO Classification of Tumours – Pathology & Genetics Head and Neck Tumours: Odontogenic Tumours (humans) [6–8]. Recent reviews have concluded that the 2005 human classification scheme may have the most utility for animals. While the 2003 WHO classification system for animals includes tumors that are specific to animals, it fails to accommodate some of the uncommon and complex odontogenic tumors that do occur in animals [1]. To date, not all of the odontogenic tumors identified in humans have been identified in veterinary species (e.g. *adenomatoid ameloblastoma*). It is also true that not all of the odontogenic tumors described in veterinary species have been identified in humans! Thus, for the moment, none of these classification systems is perfect.

The odontogenic tumor classification system proposed in this textbook is based upon all three of these World Health Organization systems, but has been organized to reflect the diagnostically relevant germinal tissues

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described above: odontogenic epithelium, mineralized dental matrices, dental papilla and dental follicle. Because they share many of the same features, and are very rare, malignant versions of odontogenic tumors have been classified along with their benign counterparts. This organizational scheme facilitates the diagnostic algorithm described below.

The proposed diagnostic algorithm goes something like the following for a suspect odontogenic tumor. The pathologist begins by asking a question such as – "is odontogenic epithelium present in the lesion"? If the answer is *yes*, then the lesion "resides" within or at the interface with the *red box* in Figure 7.4. The pathologist then asks a series of additional questions. – "are dental papilla-derived tissues, mineralized dental matrices, or dental follicle-derived tissues present in the lesion"? If the answer to any of these questions is *yes*, the identity (categorization) of the odontogenic lesion in question resides *within or interfacing* with the appropriate yellow (dental papilla), blue (dental matrix) or green boxes (dental follicle) in Figure 7.4. Many odontogenic epithelial tumors (red box) also have a dental follicle-derived fibrous stromal component (green box).

If the pathologist decides that the lesion in question is comprised of odontogenic epithelium, dental papilla and ectomesenchyme of the dental follicle, *but not* mineralized dental matrices, the lesion identity lies at the interface of the red, yellow, and green boxes. For veterinary species, lesions included in this group are AF and feline inductive odontogenic tumor (FIOT). If the tissue was derived from a cat, especially if associated with a maxillary canine tooth (as is typically the case) the diagnosis is likely FIOT. This is an example of how to incorporate the clinical features of the case into the proposed diagnostic algorithm.

The diagnosis of odontogenic tumors in actual practice is rarely this easy.

Keep in mind that odontogenic tumors are generally rare in veterinary species, with the exception of two canine lesions: CAA and the peripheral odontogenic fibroma (aka FEPLO/POF). Also, it is quite possible that the diagnostically useful odontogenic tissues may represent a relatively minor component of the overall lesion. Being absolutely sure that the lesion in question

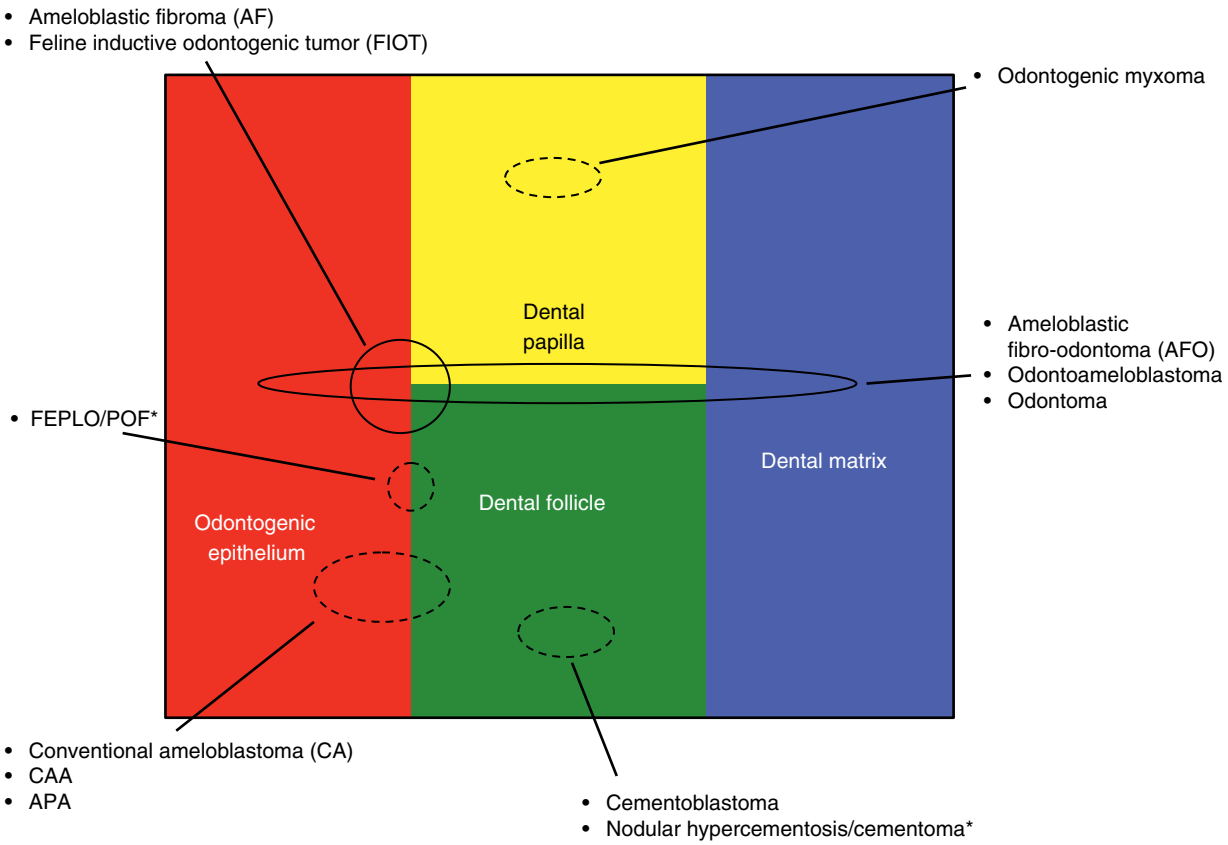


Figure 7.4 Odontogenic tumor classification method. Solid circles represent tumors *with odontogenic induction* while dashed circles/ellipses are tumors lacking odontogenic induction.
Note: Rather than odontogenic tumors, the authors consider cementoma (nodular hypercementosis) and FEPLO/POF to be reactive/proliferative mass lesions that originate from tissues of the odontogenic follicle. See Chapter 10 on tumor-like proliferative lesions.

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demonstrates a particular odontogenic feature is sometimes more difficult and less straightforward than it may seem to the uninitiated. Nonetheless, a number of pathologists have used this strategy for the diagnosis of odontogenic tumors for more than a decade with some degree of success.

It is important to note that there likely remain some unclassified and unreported odontogenic lesions out there that do not conveniently fit into this diagnostic framework; some odontogenic tumors simply defy current classification schemes. A strategy adopted by some pathologists is to diagnose the most histologically aggressive aspect of the lesion and to attempt to convey the complexity of the lesion in the description and comment portion of the pathology report. Providing a list of differential diagnoses to the submitting clinician is almost always a good plan. It is a wise pathologist who declares a degree of uncertainty in the face of these difficult problems. Biology being biology, chimeric, or hybrid lesions do exist!

Odontogenic tumors occur on an overlapping spectrum. At times, assigning a specific diagnosis can be somewhat subjective as multiple entities may share the same or similar histologic features. Bear in mind that the particular sections examined will dictate the morphologic diagnosis, and these may or may not represent the *in vivo* lesion well.

References

1 Bell, C.M. and Soukup, J.W. (2014). Nomenclature and classification of odontogenic tumors- part II: clarification of specific nomenclature. *J. Vet. Dent.* 31: 234–243.

2 Soukup, J.W. and Bell, C.M. (2014). Nomenclature and classification of odontogenic tumors- part I: historical review. *J. Vet. Dent.* 31: 228–232.

3 Regezi, J.A., Sciubba, J.J., and Jordan, R.C.K. (2008). *Oral Pathology: Clinical Pathologic Correlations*, 5e. St. Louis, Mo: Saunders/Elsevier.

4 Arzi, B., Murphy, B., Nemec, A. et al. (2011). Expression of cytokeratins in the epithelium of canine odontogenic tumours. *J. Comp. Pathol.* 145: 345–351.

5 Fulton, A., Arzi, B., Murphy, B. et al. (2014). The expression of calretinin and cytokeratins in canine acanthomatous ameloblastoma and oral squamous cell carcinoma. *Vet. Comp. Oncol.* 12: 258–265.

6 Head, K.W. and Armed Forces Institute of Pathology (U.S.), American Registry of Pathology., WHO Collaborating Center for Worldwide Reference on Comparative Oncology (2003). *Histological Classification of Tumors of the Alimentary System of Domestic Animals*. Washington, DC: Published by the Armed Forces Institute of Pathology in cooperation with the American Registry of Pathology and the World Health Organization Collaborating Center for Worldwide Reference on Comparative Oncology.

7 El-Naggar, A.K., Chan, J.K.C., Rubin Grandis, J. et al. (2017). *WHO Classification of Head and Neck Tumours*. Lyon: International Agency for Research on Cancer.

8 Barnes, L., UniversitätsSpital Zürich, and Departement Pathologie., International Academy of Pathology., World Health Organization., International Agency for Research on Cancer (2005). *Pathology and Genetics of Head and Neck Tumours*. Lyon: IARC Press.

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7.2 Tumors Composed of Odontogenic Epithelium and Fibrous Stroma

The most commonly diagnosed odontogenic tumors in veterinary species are those that are principally comprised of odontogenic epithelium. This group includes conventional ameloblastoma (CA), canine acanthomatous ameloblastoma (CAA), and amyloid producing ameloblastoma (also known as calcifying epithelial odontogenic tumor/amyloid producing odontogenic tumor). Importantly, *this group of tumors are not considered to be mixed tumors*, as their pathogenesis does not involve the induction of ectomesenchyme of the dental papilla. However, the neoplastic odontogenic epithelium is supported by a fibrovascular connective tissue-like stroma, thought to be derived from the dental follicle, which provides the blood supply to nourish the neoplastic epithelium.

Although it is not (currently) possible to know with certainty if the tumor-associated stroma is derived from tissues of the dental follicle, in most cases, the stroma tends to demonstrate histologic features of the periodontal ligament. Most importantly, this fibrovascular stroma lacks the histological features of ectomesenchyme of the dental papilla. As a result, these tumors are not considered to be mixed tumors (that is, they do not demonstrate odontogenic induction). Although the proportion of neoplastic epithelium to supportive stroma can vary, the bulk of the tumor mass is epithelial, not mesenchymal.

Box 7.4 Differential Diagnoses for Conventional Ameloblastoma

Canine acanthomatous ameloblastoma
Ameloblastic carcinoma
Squamous cell carcinoma
FEPLO/POF
Amyloid producing ameloblastoma
Ameloblastic fibroma
Odontogenic cysts

7.2.1 Conventional Ameloblastoma (CA)

Ameloblastoma is a locally aggressive oral tumor that has been recognized for over 150 years. It is an epithelium-derived odontogenic tumor that is relatively commonly diagnosed in adult humans, but is uncommonly identified in veterinary species. Older terms for ameloblastoma that are no longer in favor include *adamantinoma* (adamas from Greek-"hard") and *enameloblastoma*. Ameloblastoma has been diagnosed in a wide variety of species including humans and other primates, dogs, cats, horses, new world camelids, sheep, rabbits, various rodents, a black rat snake (*Pantherophis alleghaniensis*), and Chinook salmon (*Oncorhynchys tshawytscha*). Many of the earlier reports of ameloblastoma (or adamantinoma) in cattle have subsequently been reclassified as the mixed tumor ameloblastic fibroma. In companion animal species, ameloblastoma has most often been diagnosed in dogs. The authors of this textbook prefer the term conventional ameloblastoma, (CA), in companion animal species, as this term highlights the similarity with the human counterpart and distinguishes the lesion from the more common CAA.

CA is thought to arise from transformed odontogenic epithelium – the enamel organ, dental lamina, odontogenic rests, reduced enamel epithelium, and/or the lining epithelium of odontogenic cysts. The majority of these tumors present as firm jaw swellings arising from within the mandible/maxilla (central or intraosseous CA), and less often as a solitary gingival mass (peripheral or extraosseous CA). Bear in mind that masses within the gingival mucosa may well have originated within the jaw. Maxillary CA can also extend into the nasal cavity or sinuses. Although considered to be benign, CA lesions are progressive, expansile, and can be associated with extensive bone destruction. In people, spread into the adjacent soft tissues is considered to be highly unusual and suggests the possibility of ameloblastic carcinoma (ACa) (see below). The etiology of, or risk factors for, CA in animals are currently unknown.

CA typically exhibits all four of the cardinal histologic features of odontogenic epithelium, although within a lesion, these features may be only sporadically evident. In dogs, CA can be histologically confused with the much more common CAA, as these lesions are microscopically similar. One of the distinguishing features separating CA from CAA is the character of the central epithelial cells. Recall that one of the cardinal features of odontogenic epithelium is that centrally, the odontogenic epithelial islands are comprised of stellate cells with long intercellular desmosomal bridges reminiscent of the stellate reticulum of the enamel organ (see Approach to odontogenic neoplasms). While these long spider web-like cell to cell extensions are readily identifiable in CA lesions (Figures 7.5 and 7.6), they *are not a feature of CAA*. Rare to scattered mitotic figures can be found in CA lesions and are of no particular prognostic significance.

The neoplastic epithelium in CA lesions can adopt any of the previously described architectural arrangements that were previously described for odontogenic epithelium: follicles, plexiform ribbons, interlinking trabeculae, and/or "ink drop" structures (Approach to odontogenic neoplasms). Frequently, CA lesions demonstrate a variety of architectural structures within a single lesion. CA lesions exhibiting follicles and branching plexiform ribbons may be comprised of plump, peripheralized epithelial cells with few, central, closely packed, "non-acanthomatous" spindle-shaped cells. Focal to multifocal keratinization of the odontogenic epithelium may or may not be present in

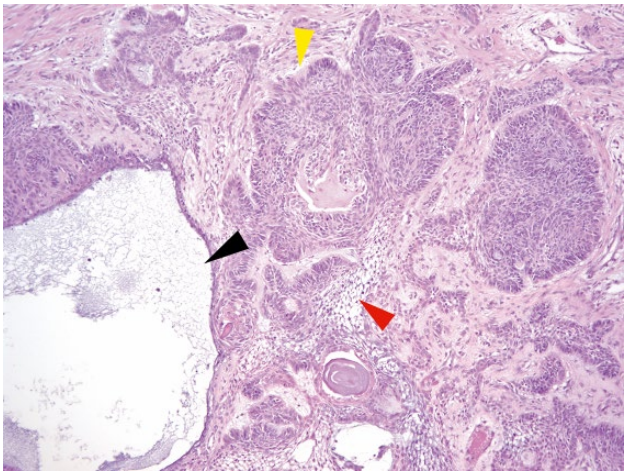


Figure 7.5 Histologic image of a conventional ameloblastoma of the mandible, 10-year-old Australian shepherd dog (same lesion as Figure 7.7). Palisading epithelial cells with antibasilar nuclei (yellow arrowhead) form "ink drop"-like architectural structures with bosselated margins. The lesion also demonstrates cyst formation (black arrowhead) and centrally located stellate reticulum-like cells (red arrowhead).

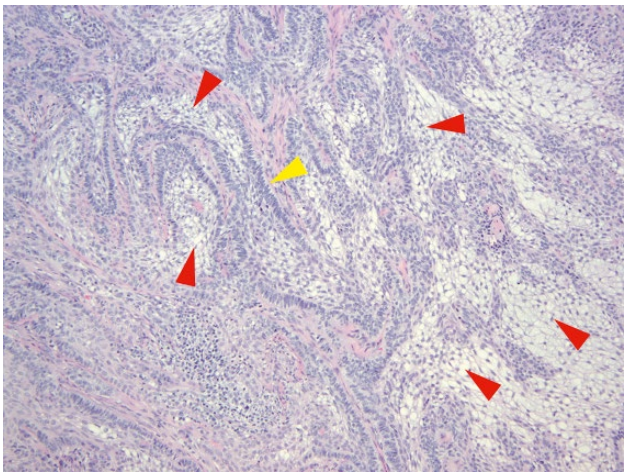


Figure 7.6 Histologic image of a conventional ameloblastoma in a 10-year-old MN DSH cat. This odontogenic tumor demonstrates the cardinal features of odontogenic epithelium such as palisading epithelial cells with antibasilar nuclei (yellow arrowhead) and centrally located stellate reticulum-like cells (red arrowheads). *Source:* J. Wood, Veterinary Diagnostics, Davis, CA.

ameloblastomas, and keratin, if present, may become calcified through the process of dystrophic mineralization. In prior classification schemes, whether or not an ameloblastoma exhibited keratinization was considered to be a diagnostically relevant feature. Such tumors were previously referred to as *keratinizing ameloblastoma*. However, both the 2003 (veterinary species) and the 2005 and 2017 (human) WHO histological classification systems have eschewed this subclassification [9–11]. Mineralized keratin in an ameloblastoma needs to be distinguished from the mineral present within amyloid-producing ameloblastoma, and the epithelial lining of odontogenic cysts. This histological distinction can be facilitated by demineralizing the paraffin tissue block through a brief treatment with formic acid (*face decalcification,* see Appendix). Whether CA exhibits keratinization is not particularly prognostic, but keratinization can be a problematic feature for the pathologist as it may create diagnostic confusion with the more common oral squamous cell carcinoma (OSCC).

Careful examination of the neoplastic epithelium for evidence of odontogenic features is generally sufficient to distinguish between CA and OSCC. However, the pathologist needs to be wary of ACa (below), as some types of OSCC lesions are histologically similar. CA lesions may or may not be associated with islands of metaplastic osteoid and/or mineralized bone formation within the adjacent stroma. Cystic degeneration within the neoplastic epithelium is a relatively common finding in ameloblastomas arising in both veterinary species and people (Figures 7.7 and 7.5). Rarely, the neoplastic epithelium of the ameloblastomas may be pigmented.

(a)



(b)

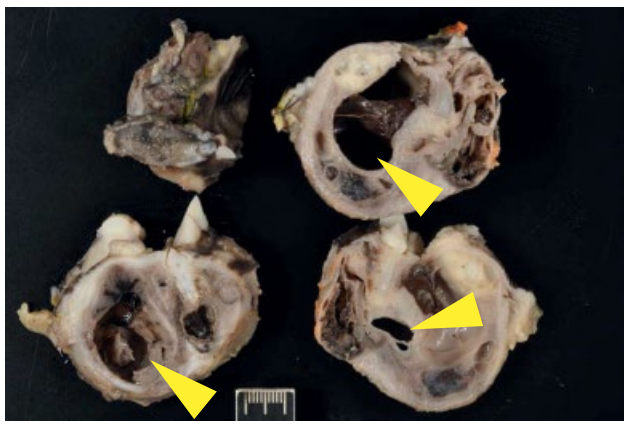


Figure 7.7 Conventional ameloblastoma of the mandible, 10-year-old Australian shepherd dog. (a) Gross image of affected mandible and (b) serial transverse sections of the lesion demonstrating cystic spaces (yellow arrowheads). *Source:* H.O. Aina, University of California, Davis.

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In human oral pathology, ameloblastomas have been subdivided into four different *biological subtypes*: (i) conventional (also known as classic intraosseous), (ii) extraosseous/peripheral, (iii) unicystic, and (iv) metastasizing ameloblastoma [11]. In people, these four subtypes have discrete biological outcomes, justifying the use of these terms. In human lesions, multiple *histologic variants* of ameloblastoma have also been described, including follicular, plexiform, acanthomatous, basaloid, granular cell, and desmoplastic ameloblastomas. Follicular ameloblastomas are the most common histologic variants identified in human patients [12]. Unlike the biological subtypes, histologic variants in people have not been associated with different outcomes. Whether veterinary species actually have biological subtypes of ameloblastoma associated with different outcomes remains to be determined.

CA occurs only rarely in cats [13] (Figure 7.6). Because oral SCC is such a common lesion in cats, the pathologist should think very carefully before assigning a diagnosis of CA in this species. Odontogenic features should not be present in SCC. Interestingly, circumscribed lesions in the cheek tissue of rabbits have been described to be histologically consistent with ameloblastomas [14]. The authors have identified at least three additional cases of ectopic ameloblastoma-like lesions in the buccal mucosa of rabbits (unpublished observations, Figure 7.8). Whether these unusual buccal lesions in rabbits arise from ectopic tooth germ tissue (choristoma-like lesion) or from altered/neoplastic dermal adnexa (adamantinoid trichoblastoma) is not currently known.

7.2.1.1 Clinical Features

CA most often presents as a focal swelling and expansion within the jawbone of middle-age dogs. CA appears to occur more often in the maxilla, rather than the mandible as in CAA. Because of the typical cystic nature, the lesion often possesses fluctuant areas covered by dark purple-blue mucosa. Imaging features are typically consistent with a cyst (central radiolucency with corticated border) and more often have a multicystic/ multilocular pattern with cortical expansion. While clinical and imaging features are distinct, the overall biological behavior and prognosis are similar to CAA. As such, the treatment recommendation is similar – surgical excision with 1 cm margins. The prognosis with clean surgical margins is good to excellent, and recurrence after surgery is unlikely.

7.2.1.2 Ameloblastic Carcinoma and Malignant Ameloblastoma

ACa is an uncommon tumor in people and has only rarely been reported in dogs [15] and a horse [16]. ACa retains *some features* of ameloblastic differentiation along with additional cytologic features of malignancy – cellular pleomorphism, anaplasia, hyperchromatism, high cytoplasmic to nuclear ratio, increased mitotic rate, necrosis, loss of odontogenic features, and epithelial invasion through the basement membrane.

ACa sits at the diagnostic/histologic interface between ameloblastoma and squamous cell carcinoma (Figure 7.9). Essentially, ACa is a SCC with some odontogenic features. As these two lesions share multiple common histologic features, the pathologist may find it difficult to definitively

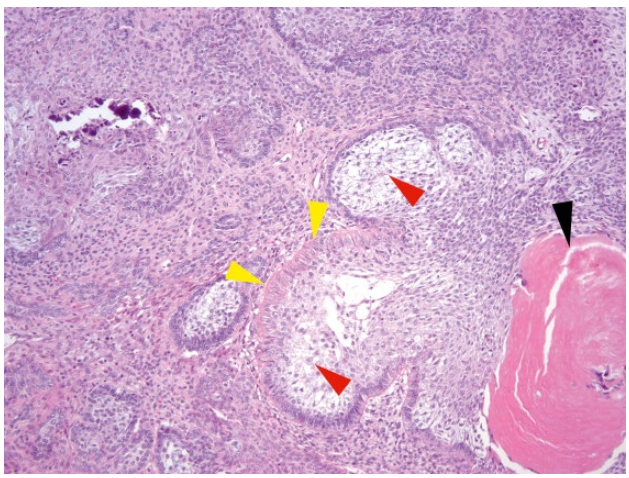


Figure 7.8 Histologic image of an ectopic ameloblastoma-like lesion, buccal mucosa of an eight-year-old spayed female rabbit. This ameloblastoma-like lesion demonstrates palisading epithelial cells with antibasilar nuclei (yellow arrowhead), intraepithelial keratin deposition (black arrowhead) and centrally located stellate reticulum-like cells (red arrowhead). *Source:* D. Imai-Leonard, University of California, Davis.

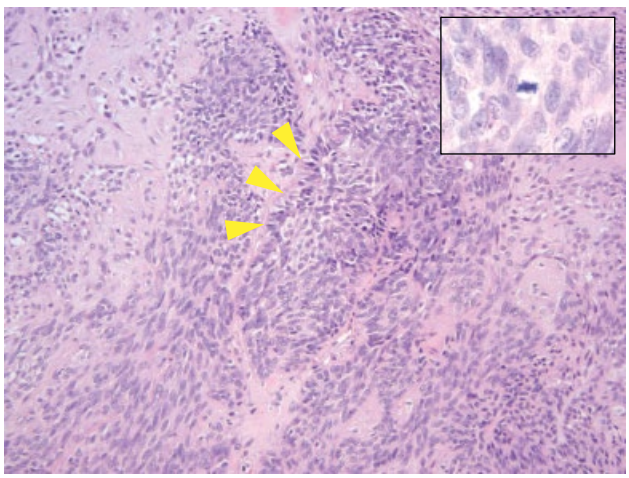


Figure 7.9 Histologic image of an ameloblastic carcinoma, 11-year-old Siberian husky dog. This poorly differentiated tumor has closely packed, spindle-shaped epithelial cells with rare peripheral palisading and antibasilar nuclei (yellow arrowheads). An increased mitotic rate is evident in the centrally located, spindloid epithelial cells (inset). The spindle-shaped cells were diffusely positive for cytokeratin expression by IHC (not shown).

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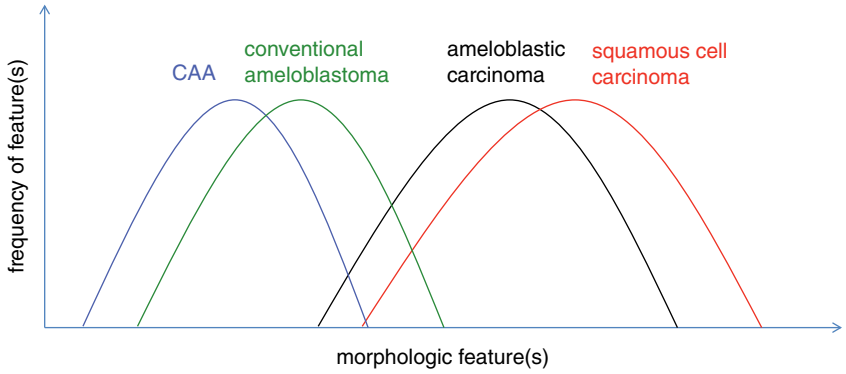


Figure 7.10 Bell curves demonstrating the histologic relationships between CAA, conventional ameloblastoma, ameloblastic carcinoma, and squamous cell carcinoma.

distinguish between ACa and SCC. The presence or absence of keratinization is not sufficient to distinguish between these entities; bear in mind that not all oral SCC lesions exhibit overt keratinization [17]. As a guideline, if the lesion in question arises from the oral mucosa or jaws, and the neoplastic epithelium demonstrates some odontogenic features in the context of unequivocal evidence of cytologic malignancy, one should consider the diagnosis ACa. Although too few cases have been reported to draw meaningful conclusions, the prognosis for ACa and SCC may be similar. The proliferation marker Ki67 has proven to be a useful prognostic tool in human oral pathology and may have some diagnostic utility for veterinary species as well (see Figure 7.10).

Malignant ameloblastoma is defined as a histologically typical CA that metastasizes to regional lymph nodes or distant organ sites (lung/bone) despite its relatively innocuous histologic appearance. In human oral pathology, this lesion is now known as *metastasizing ameloblastoma* [11]. The authors of this textbook have identified a case of a rat with an ACa that metastasized to the mandibular lymph node (malignant ACa) [18].

References

9 Barnes, L., Universitäts Spital Zürich. Departement Pathologie, International Academy of Pathology et al. (2005). *Pathology and Genetics of Head and Neck Tumours*. Lyon: IARC Press.

10 Head, K.W., Armed Forces Institute of Pathology (U.S.), American Registry of Pathology, and & WHO Collaborating Center for Worldwide Reference on Comparative Oncology (2003). *Histological Classification of Tumors of the Alimentary System of Domestic Animals*. Washington, DC: Armed Forces Institute of Pathology in cooperation with the American Registry of Pathology and the World Health Organization Collaborating Center for Worldwide Reference on Comparative Oncology.

11 El-Naggar, A.K., Chan, J.K.C., Rubin Grandis, J., and International Agency for Research on Cancer (2017). *WHO Classification of Head and Neck Tumours*. Lyon: International Agency for Research on Cancer.

12 Wright, J.M. and Vered, M. (2017). Update from the 4th edition of the World Health Organization Classification of Head and Neck Tumours: odontogenic and maxillofacial bone tumors. *Head Neck Pathol.* 11: 68–77.

13 Gardner, D.G. (1998). Ameloblastomas in cats: a critical evaluation of the literature and the addition of one example. *J. Oral Pathol. Med.* 27: 39–42.

14 Madarame, H. and Enaga, S. (2009). Peripheral acanthomatous ameloblasoma in a rabbit with review of previous submissions of the Armed Forces Institute of Pathology Wednesday Slide Conference. *J. Vet. Med. Sci.* 71: 987–989.

15 Jimenez, M.A., Castejon, A., San Roman, F. et al. (2007). Maxillary ameloblastic carcinoma in an Alaskan Malamute. *Vet. Pathol.* 44: 84–87.

16 De Cock, H.E., Labelle, P., and Magdesian, K.G. (2003). Ameloblastic carcinoma in a horse. *J. Comp. Pathol.* 128: 210–215.

17 Nemec, A., Murphy, B., Kass, P.H., and Verstraete, F.J. (2012). Histological subtypes of oral non-tonsillar squamous cell carcinoma in dogs. *J. Comp. Pathol.* 147: 111–120.

18 Murphy, B., Michel, A., LaDouceur, E.B. et al. (2017). Ameloblastoma of the jaw in three species of rodent: a Domestic Brown Rat (*Rattus norvegicus*), Syrian Hamster (*Mesocricetus auratus*) and Amargosa Vole (*Microtus californicus scirpensis*). *J. Comp. Pathol.* 157: 145–149.

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7.2.2 Canine Acanthomatous Ameloblastoma (CAA)

Canine acanthomatous ameloblastoma (CAA) is a very important odontogenic tumor of dogs. Not only is it a common oral lesion, CAA can be a serious condition, as this odontogenic tumor can behave in a locally invasive and disfiguring manner. CAA was formerly known by a variety of names including acanthomatous epulis of periodontal ligament origin, peripheral ameloblastoma, basal cell carcinoma and adamantinoma. The diversity of names for this common canine entity reflects the historically convoluted history of odontogenic lesion nomenclature and a certain level of confusion based upon the fact that no odontogenic tumor in humans is precisely analogous to CAA in dogs.

Box 7.5 Differential Diagnoses for Canine Acanthomatous Ameloblastoma

Ameloblastoma
Squamous cell carcinoma
Amyloid-producing ameloblastoma (CEOT/APOT)
Fibromatous epulis of periodontal ligament origin/POF
Proliferative gingivitis
Odontogenic cysts

CAA is a subtype of ameloblastoma that is relatively unique to dogs. It shares features with two different ameloblastomas of human beings, the acanthomatous histologic variant of the solid/ multicystic ameloblastoma and the peripheral ameloblastoma, although the actual relationship of CAA to these tumors is not clear. CAA is histologically and functionally distinct from both. CAA can occur peripherally within the gingiva (more common), or arise centrally (less common) from the tissues of the periodontal ligament adjacent to tooth and bone. Although technically a benign lesion that does not metastasize, CAA can behave in a locally aggressive manner, often requiring an *en bloc* surgical resection involving both bone and soft tissues to achieve a cure. CAA seems to have a particular tropism for bone – alveolar, cortical, and medullary, often resulting in extensive osteolysis and tooth loss. CAA is less likely to invade soft tissues.

Although CAA is known to occur in both the rostral and caudal aspects of either jaw, it appears to have an anatomic preference for the rostral mandible. CAA often manifests grossly as a gray to pink, irregular, exophytic, verrucous mucosal mass that arises immediately adjacent to teeth (Figure 7.11). However, the gross appearance of CAA varies markedly and can be indistinguishable from other common oral lesions in dogs like FEPLO/POF, oral squamous cell carcinoma, pyogenic granuloma and gingival hyperplasia. The relative gross plasticity and the potentially serious consequence of a diagnosis of CAA for the patient (and owner) argue the need for a surgical biopsy prior to a definitive treatment.

Since CAA is a form of ameloblastoma, it is thought to arise from odontogenic epithelium. One of the authors (CB) believes that CAA demonstrates histologic features of the dental lamina *prior to the development of the enamel organ*. As is true for all ameloblastomas, the diagnosis of CAA is facilitated through the identification of the (variably present) *cardinal histologic features* of odontogenic epithelium and the *architectural arrangement* of the neoplastic epithelium (Boxes 7.2 and 7.3). Importantly, the pathologist needs to be aware of a unique and defining histologic feature of CAA. Although the centrally located sheets of odontogenic epithelium in most ameloblastomas demonstrate long, spider-like intercellular desmosomal attachments that are reminiscent of *stellate reticulum*, the centrally located epithelial cells in CAA do not demonstrate this feature. The adjective *acanthomatous* (*acantho* – thorn-like) in the name CAA refers to this important difference – an internal sheet of interlocking polygonal epithelial cells reminiscent of the epithelial cells of the *stratum spinosum* of the skin or oral mucosa (Figure 7.13). Relative to conventional ameloblastoma, CAA seems to demonstrate more histologic homogeneity.

In addition to the histologic features described above, the subepithelial stroma of CAA lesions is reminiscent of the dental follicle-derived periodontal ligament. Recall that the histologic features of periodontal ligament include variably dense arrangements of triangular to stellate fibroblast-like cells amidst a dense finely fibrillar collagen background with regularly positioned empty blood vessels (Figure 7.14). In some CAA lesions, at the tumor-subepithelial interface, the stroma may demonstrate a slight basophilia [19]. The periodontal ligament-like stroma is capable of forming islands of cemento-osseous matrix. Although the CAA stroma may contain metaplastic bone, this tumor does not seem to induce a pronounced osteoproliferative response in the adjacent preexisting bone. It is important to note that this periodontal ligament-like stroma associated with the neoplastic epithelium *may or may not* be overtly evident in the CAA lesion in question.

As is true for other ameloblastoma lesions, the neoplastic epithelium in CAA may demonstrate a few mitotic figures, be variably keratinized, or have central epithelial degeneration with cyst formation (Figure 7.14). Although these features are not prognostically relevant, they can be helpful in the diagnosis. Atypical cytologic features (mitotic figures, cellular pleomorphism) tend to be more common in inflamed regions of the CAA lesion; as a result, these

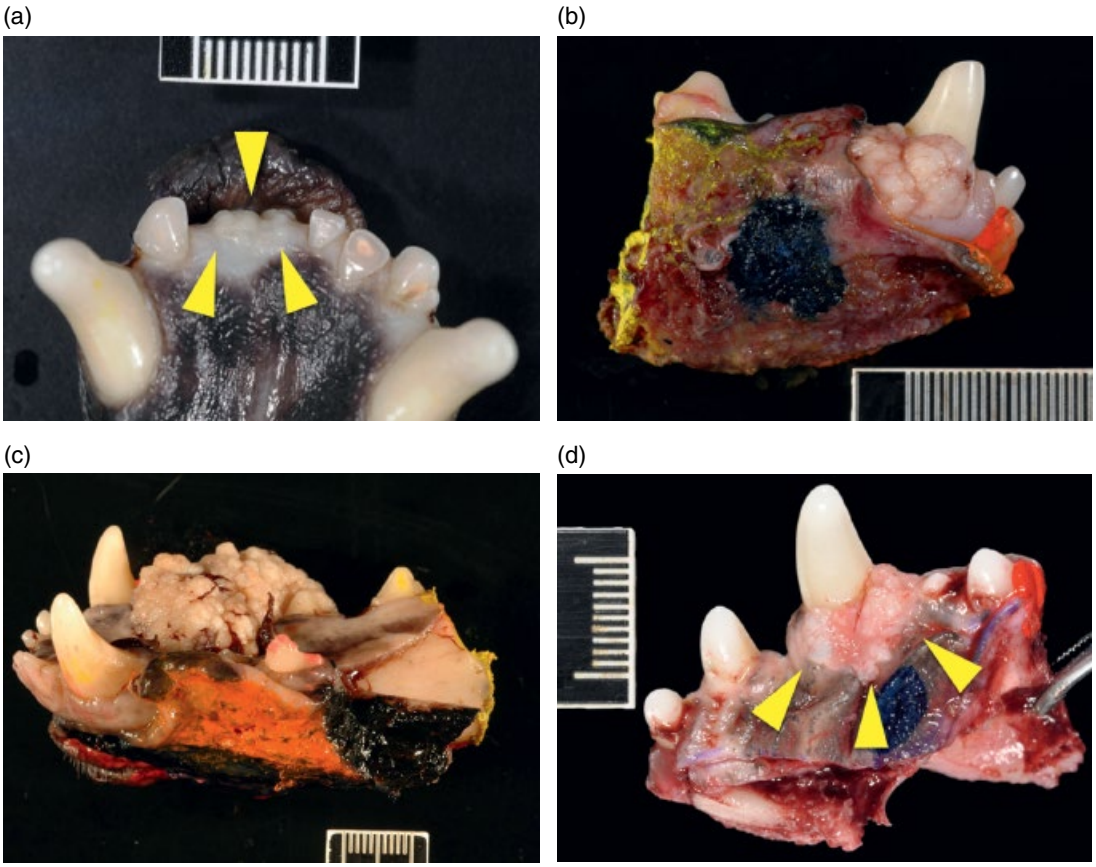


Figure 7.11 Gross images of canine acanthomatous ameloblastoma (CAA). (a) Gross image of CAA in the rostral mandible of a nine-year-old FS Australian shepherd dog. The oral component of the lesion is relatively subtle (yellow arrowheads) due to prior incisional biopsy. *Source:* R. P. Translavina, University of California, Davis. (b) Gross image of a mandibular CAA adjacent to the canine tooth in a 12-year-old FS Labrador retriever dog. Note the extensive use of different colors of dyes. *Source:* B. M. Gericota, University of California, Davis. (c) Gross image of a peripheral CAA arising between the canine and premolar teeth in the mandible of an 11-year-old FS Golden retriever dog. Note the extensive use of different colors of dyes. *Source:* H. O. Aina, University of California, Davis. (d) Gross image of a central CAA arising from the rostral maxilla (yellow arrowheads), five-year-old MC mixed breed dog. *Source:* R.O. Zavodovskaya, University of California, Davis.

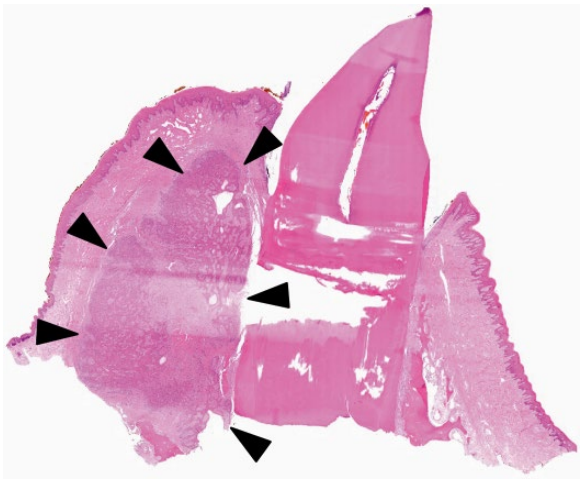


Figure 7.12 Histologic image of a central canine acanthomatous ameloblastoma (CAA), mandible of an 18-year-old Staffordshire terrier. In this in situ photomicrograph of a CAA within the rostral mandible, the neoplasm (black arrowheads) invades and replaces the alveolar bone adjacent to an incisor tooth.

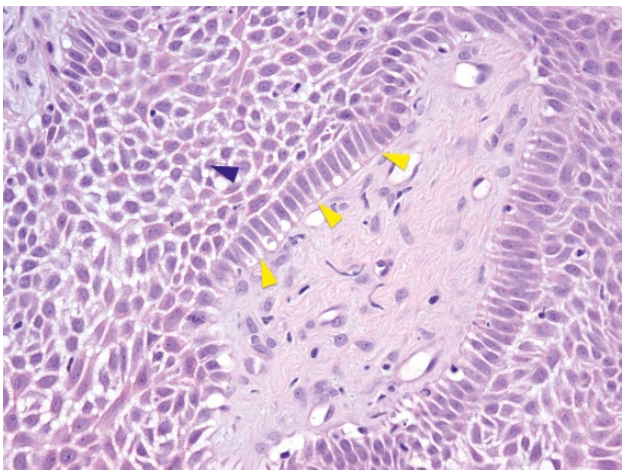


Figure 7.13 Histologic image of CAA demonstrating cardinal histologic features of odontogenic epithelium, eight-year-old MC Labrador retriever. Note the peripheral palisading of columnar epithelium with antibasilar nuclei and basilar cytoplasmic clearing (yellow arrowheads). Centrally, the epithelial cells are arranged as interlocking polygonal epithelial cells reminiscent of the stratum spinosum of the skin (blue arrowhead). Numerous intercellular "thorn-like" junctions (desmosomes) are evident, justifying the term *acanthomatous*. Note that the central and palisading odontogenic epithelial cells have a relatively uniform morphology. This is the same lesion as that depicted in Figure 7.14c and d.

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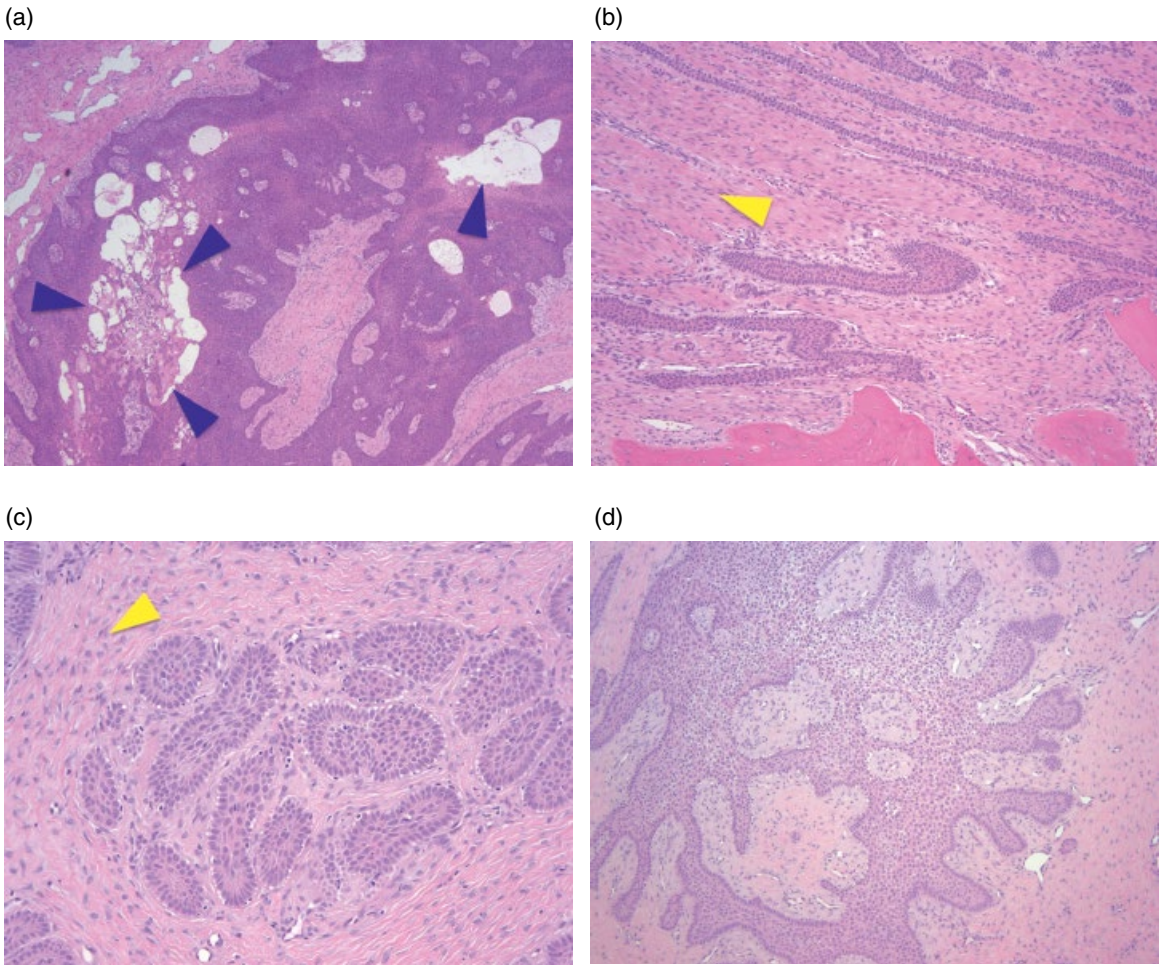


Figure 7.14 Architectural subtypes of CAA, 11-year-old FS Labrador retriever mix (a and b); eight-year-old MC Labrador retriever (c and d). (a) The trabecular, (b) plexiform ribbon, (c) follicular, and (d) "ink drop" architectural patterns of odontogenic epithelium are depicted here. As the name suggests, the "ink drop" architectural pattern is reminiscent of ink dropped onto a solid surface; this pattern is relatively pathognomonic for odontogenic epithelium and is also known as a *medusoid configuration* [19]. Note the central epithelial degeneration/cyst formation (blue arrowheads, a), and periodontal ligament-like stroma (yellow arrowheads, b and c).

portions of the lesion can be challenging to interpret. Tangential sections of inflamed and proliferative gingiva (cross-linking rete pegs with a subepithelial band of inflammation) can mimic the intra-anastomosing trabecular pattern of CAA. Pronounced intraepithelial keratinization may confound the diagnosis of CAA and SCC.

7.2.2.1 Clinical Features

Approximately 50 % of all CAA occur in the rostral mandible, although it may be found anywhere in the oral cavity adjacent to teeth [20]. Local invasion of underlying bone, particularly into osseous trabeculae in areas that may have normal radiographic bone density, is aggressive. Although treatment options may include radiation therapy and intralesional bleomycin has been described, surgical excision with a 1 cm gross surgical margin is generally preferred and provides the best chance of cure [20]. Some authors have advocated "rim excisions" in the mandible. However, care must be taken in selecting the appropriate patient as this method may not achieve complete resection in smaller animals. Recurrence is unlikely even with narrow margins [20].

References

19 Meuten, D.J. (2017). *Tumors in Domestic Animals*, 5e. Ames, Iowa: Wiley.

20 Goldschmidt, S.L., Bell, C.M., Hetzel, S., and Soukup, J. (2017). Clinical characterization of canine acanthomatous ameloblastoma (CAA) in 263 dogs and the influence of postsurgical histopathological margin on local recurrence. *J. Vet. Dent.* 34: 241–247.

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7.2.3 Amyloid-Producing Ameloblastoma (CEOT/APOT)

Amyloid-producing ameloblastoma (APA) is a rare odontogenic tumor in veterinary species. Over the past 50 years or so, there has been considerable controversy over the nomenclature of this lesion. The closely related lesion, calcifying epithelial odontogenic tumor (CEOT), or *Pindborg tumor* after J. J. Pindborg who initially described the lesion in humans (1958), is a benign oral tumor derived from odontogenic epithelium with interspersed foci of both intracellular and extracellular amyloid material, which is often mineralized (hence, *calcifying*). The controversy is focused on whether or not the CEOT lesion actually exists in veterinary species.

Box 7.6 Differential Diagnosis for Amyloid-Producing Ameloblastoma (APA)

Carcinoma
Complex odontoma
Ameloblastoma
Ossifying fibroma

From 1976 to 2004, several peer-reviewed reports of CEOT occurring in dogs and cats were published. In 1994, Gardner and co-authors made the case that the CEOT lesion, as described in humans, is histologically distinct from the tumor occurring in veterinary species [21]. For the CEOT-analog in dogs and cats, these authors proposed the term *amyloid-producing odontogenic tumor (*APOT*)*. In 2010, Hirayama, Watanabe, and co-workers proposed renaming the canine lesion *APA* [22]. In a 2014 review of odontogenic tumor nomenclature in veterinary species, Bell, and Soukup made the case that CEOT and APOT share many key histologic features – both are benign tumors derived from odontogenic epithelium, which may be keratinized and have interspersed amyloid deposition [23]. They argue further that the histologic differences between APOT and CEOT can be relatively subjective and that these subtle differences may represent variants within a spectrum of a single entity. In agreement with the Hirayama group, we have chosen to use the term APA in lieu of the terms APOT or CEOT.

Although APA has most commonly been identified and reported in cats [24, 25] and dogs (Figure 7.15), APOT has been identified in a goat [26], horse, rabbit, moose, and Bengal tiger [27]. Lesions that are histologically consistent with APOT (and APA) have recently been identified ectopically within the facial skin of cats [28]. These interesting findings are reminiscent of

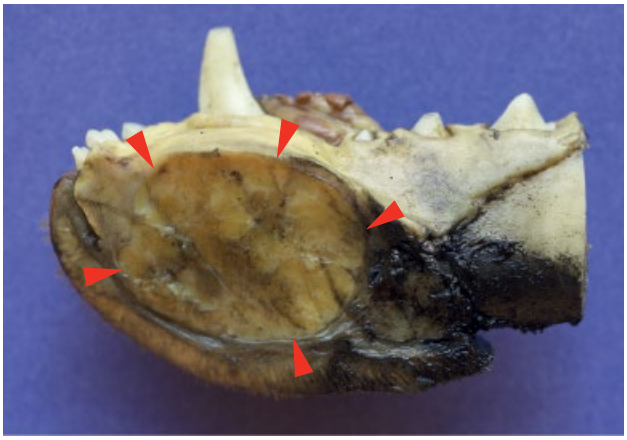


Figure 7.15 Gross image of APA of the rostral mandible, seven-year-old Lhasa apso dog. In this surgical mandibulectomy specimen, the well circumscribed tumor arising from the incisor teeth of the rostral mandible (red arrowheads). *Source:* J. Peauroi, VDx – Veterinary Diagnostics, Davis CA.

ameloblastomas arising ectopically in the cheek tissue of rabbits [29]. Whether the occurrence of these odontogenic tumors in sites other than the jaws indicates the ectopic presence of odontogenic rests or a histologic convergence between cutaneous adnexa and tooth germ remains to be determined.

APA are unencapsulated neoplasms that can arise both centrally and peripherally from either the mandible or maxilla. Although considered to be benign, some APA lesions aggressively invade bone and paradental tissues in a manner similar to canine acanthomatous ameloblastoma. The tissue of origin is currently unknown but is suspected to be some component of the odontogenic epithelium (e.g. dental lamina, stratum intermedium of the enamel organ, or Hertwig's epithelial root sheath) that produces and secretes amyloid-like material. As a result of the range of mineralization found in the APA, the radiographic pattern of these lesions can demonstrate considerable variation. In humans, the related CEOT lesion is often associated with impacted teeth [30].

Histologically, the APA is a relatively bizarre tumor. Regions of the tumor *may* demonstrate recognizable epithelial follicles, irregular anastomosing trabeculae, and plexiform cords, with remnant odontogenic features embedded within a (sometimes extensive) collagenous stroma. These portions of the APA resemble a conventional ameloblastoma with palisading basal cells forming a border circumscribing sheets of epithelium demonstrating features of stellate reticulum. Micro- or macrocyst formation resulting from central degeneration of the epithelial cells is a relatively common finding in APA (Figure 7.16).

However, in some APA lesions, there is little resemblance to ameloblastoma, and the epithelial cells comprising the tumor can be so poorly differentiated that they may

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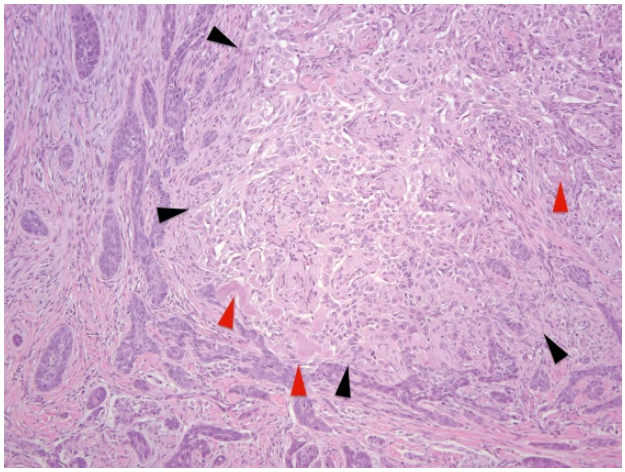


Figure 7.16 Histologic image of APA in maxilla, 11-year-old Lhasa apso dog. The neoplastic odontogenic epithelium within this lesion is both moderately well-differentiated (forming plexiform ribbons and follicles, left side and lower aspect of the image) and poorly differentiated (region delineated by black arrowheads). Epithelium associated globules of eosinophilic amyloid-like material are indicated by red arrowheads.

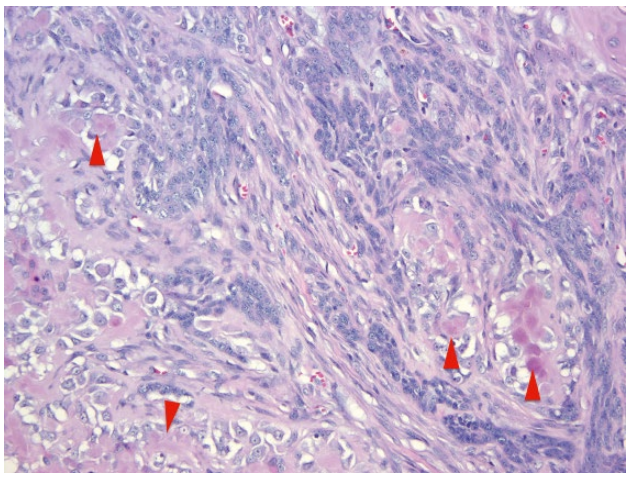


Figure 7.17 Histologic image of APA of the rostral mandible, seven-year-old Lhasa apso dog. The tumor is characterized by cords and individualized, pleomorphic neoplastic epithelial cells that are closely associated with amyloid-like material (red arrowheads). This is the same lesion as the gross image in Figure 7.15. *Source:* J. Peauroi, VDx – Veterinary Diagnostics, Davis CA.

actually defy classification as epithelial. Although odontogenic features can be difficult to identify in these lesions, a careful examination of several sections may reveal recognizable odontogenic epithelium. In less differentiated regions, the neoplastic epithelium forms poorly delineated sheets of primitive, closely packed, round to spindloid cells lacking discernable

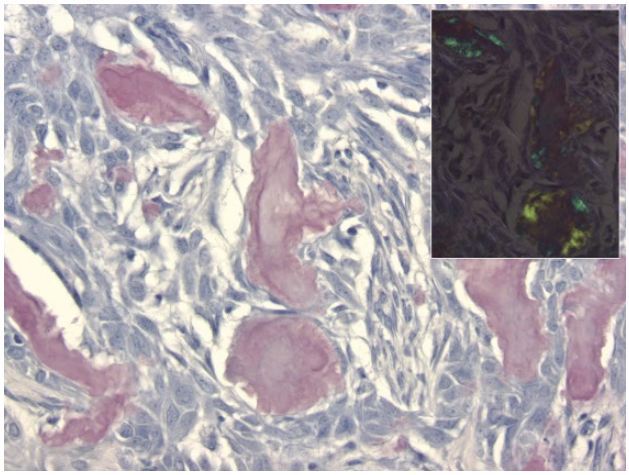


Figure 7.18 Histologic image of a maxillary APA, 11-year-old Lhasa apso dog. Congo red stain of the same lesion as Figure 7.16. Epithelium-associated material stains orange-pink with Congo red and has apple green birefringence when polarized (inset), consistent with amyloid.

cytoplasmic margins that fail to form architectural structures consistent with epithelium. In this situation, immunohistochemistry for cytokeratin and vimentin intermediate filaments can be of use to distinguish between the epithelial components of the tumor and the closely intermixed collagenous stroma. The pathologist needs to bear in mind that in some odontogenic tumors, the epithelial component of the lesion can be positive with *both* markers.

The epithelial cells may demonstrate squamous differentiation and extensive keratinization. Brown cytoplasmic granules, interpreted as melanin, have been identified in some feline APA lesions, suggesting a potential differential diagnosis of melanoma. In some lesions, individual to clusters of keratinized cells have a loss of staining intensity and cytological detail (ghost cells). In human CEOT lesions, multinucleate, and pleomorphic epithelial cells can be a common finding. These features are rarely identified in APA lesions of veterinary species, and mitotic figures are typically rare in APA.

Multifocal epithelium-associated mineralization is critical to the diagnosis of APA. Scattered at variable densities throughout the neoplastic epithelium are variably sized islands, globules, and droplets of pink hyalinized to glassy extracellular material that *may or may not* demonstrate calcification. The pattern of calcification may result in the appearance of concentric rings with an annular staining pattern (so-called *Liesegang rings*). Congo red stain (with light polarization) and/or thioflavin T fluorescence microscopy typically reveal this hyalinized material to be amyloid (Figure 7.18). In some APA lesions, this hylanized material has a fibrillar structure that is evident in higher magnification (Figure 7.19). It should be noted that the

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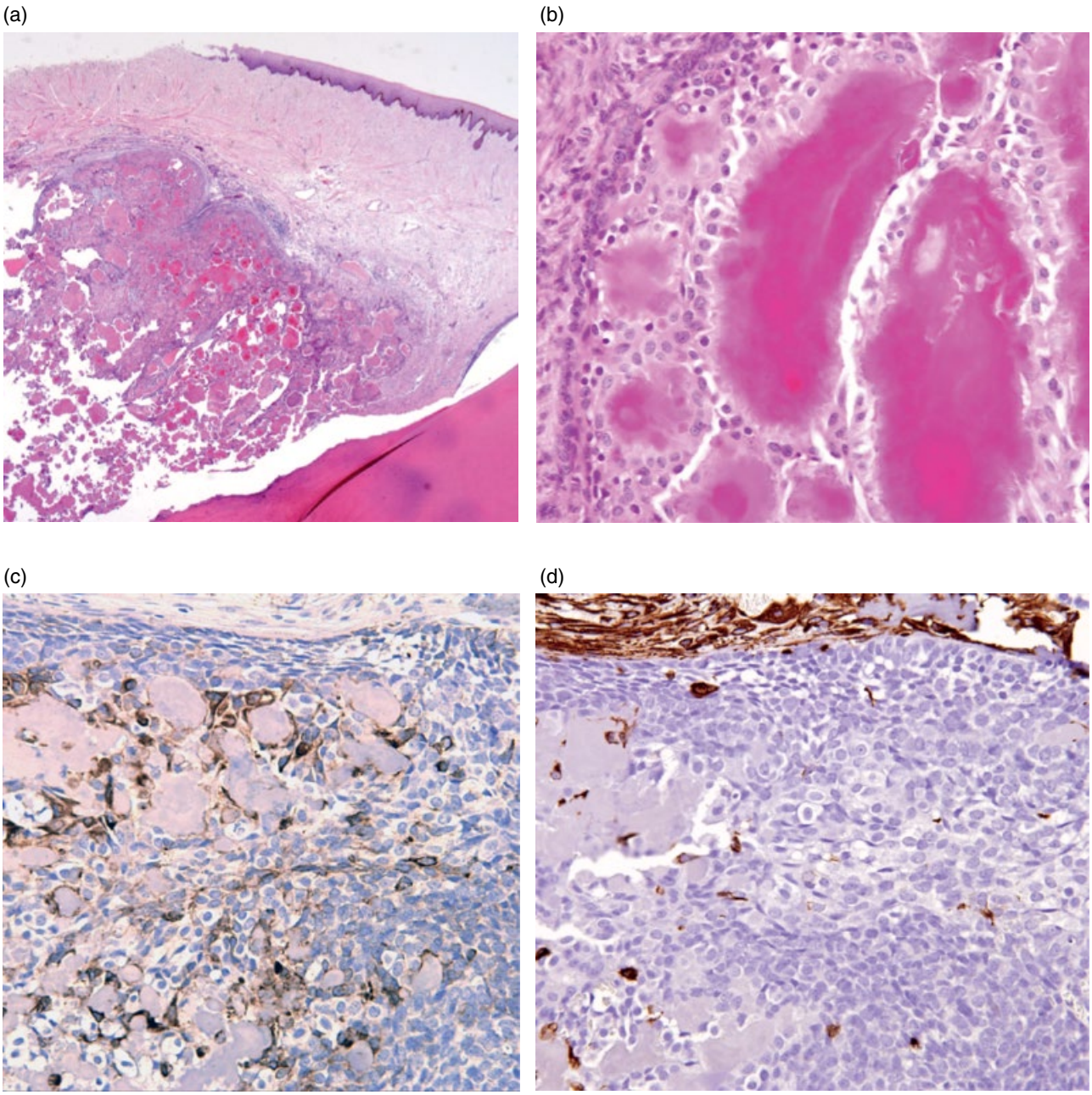


Figure 7.19 Histologic images of canine APA. (a) Low magnification, (b) and high magnification H&E images of APA demonstrating the fibrillar nature of the epithelium associated amyloid-like material. Images of (c) cytokeratin and (d) vimentin immunohistochemistry stained sections, respectively.

authors of this textbook have identified several lesions from dogs and cats that are otherwise dead ringers for APA lesions and yet are *Congo red and thioflavin T negative*, indicating that this material is not amyloid (or at least Congo red/thioflavin T negative). We have yet to determine what this finding means.

The authors of this textbook consider the amyloid-like material in APA to represent a form of dysplastic tooth matrix formation. Several recent reports using immunohistochemistry and mass spectrometry indicate that the interspersed amyloid in APA lesions from both cats and dogs is derived from ameloblasts, providing further evidence of an odontogenic histogenesis for this histologically bizarre and divergent tumor. Hirayama et al. have determined that the amyloid-like material in APA is derived from enamel proteins (ameloblastin, sheathlin, and amelogenin) secreted by ameloblasts [22]. Basement membrane components have also been demonstrated in

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the amyloid-like deposits of odontogenic tumors in animals [25]. Some strains of genetically modified mice with dysplastic enamel organs have lesions focally reminiscent of APA [31, 32]. Exactly how enamel matrix might be formed without overt reciprocal induction (concurrent presence of odontoblasts and mineralized dentin) remains to be determined.

Isolated and atrophied epithelial cells, often demonstrating no odontogenic features at all, may be marooned within this extracellular material, and the epithelium/amyloid aggregates may form complex jumbled masses. Although much of this amyloid material appears to be deposited in an extracellular location, it can be difficult to determine if amyloid actually accumulates intracellularly as well. It is worth emphasizing that the amyloid material generally seems to be *closely associated with the neoplastic epithelial cells, and these epithelial cells may be individualized*.

The locally invasive APA can also be associated with extensive bone remodeling, frequently resulting in the creation of complex, interanstomosing trabeculae of woven bone and/or cementum replacing the tooth-associated alveolar-lamellar bone. This remodeled "cemento-osseous bone" closely borders, and may be infiltrated by, the APA. As a result, the pathologist may be challenged by the need to distinguish between multiple concurrent pink-staining materials: amyloid, keratin, woven bone, cementum, and parent lamellar bone. These matrices may or may not be calcified, resulting in a matrix that is partially to completely obscured by magenta-staining mineral. If the tissue was not decalcified prior to sectioning, face-decalcification (see Appendix), followed by slide preparation of the paraffin-embedded tissue block, may reveal the cryptic nature of the mineralized matrix in question.

7.2.3.1 Clinical Features

Although too few studies regarding the biological behavior of APA exist to make solid conclusions, experience suggests that these lesions behave very similarly to conventional ameloblastoma. Thus, the clinical and imaging features are similar; namely, APA tend to occur as multilocular lesions with osseous septae between compartments. Likewise, APA is a benign but locally aggressive odontogenic neoplasm. Surgical excision with 1 cm margins is indicated and complete resolution can be expected with appropriate surgical resection. In one of the authors' (JWS) experience, lesions in cats often occur in the caudal maxilla, making them difficult to fully resect. However, if the lesion is clearly cystic and delineated, conservative enucleation may provide a positive outcome.

References

21 Gardner, D.G., Dubielzig, R.R., and McGee, E. .V. (1994). The so-called calcifying epithelial odontogenic tumour in dogs and cats (amyloid-producing odontogenic tumour). *J. Comp. Pathol.* 111: 221–230.

22 Hirayama, K., Miyasho, T., Ohmachi, T. et al. (2010). Biochemical and immunohistochemical characterization of the amyloid in canine amyloid-producing odontogenic tumor. *Vet. Pathol.* 47: 915–922.

23 Bell, C.M. and Soukup, J.W. (2014). Nomenclature and classification of odontogenic tumors – part II: clarification of specific nomenclature. *J. Vet. Dent.* 31: 234–243.

24 Bock, P., Hach, V., and Baumgartner, W. (2011). Oral masses in two cats. *Vet. Pathol.* 48: 906–910.

25 Delaney, M.A., Singh, K., Murphy, C.L. et al. (2013). Immunohistochemical and biochemical evidence of ameloblastic origin of amyloid-producing odontogenic tumors in cats. *Vet. Pathol.* 50: 238–242.

26 Lohr, C.V. (2013). One hundred two tumors in 100 goats (1987–2011). *Vet. Pathol.* 50: 668–675.

27 Kang, M.S., Park, M.S., Kwon, S.W. et al. (2006). Amyloid-producing odontogenic tumour (calcifying epithelial odontogenic tumour) in the mandible of a Bengal tiger (*Panthera tigris tigris*). *J. Comp. Pathol.* 134: 236–240.

28 Hirayama, K., Endoh, C., Kagawa, Y. et al. (2017). Amyloid-producing odontogenic tumors of the facial skin in three cats. *Vet. Pathol.* 54: 218–221.

29 Madarame, H. and Enaga, S. (2009). Peripheral acanthomatous ameloblasoma in a rabbit with review of previous submissions of the Armed Forces institute of Pathology Wednesday Slide Conference. *J. Vet. Med. Sci.* 71: 987–989.

30 Regezi, J.A., Sciubba, J.J., and Jordan, R.C.K. (2008). *Oral Pathology: Clinical Pathologic Correlations*, 5e. St. Louis, Mo: Saunders/Elsevier.

31 Irizarry, A.R., Yan, G., Zeng, Q. et al. (2017). Defective enamel and bone development in sodium-dependent citrate transporter (NaCT) Slc13a5 deficient mice. *PLoS One* 12: e0175465.

32 Wazen, R.M., Viegas-Costa, L.C., Fouillen, A. et al. (2016). Laminin gamma2 knockout mice rescued with the human protein exhibit enamel maturation defects. *Matrix Biol.* 52-54: 207–218.

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7.3 Tumors Composed of Odontogenic Epithelium, Ectomesenchyme of the Dental Papilla and Follicle

Currently, this group of tumors has only two members – ameloblastic fibroma (AF) and feline inductive odontogenic tumor. Both of these lesions are examples of *mixed odontogenic tumors* that are moderately differentiated and characterized by the presence of (i) neoplastic odontogenic epithelium and (ii) induced ectomesenchyme of the dental papilla (as gives rise to pulp stroma and odontoblasts) and (iii) fibrous stroma reminiscent of the dental follicle. Ribbons of odontogenic epithelium and adjacent ectomesenchyme of the dental papilla are typically arranged as nodules within follicle like stroma. In mixed odontogenic tumors, the neoplastic odontogenic epithelium *induces* the proliferation of the non-neoplastic ectomesenchymal component.

7.3.1 Ameloblastic Fibroma

AF is an uncommon, mixed (biphasic) inductive tumor closely related to ameloblastic fibro-odontoma (AFO). The difference between these two odontogenic lesions is the presence (AFO) or absence (AF) of dental matrices (dentin/ enamel). In terms of odontogenesis, AF demonstrates only the initial step of induction, which is organization of the dental papilla in proximity to odontogenic epithelium. In comparison, induction in AFO progresses to differentiation of odontoblasts within the dental papilla with production of dentin (+/– differentiation of ameloblasts with production of enamel). Since AF does not produce a dental matrix, it is thought to be a *less differentiated variant* of AFO. This may be relevant to prognosis; the more differentiated odontoma has limited growth potential relative to the less differentiated AF.

Box 7.7 Differential Diagnoses for Ameloblastic Fibroma (AF)

Dysplastic dental follicle
Conventional ameloblastoma
Ameloblastic fibro-odontoma (AFO)
Feline inductive odontogenic tumor (cats)

AF is rarely identified in humans, and occurs as a central or peripheral lesion most often in adolescents (mean age of occurrence is 14.8 years) [33]. AF is a benign, slow-growing, expansile, and non-infiltrative tumor. In affected adolescents, AF typically results in a painless swelling in the caudal mandible that results in a disturbance in tooth eruption. Radiographically, AF is characterized by a well-circumscribed radiolucency that is sometimes associated with an impacted tooth. This association of AF and tooth impaction has led some investigators to the conclusion that the lesion is actually a form of dysplasia or hamartoma and not an actual tumor, per se. The AF lesion may have a radiopaque boundary (shell of bone) and can mimic a dentigerous cyst when associated with an unerupted tooth. Typical treatment consists of enucleation and curettage.

Rarely, AF may progress to a malignancy referred to as ameloblastic fibrosarcoma, or more simply, ameloblastic sarcoma. In this malignant tumor, the odontogenic epithelial component is histologically benign while the ectomesenchyme-derived tissue exhibits malignant cytological features. Although AF has been diagnosed only rarely in veterinary species, it is reported to be one of the more common odontogenic tumors in cattle (generally less than 1.5 years of age). AF has been reported in two dogs, presenting as a maxillary lesion in a four-year-old Golden retriever [34] and the maxilla of a four month old Labrador retriever puppy (Figure 7.20) [35] and a cat [36]. Although several cases of AF have been previously reported in cats, many if not all of these lesions have been subsequently reclassified as the related lesion *feline inductive odontogenic tumor*.

In cattle, AF is most often, but not exclusively, identified in the mandibular incisor region of young cattle [37]. In the past, these tumors in cattle were reported as ameloblastomas or by the outdated term *adamantinoma*.

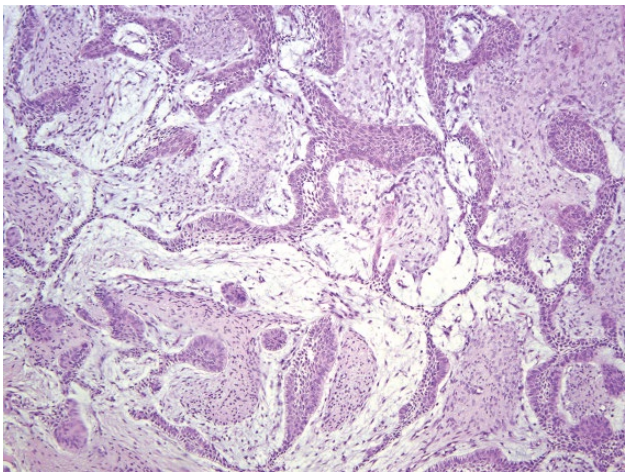


Figure 7.20 Histologic image of a maxillary ameloblastic fibroma (AF), four-month-old Labrador retriever puppy. Note the neoplastic odontogenic epithelium (peripheral palisading, antibasilar nuclei and central stellate reticulum-like cells) arranged in anastomosing plexiform ribbons. The epithelium is embedded in abundant ectomesenchyme with histologic features of the dental papilla (basophilia, variable edema, spindloid mesenchymal cells).

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Where available, case review has generally allowed reclassification to AF based on evidence of ectomesenchymal induction that previous authors had not identified or interpreted as such. The clinical behavior of AF in cattle is suspected to be similar to the disease course in man. Grossly, AF in cattle are firm, lobulated, roughly spherical masses often containing intralesional cysts. In the two reported canine cases, the AF were associated with persistent facial swelling and disruption of the nasal turbinates or slight deviation of a maxillary incisor tooth. In contrast to the imaging features of AF in humans, no cystic component was evident in the canine lesions. *En bloc* surgical resection of the tumor and adjacent tissues was apparently curative in both of these cases.

The majority of the AF lesion is comprised of dental follicular stroma with multifocal interspersed aggregates of dental papilla-like ectomesenchyme associated with odontogenic epithelium. This characteristic is also true of the closely related AFO lesion. Although specific immuno-markers for papillary ectomesenchyme are not currently available, the extracellular matrix typically demonstrates a basophilic staining quality (as a result of the high proteoglycan content). However, it should be noted that staining characteristics of the papillary extracellular matrix vary markedly within pathologic lesions, ranging from eosinophilic to basophilic. The cells that are in the papilla-like areas are relatively primitive, cytologically bland, amitotic, plump, spindle to stellate cells, and arranged in variably dense, haphazard sheets.

Embedded within the supporting stroma and often adjacent to the proliferative ectomesenchyme are thin, branching/anastomosing strands of histologically primitive odontogenic epithelium typically arranged as plexiform ribbons. This arrangement of epithelium is reminiscent of the dental lamina or bud stage of the enamel organ and generally lacks most of the cardinal features of differentiated ameloblasts. The epithelial component of AF may be reminiscent of ameloblastoma, and variably sized cysts may be present. A thin shell of interlocking spicules of woven bone may surround the AF lesion. By definition, hard dental matrices are not present in AF.

7.3.1.1 Clinical Features

Although very little information regarding the biologic behavior of AF and AFO is available in the literature, they are generally considered to be benign and slow-growing and tend not to infiltrate bone or metastasize. Radiographically, they often present as unilocular expansile lesions of the jaws with a central radiolucency. Due to the paucity of literature regarding treatment, appropriate surgical management is based primarily on the human literature. Although the treatment method was not clearly stated, Poulet and others showed no recurrence after treatment of an AF in a 14-year-old cat [36]. The available literature on the management of AFs in humans supports an *en bloc* resection (AF) and a good to excellent prognosis.

References

33 Regezi, J.A., Sciubba, J.J., and Jordan, R.C.K. (2008). *Oral Pathology: Clinical Pathologic Correlations*, 5e. St. Louis, Mo: Saunders/Elsevier.

34 Miles, C.R., Bell, C.M., Pinkerton, M.E., and Soukup, J.W. (2011). Maxillary ameloblastic fibroma in a dog. *Vet. Pathol.* 48: 823–826.

35 Huang, P., Bell, C.M., Wallace, V., and Murphy, B.G. (2018). Mixed odontogenic tumors in four young dogs: ameloblastic fibroma and ameloblastic fibro-odontoma. *J. Vet. Diagn. Investig.* 29 (5): 369–380.

36 Poulet, F.M., Valentine, B.A., and Summers, B.A. (1992). A survey of epithelial odontogenic tumors and cysts in dogs and cats. *Vet. Pathol.* 29: 369–380.

37 Gardner, D.G. (1996). Ameloblastic fibromas and related tumors in cattle. *J. Oral Pathol. Med* 25: 119–124.

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7.3.2 Feline Inductive Odontogenic Tumor

Like ameloblastic fibroma (AF), the feline inductive odontogenic tumor is a mixed tumor comprised of different odontogenic tissue elements – (i) neoplastic odontogenic epithelium, (ii) *induced* ectomesenchyme of the dental papilla and (iii) supportive fibrous stroma reminiscent of the dental follicle. The feline inductive odontogenic tumor (FIOT) is a *special kind* of AF that occurs in young domestic cats (*Felis catus*), and has not been identified in any other species of felids [38]. In the past, the FIOT lesion has been given many different names, one of which is *inductive fibroameloblastoma*. Recently, a histologically related odontogenic tumor was described in a rhesus monkey [39]. As this lesion has now been identified in a mammalian species other than cats, and to emphasize the infiltrative nature of the lesion, the name *infiltrative inductive AF* was proposed [40]. Because the authors of this textbook do not necessarily agree that FIOT is invariably an infiltrative lesion, we prefer the more established term FIOT.

The FIOT is an interesting tumor. It is a rare, mixed odontogenic tumor, which occurs either peripherally or centrally in the jaw of young cats generally less than one year of age. The tumor occurs in either the maxilla or mandible, although the rostral maxilla appears to be preferentially affected. The unique and interesting characteristic of this feline tumor is that the FIOT *epitomizes* odontogenic epithelium-induced induction of the ectomesenchyme. To a certain degree, the tumor recapitulates an early stage of odontogenesis (the cap stage), and then fails to progress beyond it.

A substantial portion of the FIOT lesion is comprised of dental follicle-derived supportive fibrous stroma. The more diagnostic elements of the FIOT lesion, which will be described shortly, are embedded within this more eosinophilic fibrous stroma (Figure 7.21). Evidence of induction takes the form of multiple, variably sized nodules and sheets of condensed ectomesenchyme (dental papilla), which are scattered throughout the tumor and are intimately associated with folds of neoplastic odontogenic epithelium. These ectomesenchymal foci are emergent dental papillae and are comprised of a relatively high density of bland, amitotic, spindloid to ovoid mesenchymal cells lacking discernable cytoplasmic margins. These cells are embedded in a collagen-poor, amphophilic to poorly staining ("watery") extracellular matrix. Unlike the related AF and AFO, the ectomesenchymal matrix in FIOT *doesn't necessarily demonstrate pronounced basophilia*. Despite this biological oversight, these nodules are widely considered to be abortive attempts at odontogenesis. The reason for this is that each ectomesenchymal nodule is partially entrapped by or associated with an enveloping fold of odontogenic epithelium. This epithelial-ectomesenchymal composite reiterates the cap stage of odontogenesis (Figure 7.22).

The odontogenic epithelium forming the cap-like structures may manifest as a plexiform ribbon, somewhat analogous to the dental lamina. However, the epithelium may also form structures like follicles, anastomosing trabeculae, and/or ink drop architectures, as might be identified in an ameloblastoma. The palisading epithelial cells forming the interface with the induced focus of ectomesenchyme may or may not demonstrate the cardinal histologic features of odontogenic epithelium. Centralized sheets of stellate reticulum-like cells may or may not be present. It is important to note that not all of the odontogenic epithelium in FIOT lesions recapitulates the cap stage of odontogenesis! In some lesions, the pathologist must hunt for good examples of it. If the lesion in question has unequivocal evidence of odontogenic epithelium and odontogenic ectomesenchyme, and the lesion is derived from a young cat, it may be worthwhile doing a bit of hunting in an attempt to identify this diagnostic "smoking gun."

Ectomesenchymal development of cytologically recognizable palisading odontoblasts generally does not occur in FIOT. In addition, development of dentin (or enamel) at the epithelial/ectomesenchymal interface does not occur. Several reports in the literature have described the presence of thin strips of dentin-like matrix, suggesting that odontoblast differentiation *can* occur in the FIOT lesion. In the opinion of the authors of this textbook, if dentinal matrix formation is present in a "FIOT lesion,"

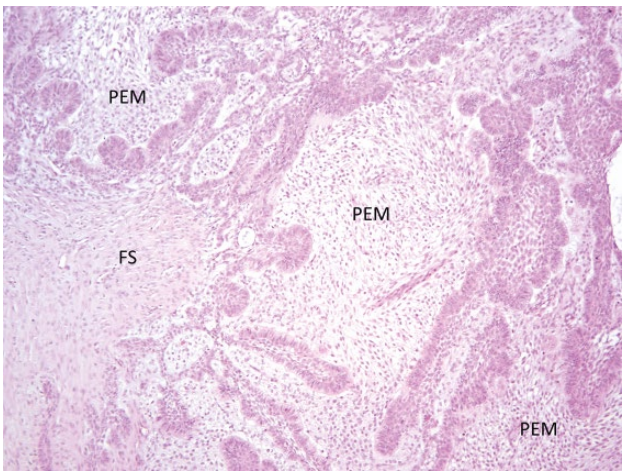


Figure 7.21 Histologic image of a maxillary feline inductive odontogenic tumor, eight month old DLH kitten. The lesion is characterized by plexiform ribbons and bosselated cords (rounded protruberances) of odontogenic epithelium embedded within fibrous stroma (FS) and associated with poorly staining papillary ectomesenchyme (PEM). *Source:* T. Spangler, VDx – Veterinary Diagnostics, Davis CA.

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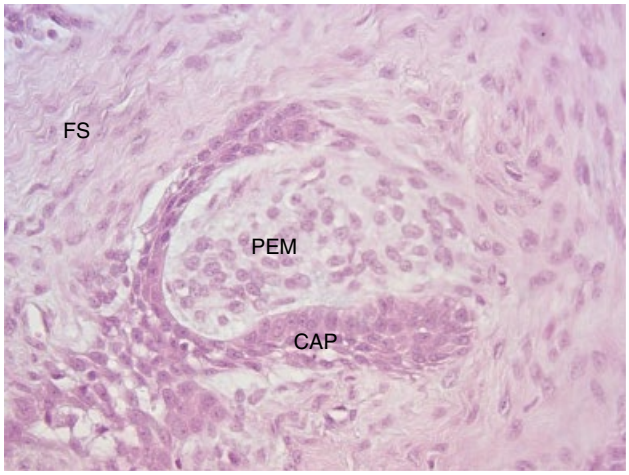


Figure 7.22 Histologic image of a maxillary feline inductive odontogenic tumor maxilla, eight month old DLH kitten (same lesion as Figure 7.21). In this high-magnification histologic image, a c-shaped arc of odontogenic epithelium (CAP) surrounds and induces the differentiation of an aggregate of papillary ectomesenchyme (PEM). This neoplastic structure recapitulates the cap stage of embryogenesis. Undulating collagen fibers are evident in the adjacent fibrous stroma (FS). *Source:* T. Spangler, VDx – Veterinary Diagnostics, Davis CA.

the diagnosis flips into the odontoma group of lesions (odontogenic epithelium + ectomesenchyme of the dental papilla + dental matrix), in the same manner that dentin/enamel production in an ostensible AF lesion flips the diagnosis to AFO.

The odontogenic epithelium in the FIOT lesion may be multifocally cystic or associated with mineralization. If intraepithelial mineralization is present, the APA (CEOT/APOT) should be entertained as a differential diagnosis. Another word of caution – FIOT is a rare tumor which is most often identified in *young cats*. If the examined lesion in question has evidence of proliferative (neoplastic) epithelium and is derived from an adult or aged cat's mouth, the much more common diagnosis of *squamous cell carcinoma* should be given some serious consideration by the pathologist (remember: common lesions are common because they are so common).

7.3.2.1 Clinical Features

As noted above, FIOT is almost exclusively a lesion of immature cats that occurs in the rostral maxilla. It is often characterized radiographically as a loculated lesion surrounded by an unerupted canine tooth. Very little is known regarding the biologic behavior of FIOT. However, the few reports that have made it into the literature suggest that its biological behavior is similar to the AF and may be treated similarly (surgical resection with 1 cm gross surgical margins). This tumor is not expected to metastasize and has a good prognosis if clean margins can be achieved.

References

38 Gardner, D.G. and Dubielzig, R.R. (1995). Feline inductive odontogenic tumor (inductive fibroameloblastoma) – a tumor unique to cats. *J. Oral Pathol. Med.* 24: 185–190.

39 Liu, D.X., Doyle, L.A., Bouljihad, M.T. et al. (2012). Locally infiltrative ameloblastic fibroma in a rhesus macaque (*Macaca mulatta*) with characterizations of its proliferating activity and biological behavior. *J. Vet. Diagn. Invest.* 24: 630–635.

40 Meuten, D.J. (2017). *Tumors in Domestic Animals*, 5e. Ames, Iowa: Wiley.

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7.4 Odontogenic Tumors Composed of Odontogenic Epithelium, Ectomesenchyme of the Dental Papilla, and Mineralized Dental Matrices

This histologically interesting group of mixed odontogenic tumors includes three pathologic entities – (i) odontoma (complex and compound), (ii) ameloblastic fibro-odontoma (AFO), and (iii) odontoameloblastoma. These tumors demonstrate concurrent histologic features of three different germinal tissues: odontogenic epithelium, ectomesenchyme of the dental papilla, and hard dental matrices (dentin and/or enamel). Of these three germinal tissues, the most difficult to identify with confidence may be ectomesenchyme of the dental papilla. In certain situations, the diagnostic differences between these lesions can be relatively subtle and are based upon the *proportion* of the various odontogenic components within the tumor (Figure 7.23 and Table 7.1). It should be noted that the 2017 edition of the World Health Organization Classification of Head and Neck Tumours (humans) no longer includes the lesions odontoameloblastoma and AFO [41]. We have chosen to include these entities here for several reasons – (i) multiple publications in the peer-reviewed literature support the existence of these lesions in veterinary species, (ii) simplification of this group of lesions into essentially a single entity (odontoma) fails to capture the diversity of veterinary lesions, (iii) the 2017 WHO Classification now considers all odontomas to be hamartomas ("tumor-like malformations"), whereas in animals, some of the entities in this group are clearly neoplastic, and (iv) human odontogenic tumors may not necessarily provide a proscriptive blueprint for lesions in other animals.

AFO lesions are principally comprised of tissue reminiscent of the ectomesenchyme of the dental papilla, while odontoameloblastoma demonstrates a predominance of neoplastic odontogenic epithelium. Odontomas (complex and compound) lie histologically between these two extremes and often demonstrate the highest proportion of dental matrices. Although the proportion varies, the parent neoplastic tissue in all of these induced mixed tumors is odontogenic epithelium (see *induction* under Approach to odontogenic neoplasms).

7.4.1 Odontoma

For many pathologists, odontomas are perhaps the most structurally interesting of the odontogenic tumors; the interweaving patterns of diverse tissue types in these lesions can be spectacular at both the gross and microscopic levels. Odontomas have varying proportions of odontogenic epithelium, papillary ectomesenchyme, and dental hard matrices. These tumors are the most common odontogenic tumor in humans but are rare in veterinary species.

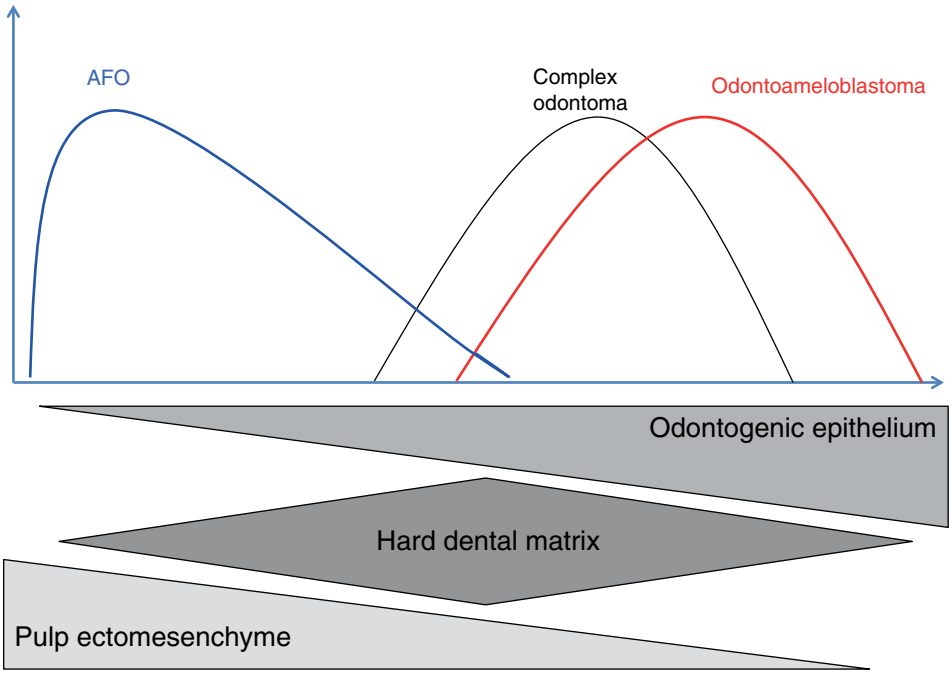


Figure 7.23 Bell curves – ameloblastic fibro-odontom (AFO), odontoma and odontoameloblastoma. Note: compound odontoma does not appear in this figure as the diagnosis of this lesion is generally clear.

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In humans, odontomas are typically identified in children, adolescents, and young adults. The most common clinical history is that of an unerupted (impacted) or missing tooth with or without a focal jaw/alveolar swelling [42]. Odontomas develop either before or after tooth eruption but rarely erupt into the oral cavity. Both central (arising within the jaw bone), and less often, peripheral lesions have been described, and the maxilla is more often affected than the mandible. Odontomas can be asymptomatic and may be discovered through routine imaging of the jaws. There is no gender predisposition and the etiology is unknown.

In veterinary species, odontomas are typically found in younger animals, and are generally unilateral and focal lesions. They have been reported in dogs, cats, horses, rodents, oxen, primates, and several species of fish. Two subtypes of odontomas are recognized, *compound* and *complex*. These terms refer to how well the lesion recapitulates actual tooth embryogenesis – *compound odontomas* are well-differentiated, often containing recognizable tooth-like structures, whereas *complex odontomas* are less well-organized, containing a scrambled mix of odontogenic germinal tissues. In many odontomas, a blend of compound and complex structures coexist, with neither subtype predominating. As a result, the diagnostic division of compound and complex odontomas is perhaps a bit arbitrary.

7.4.1.1 Compound Odontoma

Although the pathogenesis of compound odontomas is unknown, the proliferative potential of these lesions is limited. In time, compound odontomas tend to "burn out" and eventually cease growing. Some investigators consider that compound odontomas may actually be a kind of *hamartomatous malformation* rather than a true neoplasm. As a compound odontoma develops in a young animal, it often exhibits more odontogenic epithelium/soft tissue than hard dental matrix. As the animal ages and the lesion matures, the compound odontoma becomes progressively more matrix-rich and mineralized (Figure 7.24). In mature lesions, the central pulp cavity may be almost completely obliterated by dentinal deposition. The radiographic appearance can be very helpful to the diagnostician, as radiographically, compound odontomas are comprised of multiple radiodense tooth-like structures surrounded by a circumscribed radiolucent zone. Adjacent tooth roots may be displaced, but they are not resorbed.

The compound odontoma recapitulates normal tooth embryology in a relatively faithful manner. These well-differentiated disorders of growth contain few to numerous, often cone-shaped or malformed tooth-like structures referred to as *proto-teeth, denticles* or *rudimentary teeth*. This loose to compact aggregate of proto-teeth is often embedded in a fibrous stroma that may be variably ossified. Typically, each tooth-like structure has a central fibrovascular pulp chamber partially to completely surrounded by dentin and lesser amounts of enamel matrices. Transiently, an outer layer of columnar ameloblasts may palisade along the surface (crown) of the enamel matrix (Figure 7.25). Recall that enamel, being more than 95% mineral, often dissolves completely in histological preparations that have been decalcified. While this is true for mature teeth, for lesions where the enamel matrix is entrapped within surrounding tissue (as it is for compound odontoma), a portion of the enamel matrix may actually survive tissue processing. If not, a diagnostically informative *empty cleft* may delineate the former presence of the dissolved enamel. Depending upon the plane of section and the degree of lesion differentiation, a thin layer of cementum may or may not cover the surface of the dentin along the root of the tooth.

In compound odontoma lesions, not only are the organizational relationships of the germinal tissues generally preserved, often the histologic features of the various odontogenic matrices (e.g. dentinal tubules) are also maintained. The faithful recapitulation of normal tooth embryogenesis generally makes the diagnosis of these lesions relatively straightforward (and fun).

Compound odontomas have also been described in the lip and pharynx of several fish species including angelfish, koi, and walleye. The so-called *lip fibroma*

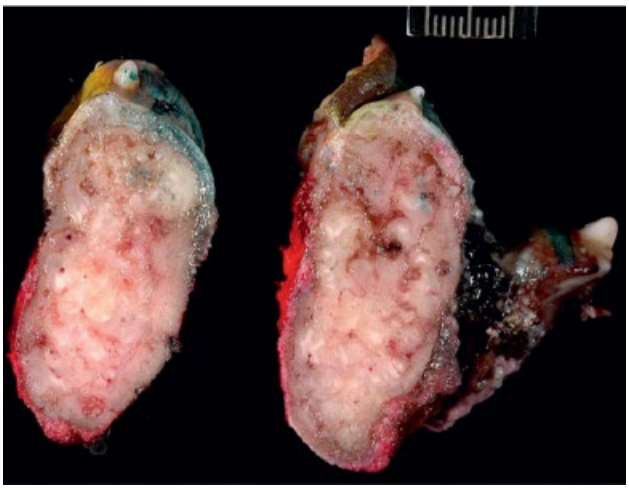
Table 7.1 Different diagnostic features of mixed odontogenic tumors.

Tumor	Amount of odontogenic epithelium	Amount of ectomesenchyme (pulp stroma)	Mineralized dental matrix
Odontoameloblastoma	Abundant	Variable, may be inapparent	Unorganized deposits
Ameloblastic fibroma	Variable	Abundant	None
Ameloblastic fibro-odontoma	Variable	Abundant	Unorganized deposits
Complex odontoma	Variable	Variable, may be inapparent	Dysplastic denticles
Compound odontoma	Variable	Variable, may be inapparent	Organized denticles

Source: Reprinted from Murphy et al., 2017 [46].

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(a)



(b)

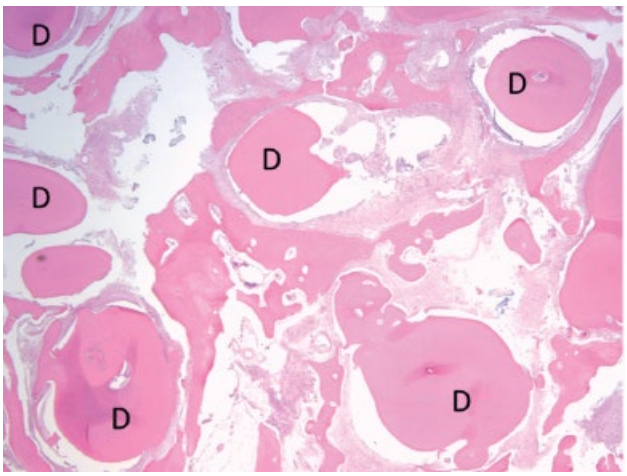


Figure 7.24 (a) Gross and (b) histologic images of a compound odontoma, three-year-old golden retriever, mandible. This "mature" lesion was very hard and primarily comprised of mineralized tissue with very little associated soft tissue. (b) Histologically, the mass is comprised of multiple round denticles (D) and minimal associated soft tissues. Intralesional soft tissues are minimal in this chronic lesion. Clear clefts are retraction artifacts and represent the location of enamel matrix that was removed during tissue processing. *Source:* M. Highland, University of California, Davis.

of angelfish (*Pterophylum scallare*) is a common and well-recognized odontogenic hamartoma (compound odontoma). The interested reader is encouraged to perform an internet search using the terms "image angelfish lip fibroma." In this *pathologically awesome* lesion, multiple, generally perfectly formed denticles are distributed within a fibro-osseous stroma (Figure 7.26). There is some evidence that an uncharacterized retrovirus may be *associated* with the angelfish lip fibroma [43]. Nevertheless, the pathogenesis of this very common lesion in angelfish remains enigmatic.

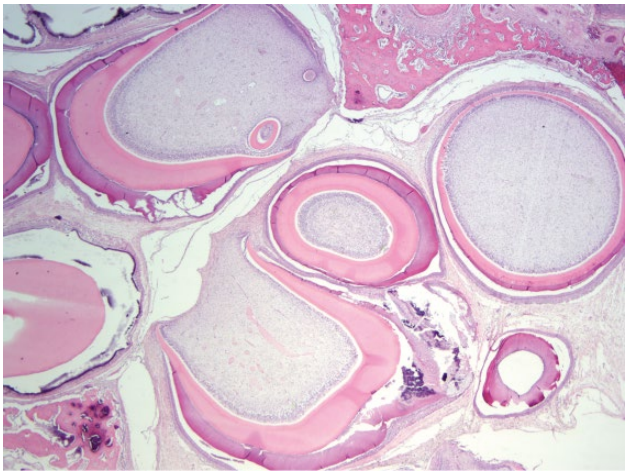


Figure 7.25 Histologic image of a mandibular compound odontoma, two-year-old Labrador retriever dog. In this image, numerous, well-formed proto-teeth aggregate into a mass. These proto-teeth have a recognizable pulp cavity with ectomesenchyme, odontoblasts, dentin (pink), enamel (purple), and ameloblasts.

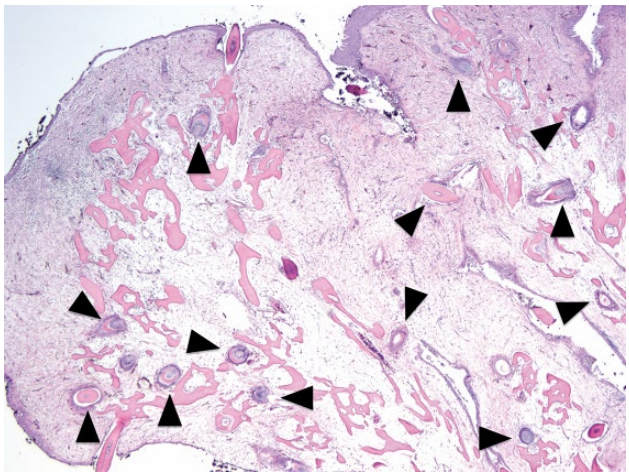


Figure 7.26 Histologic image of an angelfish (*Pterophylum scallare*) "lip fibroma" (compound odontoma). Note the numerous proto-teeth (black arrowheads) scattered amidst the loose connective tissue and bony trabeculae of the lip mass.

7.4.1.2 Complex Odontoma

Complex odontomas are benign tumors that, as is true for compound odontomas, are most often diagnosed in young animals. While compound odontoma is diagnostically straightforward, complex odontoma is often less so. While it may be possible to identify the presence of three different germinal tissues in complex odontoma, more often, these lesions seem to be comprised of a semi-chaotic mixture of odontogenic epithelium and hard dental matrices embedded in a fibrovascular stroma *typically lacking overt features of ectomesenchyme of the dental papilla*. In complex odontoma, the dental matrix

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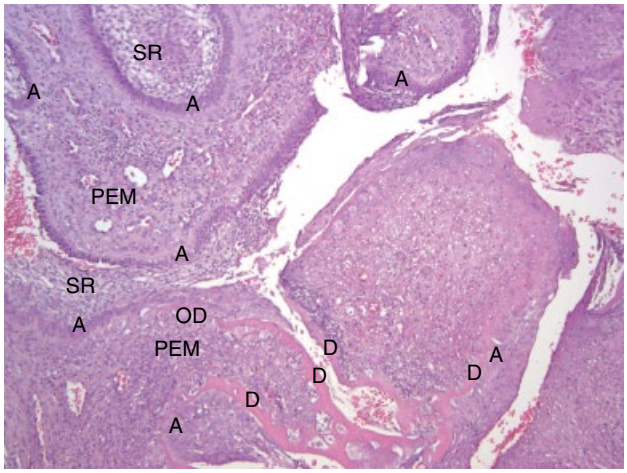


Figure 7.27 Histologic image of a complex odontoma, two-year-old Golden retriever dog, rostral maxilla. In this lesion, palisading ameloblasts (A), stellate reticulum (SR), pulp ectomesenchyme (PEM), odontoblasts (OD) and ribbons of dentinal matrix (D) are semi-chaotically arranged. Note the intralesional clear clefts that likely contained enamel matrix prior to sectional processing. *Source:* T. Spangler, VDx – Veterinary Diagnostics, Davis, CA.

is mostly composed of dentin (or osteodentin) with lesser amounts of magenta to gray-staining enamel. The fact that dentinal matrix is present in these lesions is de facto evidence that papillary ectomesenchymal tissue *must be present as well*, as the odontogenic epithelium alone (that is, without odontoblasts) is incapable of producing dentin. Nevertheless, in some lesions, papillary ectomesenchyme (and odontoblasts) may be histologically inapparent.

By definition, complex odontomas do not produce organized tooth-like structures. The lack of organization in this lesion makes it imperative that the pathologist positively identifies the presence (or absence) of the odontogenic matrix. Pink-staining dentinal matrix needs to be differentiated from fibrin, amyloid, keratin, osteoid, and cementoid. In this lesion, dentin *may* have parallel tubules, but often it does not. To make it more confusing, odontoma-associated dentin can mimic osteoid (osteodentin) with multiple lens-shaped lacunae. In complex odontoma, dentin is often deposited in serpentine linear strips (Figure 7.27) or ring-shaped structures, while these other confounding biomaterials do not. Dentin and purplish enamel matrices may also seamlessly interface with irregular sheets and islands of woven bone and/or cementum. As is true for compound odontoma, as the complex odontoma lesion ages, it can become more and more matrix-rich.

Somewhere in the complex odontoma lesion, the pathologist should also be able to identify cuboidal to columnar cells palisading along the dentinal matrix. The histogenesis of these palisading cells may appear to be ambiguous, but can be elucidated when cytokeratin (CK) and vimentin immunohistochemistry assays are performed. Palisading ameloblasts will be CK positive and (generally) vimentin negative; odontoblasts will have the opposite expression pattern. Relative to odontoameloblastoma, complex odontoma has *a more limited proportion* of neoplastic odontogenic epithelium. As is true of many odontogenic lesions, the odontogenic epithelium may or may not demonstrate the cardinal histologic features and may exhibit central degeneration and cyst formation.

The lack of normal tissue organization introduces another diagnostic problem in complex odontoma. The odontogenic epithelium and associated stroma can adopt one of two spatial conformations: (i) the epithelium forms circumscribed islands peripherally bordered by ameloblasts and surrounded by stroma, or alternatively, (ii) the stroma takes the form of an "island" seemingly entrapped by a surrounding sheet of odontogenic epithelium (Figure 7.28). Because the epithelial stellate reticulum can appear cytologically odd, it *is possible* for the pathologist to confuse it with the stroma. It is also possible that the centrally located odontogenic epithelial cells will take on a more acanthomatous or squamoid appearance. This epithelial-stromal arrangement histologically flips back and forth within the complex odontoma lesion; in such a lesion, it is very easy for the pathologist to become topologically disoriented. Again, cytokeratin and vimentin IHC studies are very helpful to identify the "inside out" and "outside in" arrangement of tissues. It is also helpful to remember that the stroma will have blood vessels whereas the odontogenic epithelium is vessel-free.

Mature compound or complex odontomas removed from older animals can be both very dense and very hard, being almost exclusively comprised of mineralized matrical tissues like dentin and enamel. As a result, these lesions may require extensive demineralization treatments, potentially resulting in the loss of the more delicate features of the associated soft tissues. Using the proper equipment to thinly section these lesions prior to final fixation and demineralization is key to achieving optimal histologic results (see Appendix).

There is a pervasive set of existing literature describing what may appear to be odontoma-like lesions in the hypsodont dentition of a variety of rodent species including squirrels, black-tailed prairie dogs, voles, rats, and mice. In 2006, S.C. Boy and G. Steenkamp proposed the term *elodontoma* for the odontoma-like lesions occurring in the hypsodont (or elodont) incisor teeth of captive tree squirrels (*Paraxerus cepapi*) [44]. These proliferative odontogenic lesions, which are

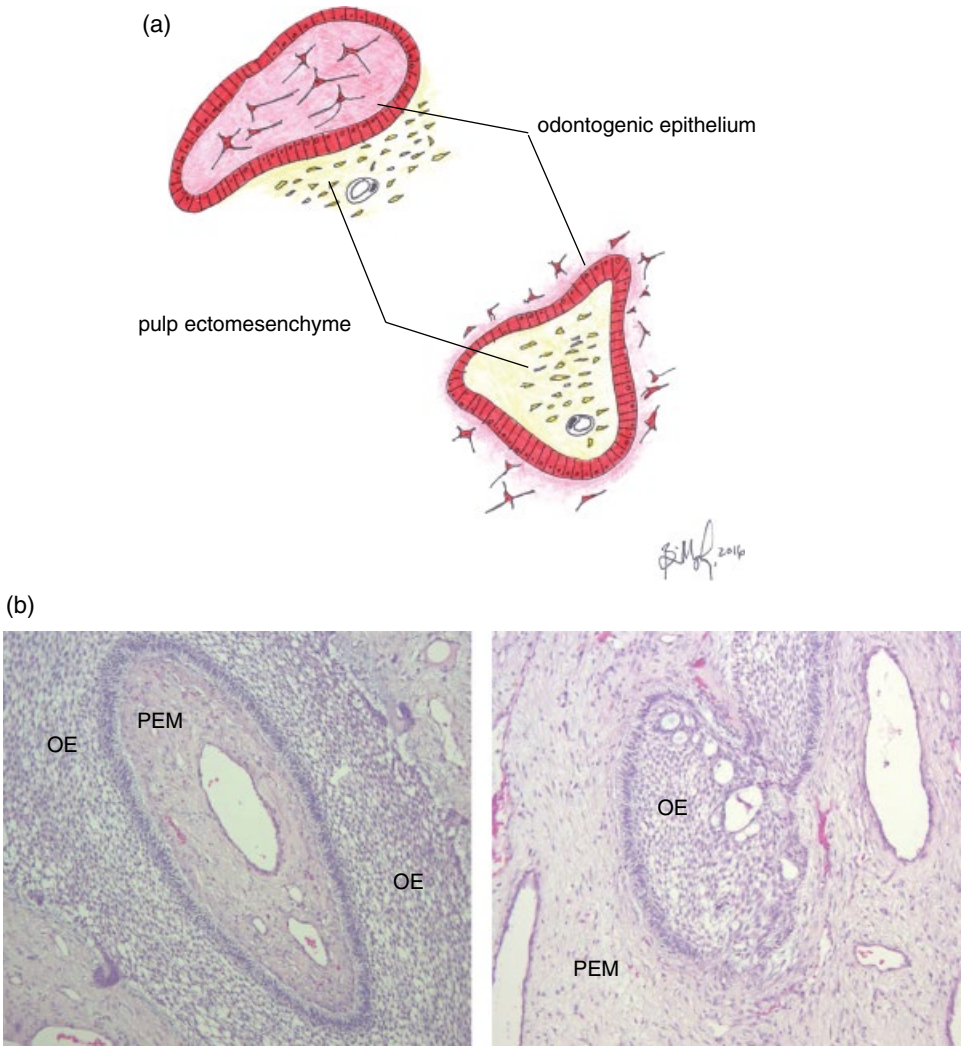


Figure 7.28 Topological (spatial) relationships of odontogenic epithelium (OE) and ectomesenchyme of the dental papilla. (a) Diagram, (b) histologic images of a complex odontoma, mandible, six-year-old Quarter horse. In the two histologic images, note the spatial relationships of the OE and papillary ectomesenchyme (PEM) with blood vessels.

often bilateral, were characterized by the authors as "odontoma-like conglomerates of haphazardly arranged odontogenic hard and soft tissue and bone." The authors proposed a traumatic pathogenesis for the creation of these "elodontomas."

As a result of the single histologic image, and a general paucity of written microscopic detail in the Boy and Steenkamp manuscript, it is difficult to make a balanced judgment on whether or not these rodent tooth lesions actually represent true odontomas. However, the authors of this textbook have personally examined multiple "odontoma-like" lesions in rats, mice, voles, and rabbits, and have determined that they are best defined as odontogenic dysplasia, *not* odontomas. This relationship of odontoma vs. odontogenic dysplasia is analogous to the cementoblastoma lesion (true neoplasm of cementocytes/–blasts) vs. the so-called equine cementoma lesion (nodular hypercementosis, inflammation/trauma-induced hyperplasia/dysplasia of cementocytes/–blasts).

Odontogenic dysplasia is a reactive lesion that is the result of the disorganized development of the continuously erupting teeth of rodents and lagomorphs due to inflammation, trauma, toxicosis or age [45]. Although the ultimate cause of odontoma lesions remains in limbo, most investigators would agree to either a neoplastic or hamartomatous pathogenesis, and *not* the result of inflammation, trauma, toxicosis or age. Interested readers are referred to Section 4.2.7 on odontogenic dysplasia of rabbits and rodents.

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References

41 El-Naggar, A.K., Chan, J.K.C., and Rubin Grandis, J. International Agency for Research on Cancer. 2017. In: *WHO classification of head and neck tumours*. Lyon: International Agency for Research on Cancer.

42 Regezi, J.A., Sciubba, J.J., and Jordan, R.C.K. (2008). *Oral Pathology: Clinical Pathologic Correlations*, 5e. St. Louis, Mo: Saunders/Elsevier.

43 Coffee, L.L., Casey, J.W., and Bowser, P.R. (2013). Pathology of tumors in fish associated with retroviruses: a review. *Vet. Pathol.* 50: 390–403.

44 Boy, S.C. and Steenkamp, G. (2006). Odontoma-like tumours of squirrel elodont incisors – elodontomas. *J. Comp. Pathol.* 135: 56–61.

45 Head, K.W. and Armed Forces Institute of Pathology (U.S.), American Registry of Pathology., & WHO Collaborating Center for Worldwide Reference on Comparative Oncology (2003). *Histological classification of tumors of the alimentary system of domestic animals*. Published by the. Washington, DC: Armed Forces Institute of Pathology in cooperation with the American Registry of Pathology and the World Health Organization Collaborating Center for Worldwide Reference on Comparative Oncology.

46 Murphy, B., Bell, C., Koehne, A., and Dubielzig, R.R. (2017). Mandibular odontoameloblastoma in a rat and a horse. *J. Vet. Diagn. Invest.* https://doi.org/10.1177/1040638717711996.

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7.4.2 Ameloblastic Fibro-Odontoma

Ameloblastic fibro-odontoma (AFO) is a mixed odontogenic tumor that, like the other lesions in this group, is comprised of both neoplastic odontogenic epithelium and induced ectomesenchyme of the dental papilla. Importantly, these lesions also demonstrate evidence of hard dental matrix production (dentin and enamel). AFO is diagnostically separated from the odontomas and odontoameloblastoma by the proportion of papillary ectomesenchyme, as AFO is *predominantly composed of ectomesenchyme of the dental papilla*.

It should be noted that the AFO lesion has been dropped from the latest version of the World Health Organization (WHO) classification of head and neck tumors in humans [47]. The nature of these lesions has long been debated and the most recent human WHO working group has decided that AFO and odontoameloblastoma represent part of the spectrum of histological changes seen in lesions that otherwise are classified as odontoma (they have been "lumped") [48].

In the previous WHO edition [49], AFO is described as a benign odontogenic tumor that is uncommon in humans and has rarely been reported in animals. In humans, AFO is most often diagnosed in children or young adults [50]. The tumor may be completely asymptomatic but can also result in tooth impaction (failure to erupt). In such cases, the neoplastic lesion may be revealed via radiographic imaging. AFO lesions are typically well-circumscribed, unilocular to multilocular, with a sclerotic lesion margin and varying degrees of central radiopacity depending upon the particular extent of lesion mineralization (extent of the odontoma component). Recurrence after definitive treatment is rare and the prognosis is generally good.

In veterinary species, AFO is a rare tumor that has been described in the dog, horse, and ox. In dogs, AFO has been most frequently identified in puppies [51]. This benign tumor generally behaves like ameloblastoma, in that it is locally invasive and generally does not metastasize. AFO is closely related to another odontogenic mixed tumor, ameloblastic fibroma (AF). The only diagnostic difference between AFO and AF is the presence or absence of the mineralized dental matrix, respectively. AFO lesions have been identified in both the maxilla and mandible.

Histologically, AFO is a tripartite lesion comprised of (i) ectomesenchyme of the dental papilla, (ii) odontogenic epithelium, and (iii) mineralized dental matrix. Although all three of these elements need to be identified to establish the diagnosis, the predominant histologic feature is the ectomesenchyme of the dental papilla (Figure 7.29). This induced ectomesenchyme is a primitive-appearing myxoid connective tissue that is "papillary-like" and has a general absence of pink-staining collagen. The "papillary-like" fibroblasts are generally equally distributed and have bland, typically featureless, ovoid to polygonal nuclei, and inapparent cytoplasmic margins. Mitotic figures and anisokaryosis are generally absent. Small numbers of vessels are scattered throughout the amphophilic to basophilic pulp tissue. The staining qualities of the extracellular matrix are presumably the result of the high proteoglycan-to-collagen content in pulp-derived tissue. Induction between the odontogenic epithelium and dental matrix-producing tissues form dysplastic structures of dental matrix upon a background of loose ectomesenchyme.

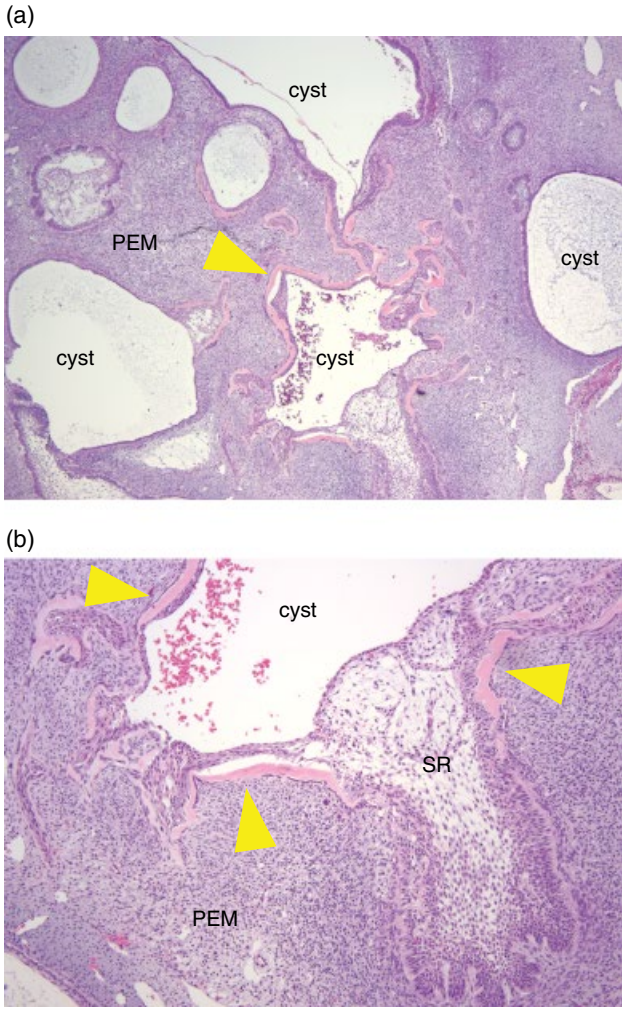


Figure 7.29 Histologic images of a maxillary ameloblastic fibro-odontoma (AFO), four-month-old Labrador retriever puppy. Note the abundant papillary ectomesenchyme (PEM), ribbons and sheets of odontogenic epithelium (stellate reticulum, [SR]), and undulating ribbons of dental matrix (yellow arrowheads). Also note the basophilic staining properties of the PEM. Multiple cysts are scattered throughout the lesion. (a) Low magnification and (b) high magnification images.

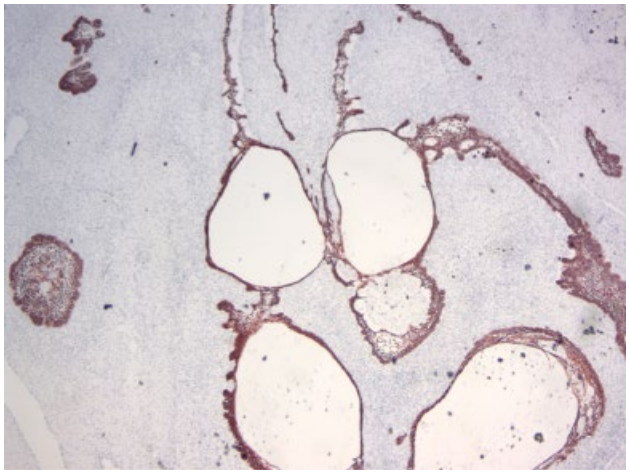
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In actual AFO lesions, the cellular density and staining characteristics of the papillary ectomesenchyme can vary from overtly basophilic all the way to eosinophilic. However, somewhere in the AFO lesion, the papillary ectomesenchyme should demonstrate basophilic staining properties, and the pathologist should strive to identify this. Although the AFO lesion is predominantly comprised of ectomesenchyme, currently it is thought to be a non-neoplastic component induced into proliferation by the associated neoplastic odontogenic epithelium. To our knowledge, this hypothesis of pathogenesis has yet to be rigorously tested.

The proportion of the embedded odontogenic epithelium comprising the AFO lesion can vary from relatively insubstantial to abundant. However, there is *always* less odontogenic epithelium than papillary ectomesenchyme. In some lesions, embedded odontogenic epithelium may be very rare indeed- the diagnosis hinges on locating it! The cardinal histologic features of odontogenic epithelium vary from present to absent and the architectural arrangement of the epithelium can take on a follicular, plexiform ribbon or "ink-drop" arrangement (the interanastomosing trabecular arrangement is rarely identified in AFO, see Approach to odontogenic neoplasms). In addition, some AFO lesions have sheets of pulp ectomesenchyme circumscribed into irregular lobules by an undulating rim of odontogenic epithelium. This is distinct from the human AFO lesion in which the odontogenic epithelium generally demonstrates an architectural pattern of evenly distributed plexiform ribbons or follicles. As is true for any tumor containing odontogenic epithelium, central epithelial degeneration and cyst formation can be multifocally present (Figure 7.29).

As AFO lesions are a kind of odontoma, they *must* demonstrate evidence of dental matrix production. The proportion of this eosinophilic to magenta-staining matrix varies from lesion to lesion, but is secondary to the proportion of pulp ectomesenchyme. As is true for odontomas, if the AFO lesion goes undetected and matures, the proportion of the lesion comprised of dental matrix increases with time. Lesional dentin may or may not demonstrate a tubular architecture, and enamel may or may not have the "appropriate" staining characteristics. However, the dental matrix often is arranged into undulating, linear ribbons or ring-like structures (Figure 7.29). Because AFO is a neoplasm, the dental matrix can also anastomose into complicated structures, often palisaded by epithelium-derived ameloblasts (CK positive, vimentin negative) or aggregating ectomesenchyme-derived odontoblasts (CK negative, vimentin positive) (Figure 7.30). Lesion-associated enamel matrix is always less abundant than dentin.

(a)



(b)

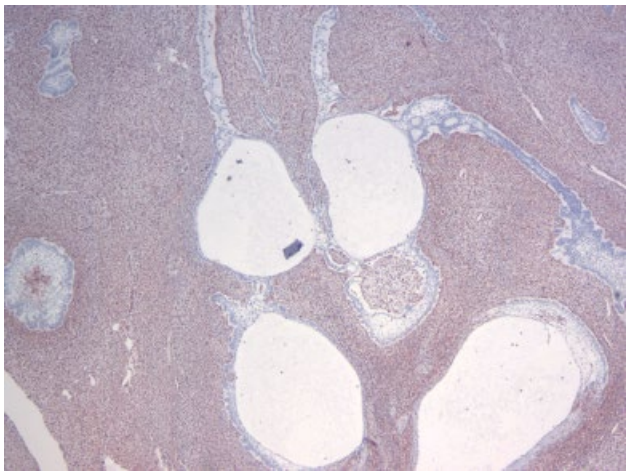


Figure 7.30 (a) Cytokeratin and (b) vimentin immunohistochemistry of AFO, four-month-old Labrador retriever puppy. Cytokeratin labels the neoplastic odontogenic epithelium while vimentin labels the induced papillary ectomesenchyme; these two immunohistochemical stains form negative images of one another. This is the same lesion as Figure 7.29.

The AFO lesion may be partially to completely encased in a thin shell of metaplastic woven bone. This is radiographically revealed as a sclerotic rim surrounding the lesion. In some cases, the dentinal matrix of the lesion may actually blend into the adjacent metaplastic bone; the pathologist needs to be wary! It is also possible that in some cases, AFO may actually be a hybrid lesion with AF and an additional focus of odontoma. Ueki and co-authors have described a malignant version of AFO in an 11-year-old Collie dog [52]. In this report, the AFO apparently metastasized to the lymph nodes, lung, liver, and orbital cavity. The authors of this report considered the ectomesenchymal portion of the tumor to be a malignant fibrosarcoma.

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References

47 El-Naggar, A.K., Chan, J.K.C., Rubin Grandis, J., and International Agency for Research on Cancer (2017). *WHO Classification of Head and Neck Tumours*. Lyon: International Agency for Research on Cancer.

48 Speight, P.M. and Takata, T. (2018). New tumour entities in the 4th edition of the World Health Organization classification of head and neck tumours: odontogenic and maxillofacial bone tumours. *Virchows Arch.* 472: 331–339.

49 Barnes, L. and UniversitätsSpital Zürich, Departement Pathologie., International Academy of Pathology., World Health Organization., International Agency for Research on Cancer (2005). *Pathology and Genetics of Head and Neck Tumours*. Lyon: IARC Press.

50 Regezi, J.A., Sciubba, J.J., and Jordan, R.C.K. (2008). *Oral Pathology: Clinical Pathologic Correlations*, 5e. St. Louis, Mo: Saunders/Elsevier.

51 Huang, P., Bell, C.M., Wallace, V., and Murphy, B.G. (2018). Mixed odontogenic tumors in four young dogs: ameloblastic fibroma and ameloblastic fibro-odontoma. *J. Vet. Diagn. Investig* 31: 98–102.

52 Ueki, H., Sumi, A., Takaishi, H. et al. (2004). Malignant ameloblastic fibro-odontoma in a dog. *Vet. Pathol.* 41: 183–185.

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7.4.3 Odontoameloblastoma

Odontoameloblastoma (OA) is an odontogenic mixed tumor. As is true for the other two members of this group, ameloblastic fibro-odontoma and odontoma, OA is a tripartite tumor comprised of (i) odontogenic epithelium, (ii) ectomesenchyme of the dental papilla and (iii) mineralized dental matrix. In a given lesion, not all of these odontogenic tissues are necessarily equally represented and some of the tissues may even be difficult to identify. Of the three tumors in this group, *OA has the greatest proportion of neoplastic epithelium* (Figure 7.31). OA can be thought of as an ameloblastoma that also produces mineralized dental matrix, that is, OA is a cross between an ameloblastoma and an odontoma. This interpretation is implicit in the name.

OA is a rare tumor in both humans and veterinary species. In humans, it is a locally aggressive tumor that occurs in both the mandible and maxilla and is similar in behavior and prognosis to ameloblastoma. It is important to note that the most recent edition of the World Health Organization Classification of Head and Neck Tumours (human) no longer includes OA [53]. Most cases are associated with displaced or unerupted teeth. Radiographically, OA presents as a well-defined unilocular or multilocular radiolucent lesion with varying amounts of interspersed radiopaque material.

The history of OA in veterinary species is a winding and confusing one. OA has been historically associated with a problematic (and closely related) term that is *not directly synonymous-* ameloblastic odontoma. Today, ameloblastic odontoma is considered to represent *either* (i) OA or (ii) ameloblastic fibro- odontoma. Due to this imprecision, the future use of this antiquated term has been discouraged. Unfortunately, over the past 50 years or so, the term ameloblastic odontoma has become enmeshed within the veterinary pathology literature. As a result, our current understanding of previously reported ameloblastic odontoma lesions is a bit muddled.

Although considered to be a rare odontogenic tumor, OA, and ameloblastic odontoma have been reported in multiple mammalian species including human and nonhuman primates, dog, cat, horse, ox, sheep, llama, rat and mouse. In the five peer-reviewed

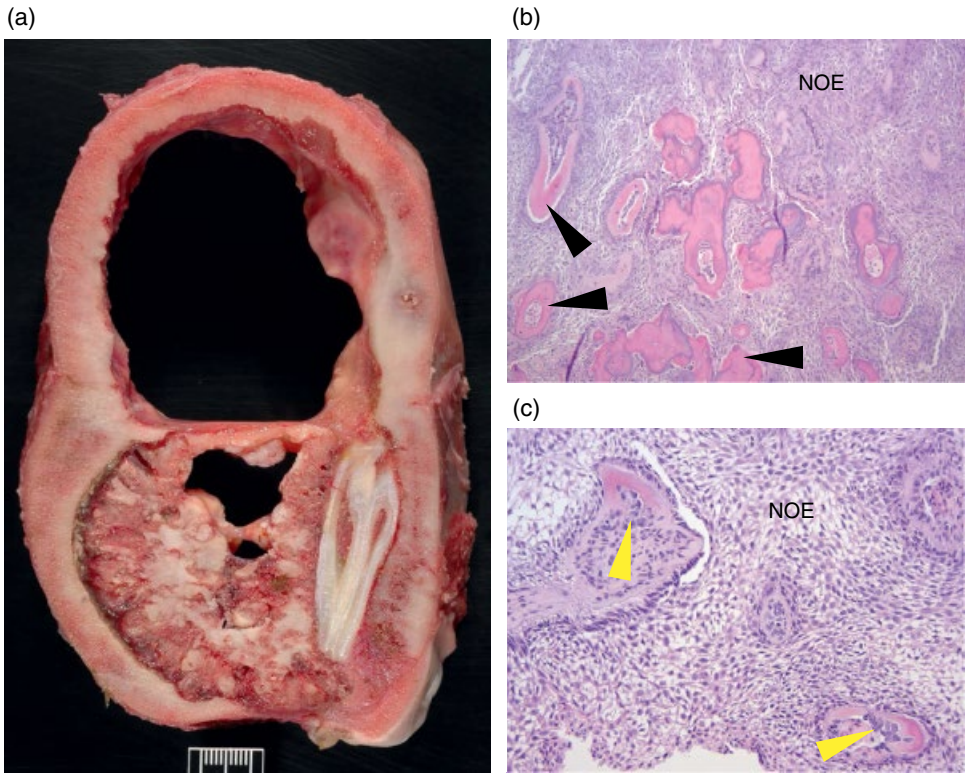


Figure 7.31 Gross and histologic images of a mandibular odontoameloblastoma OA, 2-year-old Appaloosa horse. (a) Gross image of the mandibular lesion in cross section. Note the solid and cystic portions of the neoplasm and the unerupted tooth. (b) The lesion is characterized histologically by sheets of neoplastic odontogenic epithelium (NOE) and interspersed eosinophilic/basophilic ribbons and irregular tooth like structures (dental matrix, black arrowheads). (c) In a higher magnification, the NOE has features of stellate reticulum. Dental matrix is sandwiched between the NOE and polygonal cells forming jumbled aggregates (odontoblasts, yellow arrowheads). *Source:* M. Jones, University of California, Davis [54].

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reports of OA in veterinary species (Japanese monkey [*Macaca fuscata*], horse, calf, two rats and sheep), the mandible appears to be a favored anatomical site of occurrence [54–58].

OA is a locally aggressive and expansile lesion. The bone of the jaw and alveolus is often focally destroyed and infiltrated by neoplastic odontogenic epithelium (NOE) in a manner reminiscent of ameloblastoma. Architecturally, the odontogenic epithelium is arranged in follicles, plexiform ribbons and/or anastomosing trabeculae embedded in *a scant* fibrovascular to dental papilla-like ectomesenchymal stroma. The epithelium can be cystic and the cardinal features of odontogenic epithelium are variably evident: palisading of the basilar epithelium with antibasilar nuclei, a basilar clear zone, and central epithelial cells reminiscent of stellate reticulum. The mitotic rate in the basilar cells may be high (1–5 mitotic figures per 400x high-power field). Of note, the stroma of the OA is scant, which is *very unlike* the ameloblastic fibro-odontoma lesion.

In order to satisfy the diagnostic criteria for this lesion, mineralized dental matrix must be identifiable within the OA lesion. This intralesional matrical material is often present as thin, atubular, eosinophilic wedges, rings, ribbons, or dysplastic tooth-like structures palisaded *on one face* by cytokeratin-positive columnar epithelial cells (odontogenic epithelium-derived ameloblasts) *and along the other face* by vimentin-positive, densely packed, jumbled aggregates of polygonal to fusiform cells (odontogenic ectomesenchyme-derived odontoblasts). The matrical material is often histologically consistent with osteodentin. Osteodentin is rapidly formed, tertiary dentin that often entraps odontoblasts and demonstrates few (if any) recognizable dentinal tubules; it has a histologic appearance reminiscent of bone. The mineral component of the dental matrix is typically removed during histologic preparation. Enamel matrix may also been identified in OA lesions, deposited along the surface of the dentin, presumably by ameloblasts. In some OA lesions, the proportion of the mineralized dental matrix can be pronounced. The pathologist should entertain the possibility of an amyloid-producing ameloblastoma (aka APOT/CEOT) in cases where the mineralized matrix is highly disordered and abundant.

References

53 El-Naggar, A.K., Chan, J.K.C., and Rubin Grandis, J. (2017). *WHO Classification of Head and Neck Tumours*, World Health Organization classification of tumours, 4e, 347. Lyon: International Agency for Research on Cancer.

54 Murphy, B., Bell, C.M., Koehne, A., and Dubielzig, R.R. (2017). Mandibular odontoameloblastoma in a rat and a horse. *J. Vet. Diagn. Invest.* 29 (4): 536–540.

55 Burrough, E.R., Myers, R.K., and Whitley, E.M. (2010). Spontaneous odontoameloblastoma in a female Sprague Dawley rat. *J. Vet. Diagn. Invest.* 22 (6): –1001.

56 Dubielzig, R.R. and Griffith, J.W. (1982). An odontoameloblastoma in an adult sheep. *Vet. Pathol.* 19 (3): 318–320.

57 Yanai, T., Masegi, T., Tomita, T. et al. (1995). Odontoameloblastoma in a Japanese monkey (*Macaca fuscata*). *Vet. Pathol.* 32 (1): 57–59.

58 Elvio, L., Avallone, G., Mandara, M.T., and Vitellozzi, G. (2013). Odontoameloblastoma in a calf. *J. Vet. Dent.* 30 (4): 248–250.

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7.5 Cementoblastoma

The dental follicle (or dental sac) is a loosely defined aggregate of ectomesenchyme that envelops the developing tooth germ. The dental follicle is comprised of mesenchymal cells that have a multipotential developmental ability, capable of differentiating into osteoid-producing osteoblasts, collagen-producing fibroblasts, or cementum-producing cementoblasts. These three cell types are responsible for producing and maintaining the alveolar bone, periodontal ligament, and tooth-associated cementum, respectively. Collectively, these tissues form a unique type of joint, referred to as the gomphosis, serving to anchor the teeth into the jaw. Multiple island-like remnants of odontogenic epithelium, referred to as rests of Malassez, are scattered throughout the periodontal ligament and persist throughout life.

Proliferative lesions arising from the dental follicle and its variously derived tissue types are not without controversy. Overlap among hyperplasia, dysplasia, and neoplasia of these tissues is one major source of confusion. The precise identification of the dental follicle as the source or parent tissue for a particular lesion is also difficult to establish. Such proliferative lesions include cementoblastoma and potentially a variety of other fibro-osseous lesions such as fibromatous epulis of periodontal ligament origin (also known as peripheral odontogenic fibroma), nodular hypercementosis (cementoma), odontogenic dysplasia, cemento-ossifying fibroma (cementifying fibroma), ossifying fibroma and fibrous dysplasia. Only cementoblastoma will be discussed here; the other entities are described elsewhere in this textbook.

Although rare, cementoblastoma is relatively well-characterized in human oral pathology as a *benign tumor of cementum-producing cementoblasts*. Critical to the diagnosis, cementoblastoma is intimately associated with and generally attached to the tooth root, resulting in a typical radiographic appearance [59]. This lesion may result in cortical expansion, and can be associated with oral pain. Tooth vitality is typically maintained.

Histologically, the cementoblastoma lesion in human patients is characterized by a dense mass of mineralized cementum closely associated with intervening vascularized soft tissues containing numerous, large, hyperchromatic cementoblasts palisading along the matrix. The cementum is basophilic with numerous reversal lines and scattered osteoclasts may be present [59]. The cellular component of this lesion is critical to establish the correct diagnosis. In people, cementoblastoma is histologically similar to (some would say histologically indistinguishable from) the osseous lesion *osteoblastoma*, which has been only rarely recognized in veterinary species. The distinguishing feature between these two lesions is the close attachment of the cementoblastoma to the tooth root. As a result, the correct diagnosis is essentially dependent upon the anatomic association of the proliferative mineralized tissue with the tooth root. For these reasons, many oral pathologists feel that the diagnosis of cementoblastoma *should not be based upon histologic appearance alone*.

In veterinary species, cementoblastoma is less well characterized, and in the peer-reviewed literature, has only been described in a rat and a gazelle [60, 61]. Although the reported histologic details and images are limited, the features of the described lesions are in general agreement with the cementoblastoma lesion, as defined by the World Health Organization Classification of Head and Neck Tumors [59]. Two other presumptive cases of cementoblastoma have been identified in middle-aged dogs (personal commination with Dr. R. Pool). The current paucity of published cases of cementoblastoma begs the question of whether a close analog of the human lesion actually exists in veterinary species. Patience, time and careful observation will determine the answer to this question.

The diagnosis of cementoblastoma is dependent upon the proliferative tissue arising from the outer surface of a tooth root and the pathologist's ability to accurately identify pathologic cementum in tissue sections. Differentiating between cementum and osteoid can be problematic, as both of these pink-staining matrices are comprised of collagen I, are typically mineralized, and have interspersed lens-shaped lacunae with (or without) embedded cells (cementocytes or osteocytes, respectively). In addition, both cementum and osteoid can be produced by cells derived from the dental follicle, and so potentially occupy the same anatomic niche. There are, however, a few useful histologic features distinguishing these two tissue types. Cementum is often characterized by numerous thin basophilic cementing lines, which may imbue a *topographic map* or *mosaic-like appearance* to the cementum. Proliferative cementum also tends to form irregularly margined, expansive sheets, while proliferative osteoid tends to form interconnected islands or trabeculae of woven bone. To put a fine point on it: physiologically normal osteoid/woven bone generally does not form large expansive sheets, as this feature is reserved for cortical bone. Expansive sheets of cortical bone are generally lamellarized, not woven, and lamellarized bone is easily differentiated from cementum. A good set of polarizing lenses is useful in the distinction. However, it is helpful for the pathologist to bear in mind that neoplastic/pathologic bone may be histologically indistinguishable from cementum. For this reason, the anatomy of the lesion, or topographic arrangement of the lesion can be highly informative (e.g. mass attached to the tooth root).

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In veterinary pathology, the term *cementoblastoma* has also been used as a de facto synonym for another problematic term- cementoma. Veterinary clinicians, radiologists, surgeons, and even anatomic pathologists have played a role in the controversial history of these interlinked terms. So-called cementomas are relatively commonly diagnosed in animals with hypsodont dentition, like the cheek teeth of the horse. The cementoma lesion is a chaotic and hyperplastic proliferation of cementum arising on or near the tooth root, often extending into the maxillary sinuses or nasal passages. Importantly, cementomas are mineralized concretions that do not histologically demonstrate *intervening vascularized soft tissues containing numerous, large, hyperchromatic cementoblasts*. As a result, cementomas are not histologically consistent with the definition of cementoblastoma, nor are they likely to be a tumor.

It is the opinion of the authors of this textbook that the so-called equine cementoma lesion is actually a hyperplastic/dysplastic lesion of cementocytes and does not represent a true neoplasm. As the term cementoma implies a neoplastic pathogenesis, a more appropriate term for this relatively common tooth root-associated lesion is *nodular hypercementosis* (see Chapter 4, Equine dental disease). In some ways, nodular hypercementosis shares some pathogenic features with the rabbit/rodent lesion *odontogenic dysplas*ia.

References

59 El-Naggar, A.K., Chan, J.K.C., Rubin Grandis, J. et al. (2017). *WHO Classification of Head and Neck Tumours*. Lyon: International Agency for Research on Cancer.

60 Martin, H.D., Turner, T., Kollias, G.V. et al. (1985). Cementoblastoma in a Dama gazelle. *J. Am. Vet. Med. Assoc.* 187: 1246–1247.

61 Slootweg, P.J., Kuijpers, M.H., and van de Kooij, A.J. (1996). Rat odontogenic tumors associated with disturbed tooth eruption. *J. Oral Pathol. Med.* 25: 481–483.

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7.6 Odontogenic Myxoma

In veterinary species, this "group" of odontogenic lesions derived from the ectomesenchyme of the dental papilla currently has a single member – the odontogenic myxoma (OM). This neoplasm is unlike the majority of the odontogenic tumors in that it *generally lacks evidence of neoplastic odontogenic epithelium*. As a result, OM is *not* a mixed tumor and the pathogenesis does not involve the process of induction. Unlike most of the other odontogenic tumors which involve neoplastic epithelium, the transformed cells in OM are thought to be the papillary ectomesenchyme-derived cells themselves.

In humans, OM is an intraosseous (central) tumor that predominantly occurs within the mandible [62]. Although uncommon, OM is the third most common odontogenic tumor, and the mean age of occurrence is 30 years. Radiographically, OM has a unilocular to multilocular radiolucent appearance, and may demonstrate a "soap bubble" or "honeycomb" pattern with fine trabeculations. The lesion border is variable, ranging from well-defined to poorly delineated. OM has a tendency to invade the marrow spaces of the jawbone, and associated tooth root displacement or resorption can occur. Grossly, OM has a translucent gray-white mucinous appearance with a consistency varying from gelatinous to firm. In humans, variant OM lesions with a greater amount of collagen have been referred to as *odontogenic fibromyxoma*.

In veterinary species, OM is a rare tumor, less frequently identified than other odontogenic tumors. In the older literature, OM was known as "jaw myxoma" or "myxomatous tumor of the jaw," and has been most often described in young horses or adult dogs. OM can present in either the maxilla (most of the described cases in horses) or mandible (most of the described cases in dogs). Despite being considered to be a slowly progressive, benign lesion, OM can be both destructive (osteolytic) and invasive and may result in oral ulceration [63].

In horses, OM has been anatomically associated with the maxillary arcade, arising from foci of missing, displaced or unerupted teeth. Equine maxillary lesions often extend into the nasal cavity, eventually resulting in large sinonasal lesions and a presentation of nasal discharge. Radiographic findings for OM in horses are similar to those identified in humans – an expansile lesion associated with a "honeycomb" pattern of lysis of the adjacent bone. In mandibular lesions, OM can invade the mandibular canal.

Grossly, OM is soft to rubbery, and gray-white and gelatinous on section. Histologically, the lesions are comprised of sparsely distributed, often isolated spindle to stellate cells with prominent nucleoli and a low mitotic rate embedded within a loose myxomatous matrix (*mucinous ground substance*) that is reminiscent of dental papilla, which gives rise to pulp tissue. The extracellular matrix is abundant, and rich in mucopolysaccharides (hyaluronic acid/chondroitin sulfate) and stains either basophilic or poorly with H&E [64]. As a result, the matrix of OM is strongly reactive with the mucin stain alcian blue. Vimentin expression is confirmed using immunohistochemistry. There are conflicting reports for IHC-based actin expression in OM. Small amounts of non-neoplastic odontogenic epithelium may be present in the lesion but are not required to establish the diagnosis [64].

There is some controversy about the histogenesis of OM (it is not listed in the 2003 WHO fascicles [65]). One source of confusion is the fact that myxomatous tissue may be a feature of distinctly different pathologic processes in the oral cavity. Some investigators suggest that this lesion actually represents a type of oral myxosarcoma or fibromyxoma, arising from the connective tissues of the oral mucosa or bone and *not* from dental germ tissue. Another factor is that there is currently no ancillary test to absolutely confirm that a particular myxomatous tissue is derived from pulp ectomesenchyme. OM has histological features that overlap with myxosarcoma (arising from bone or soft tissues that are NOT of dental germ tissue origin) and myxomatous change as seen in some forms of osteomyelitis of the jaws (especially in cats). Histiocytic foam cell nodules may also be histologically confused with OM (see Figure 7.32 and Section 10.1, Tumor like proliferative lesions of the oral mucosa).

What is the evidence that OM is truly odontogenic? Unfortunately, in the absence of lesion-associated odontogenic epithelium or mineralized dental matrix, there currently is no ancillary test to absolutely confirm the presence of pulp ectomesenchyme. The evidence of a pulp-derived histogenesis consists of – (i) the anatomic involvement of toothed regions of the jaw, (ii) the association with unerupted, displaced or absent teeth, and (iii) pathologic lesions grossly and histologically consistent with pulp ectomesenchyme. The authors of this textbook believe that there may be three distinct, but related entities with overlapping features – (i) OM, which would be expected to occur in young animals and accompanied by other evidence of disrupted odontogenesis (i.e. impacted, dysplastic, or missing tooth), (ii) sarcomas with variable myxomatous differentiation that arise from the jaw or soft connective tissues, usually of older animals, and (iii) cases of osteomyelitis with myxomatous change. Until a more specific molecular or morphology-based assay is developed, distinguishing between OM, myxomatous inflammation, and sarcomas with myxoid differentiation will be problematic and depend heavily on the overall clinical presentation on a case-by-case basis.

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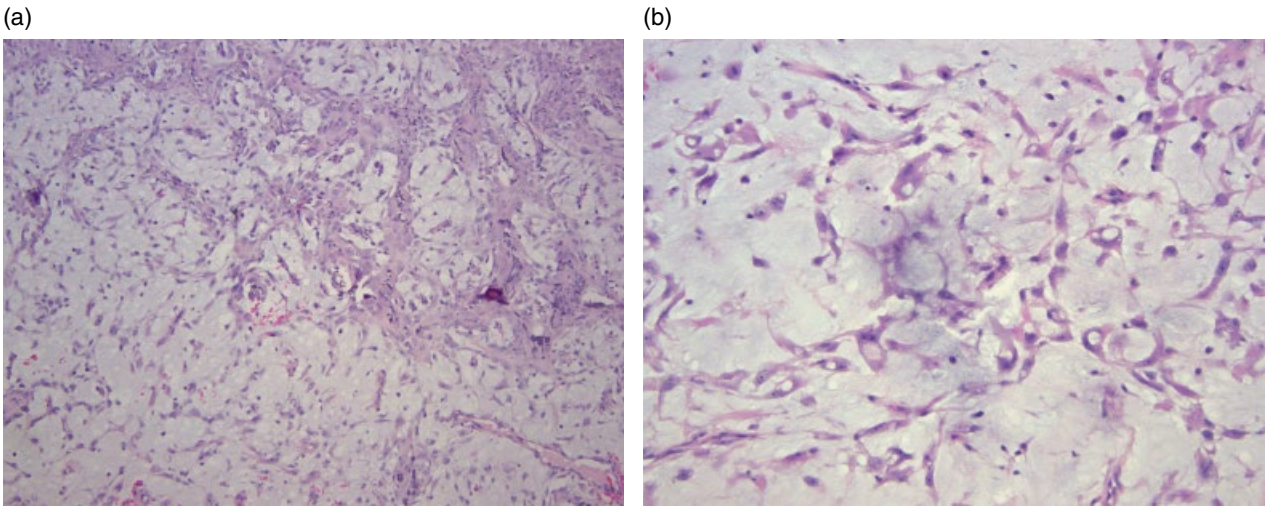


Figure 7.32 (a) Low magnification and (b) high magnification histologic images of an odontogenic myxoma, eight-year-old Labrador retriever dog. Note the plump stellate mesenchymal cells amidst mucinous ground substance reminiscent of dental pulp. *Source:* North Dakota State University and R. Barigye et al. [63].

Box 7.8 Differential Diagnoses for Odontogenic Myxoma

Myxosarcoma/myxoma of the jaw or oral mucosa
Myxomatous change associated with osteomyelitis
Histiocytic foam cell nodules

7.6.1 Clinical Features

OM generally possesses a radiolucent appearance on radiography that is characterized as a uni- to multilocular radiolucency resembling a honeycomb pattern. Given the rarity of OM, few generalities can be made regarding the clinical behavior and treatment of OMs. Previous reports of OM in dogs describe a slow growing, mandibular swelling that responded well to resection with 1-cm gross surgical margins.

References

62 Regezi, J.A., Sciubba, J.J., and Jordan, R.C.K. (2008). *Oral Pathology: Clinical Pathologic Correlations*, 5e. Saunders/Elsevier: St. Louis, MO.

63 Barigye, R., Schultz, J., Newell, T.K., and Dyer, N.W. (2011). Odontogenic myxoma in an 8-year-old Labrador Retriever dog. *J. Vet. Diagn. Invest.* 23: 167–171.

64 Meuten, D.J. (2017). *Tumors in Domestic Animals*, 5e. Ames, Iowa: John Wiley & Sons.

65 Head, K.W., Armed Forces Institute of Pathology (U.S.), American Registry of Pathology, and & WHO Collaborating Center for Worldwide Reference on Comparative Oncology (2003). *Histological Classification of Tumors of the Alimentary System of Domestic Animals*. Washington, DC: The Armed Forces Institute of Pathology in cooperation with the American Registry of Pathology and the World Health Organization Collaborating Center for Worldwide Reference on Comparative Oncology.

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8

Tumors Arising from the Soft Tissues

8.1 Melanocytic Tumors

Melanocytic tumors of the oral cavity, melanoma and melanocytoma, are frequently diagnosed in the dog and are diagnosed far less often in other species. These tumors are derived from melanocytes, spider-like cells with multiple pseudopodial processes. These cells originate as melanoblasts in the embryonic neural crest and subsequently migrate to a variety of tissues, including the basal layer of the oral mucosal epithelium. Melanocytes produce melanin pigment, which is created within the melanocyte by a chain of chemical reactions utilizing the amino acid tyrosine as a substrate and catalyzed by the enzyme tyrosinase.

Within the melanocyte, melanin is synthesized and stored within little membrane-bound packets called melanosomes. The melanin is distributed to the adjacent keratinocytes and stored within perinuclear cap-like structures. These melanin-caps serve to protect the epithelial cells' nucleic acids from UV-mediated injury. This process of melanization is grossly evident in the varying pigmentation of the oral mucosa of different animals. Melanin imparts a brown, black or blue pigmentation to the mucosa, dependent upon the amount of melanin produced and the depth of the deposit.

In human beings, a variety of melanocyte-derived oral proliferative lesions are recognized, including: melanosis (physiologic and smoking-associated), melanotic macule, Cafe-au-Lait macule, melanocytic nevus, melanoacanthoma, and melanoma (formerly known as malignant melanoma) [1]. In veterinary species, this list collapses into three entities – melanosis, melanocytoma and melanoma. Melanosis is recognized as benign black or brown pigmentation of various tissues (skin, mucosa, iris, intima or arteries, meninges) as a result of melanocyte-mediated melanin production; melanosis is not considered to be pathologic and has no clinical consequence.

8.1.1 Oral Melanocytoma

Oral melanocytoma is the counterpart to the cutaneous melanocytoma – a benign version of melanoma. These lesions are *uncommonly* identified in dogs and are rarely found in other mammalian species. The term *nevus* has been used to describe benign melanocytic lesions in both human and veterinary pathology, but lacks a good pathologic definition and should be avoided [2]. Twenty-six and 37 cases of oral melanocytoma have been diagnosed in dogs in the UC Davis pathology and CCOMP databases, respectively. Some studies have split oral melanocytic tumors (arising from the gingiva, tongue, labial mucosa, palate or pharynx), which tend to have a worse prognosis, from those involving the mucous membranes of the lips, which may have a slightly better prognosis [3, 4].

Oral melanocytomas are generally small, <1 cm diameter, with sharply delineated margins. They are derived from well-differentiated melanocytes and, as a result, may be heavily pigmented, appearing as dark brown to black mucosal lesions. Histologically, round to polygonal melanocytes form dense aggregates at the epithelial/subepithelial interface (Figure 8.1). Abundant melanin pigment production frequently obscures the cytologic and nuclear features of these cells, often requiring sectional bleaching (treatment with 1% potassium permanganate) to reveal the nuclear structure. The neoplastic melanocytes have a small nucleus with a single, centrally oriented nucleolus and minimal clumping of chromatin material; the nuclei lack features of atypia and mitotic figures.

A melanocytoma with both epithelial and subepithelial components is termed a compound melanocytic tumor [2]. In a subset of oral melanocytomas, packets or nests of neoplastic melanocytes may extend into the overlying and adjacent epithelium, potentially obscuring and disrupting the basal epithelial/ subepithelial interface. Less often, small packets of melanocytes may extend along the epithelial interface, sometimes several millimeters from the primary mass. The term *lentiginous spread* is defined as intraepithelial proliferation of migrating melanocytes which preferentially reside among basal keratinocytes. Some authors feel that the presence of lentiginous spread may indicate an early stage of malignant transformation [2].

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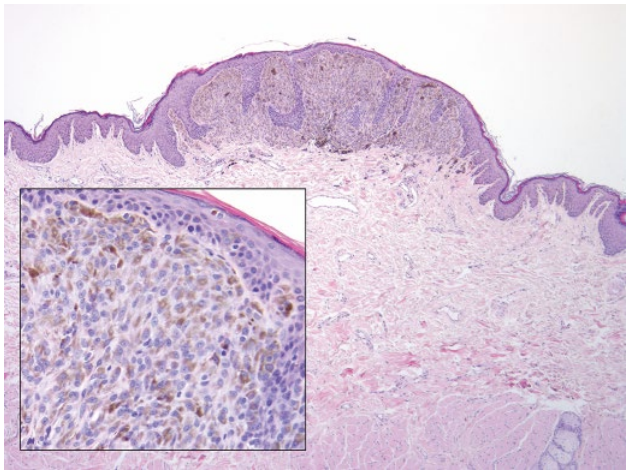


Figure 8.1 Histologic image of a melanocytoma on the lip, 12-year-old MC Brittany spaniel. A small raised mucosal mass is comprised of closely packed melanocytes with moderate amounts of cytoplasmic melanin granules. Inset – neoplastic melanocytes are pigmented and lack mitotic figures and nuclear atypia.

Following compound melanocytic tumors and those that exhibit lentiginous spread "down the road" may prove helpful in establishing the prognostic significance of these histological features.

The involved mucosal epithelium may exhibit acanthotic and papillary proliferation. Within the subepithelial connective tissue, neoplastic melanocytes may form densely arrayed sheets and nodules amidst the pre-existing coarse bundles of collagenous matrix. Individual to small aggregates of pigment-scavenging macrophages (melanophages) may be distributed at the lesion periphery and throughout the melanocytoma. Histologically, it may be difficult to conclusively differentiate between neoplastic melanocytes and reactive melanophages. Deep infiltration of the subepithelial connective tissue does not occur in melanocytoma.

The mitotic index (MI) has been utilized as the principal distinguishing criterion of cutaneous melanoma and melanocytoma. Although Kaplan–Meier survival curves have shown differences among different mitotic indices for *oral* melanocytic tumors, these results were not statistically significant [5]. Other studies have identified a combination of MI and degree of nuclear atypia as a means to prognosticate for canine melanocytic tumors [3]. Ki67 staining has also been shown to be useful as a prognostic marker for canine oral melanoma [6]. It has been difficult to definitively identify specific histologic or clinical features of oral melanocytic tumors in dogs that accurately and reliably portend their biologic behavior. Unfortunately, the use of flow cytometry has not been determined to be helpful in distinguishing between melanocytoma and melanoma.

A subset of canine melanocytic lesions originally diagnosed as melanocytomas have eventually demonstrated a malignant clinical course. Some investigators consider that *any melanocyte-derived tumor in the oral mucosa* of *dogs may potentially behave in a malignant manner*. As a result, some sources state that oral melanocytic lesions should be split into tumors of either low or high malignant potential [2]. It is the opinion of the authors of this book that until large case-controlled studies justify the elimination of the term oral melanocytoma, we will continue to support its use. Nevertheless, a diagnosis of canine oral melanocytoma is perhaps best relayed with a degree of caution.

Box 8.1 Differential Diagnoses for Canine Oral Melanoma

Melanocytoma
Round cell tumors – lymphoma, mast cell, histiocytoma, plasmacytoma
Anaplastic carcinoma
Anaplastic sarcomas
Osteogenic tumors

8.1.2 Oral Melanoma

The term *melanoma* is actually a misnomer in the same way that *lymphoma* is a misnomer, as these lesions are both malignant sarcomas. Despite this, the modifier *malignant*, which was previously paired with melanoma, as in *malignant melanoma* or *malignant lymphoma*, has been dropped. Another synonym for this lesion, *melanosarcoma*, is less often used, but is perhaps a more appropriate term than melanoma.

Melanoma is the most common oral malignancy in dogs, occurring slightly more frequently than the other two common malignant tumors of the canine oral cavity, fibrosarcoma and squamous cell carcinoma. Oddly, oral melanoma is rarely diagnosed in humans or other veterinary species. In some breeds of horses and pigs, melanoma lesions are relatively common in other anatomic regions of the body (e.g. skin), but rarely occur in the oral cavity. Oral melanoma in cats is uncommon; we have identified 4 and 7 cases of oral melanoma in the UC Davis and CCOMP databases, respectively. Feline oral melanoma occurs in the lip, buccal mucosa, palate and jaws. At least two of the feline oral melanoma cases had confirmed metastatic disease to the regional lymph nodes.

Oral melanoma occurs most frequently in older dogs, the mean age of occurrence is approximately 11 years.

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Figure 8.2 Gross image of a mandibular melanoma, 12-year-old M Labrador retriever. A hemorrhagic and black-gray pigmented mass distorts the right mandibular gingiva and sublingual mucosa. Inset – numerous metastatic black-pigmented melanoma lesions are evident in the pulmonary parenchyma. *Source:* J.A. Luff, University of California Davis.

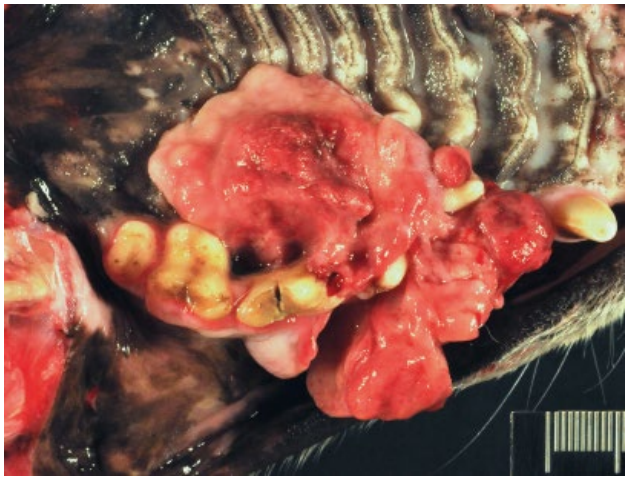


Figure 8.3 Gross image of a palatal/gingival amelanotic melanoma, eight-year-old FS Labrador retriever mix. A raised, fleshy pink to red irregular mass arises from the oral mucosa palatal and labial to the maxillary PM3 and PM4 teeth. The buccal incision into the mass is iatrogenic. *Source:* M. McCarthy, University of California Davis.

Different studies have come to conflicting conclusions regarding the prevalence of oral melanoma in different dog breeds.

Some studies have identified a higher frequency of occurrence in dog breeds with heavily pigmented oral mucosa, such as Chow Chows and Scottish Terriers, while other studies have failed to identify such a link. In the CCOMP database, Labrador and Golden retrievers appear to be overrepresented. There are 418 and 150 canine oral melanomas in the UC Davis and CCOMP databases, respectively.

Oral melanoma is a highly aggressive malignancy in dogs. In contrast to cutaneous melanocytic neoplasia in dogs, the prognosis for oral melanoma is poor, as melanoma lesions are locally invasive/destructive and prone to metastasize. Approximately equal numbers metastasize via hematogenous and lymphatic routes. Oral melanoma readily metastasizes to the regional lymph nodes (cervical/mandibular), lungs, or to distant sites like the liver or central nervous system (Figure 8.2). It is not uncommon for melanoma lesions to have metastasized by the time the initial diagnosis is made. Metastatic foci can be either pigmented or amelanotic; pigmented metastatic foci can arise from a primary amelanotic melanoma, and vice-versa. Once a dog is diagnosed with oral melanoma, the median survival time without treatment is two months and only three months with treatment. For dogs without bone, lymph node, or distant involvement at diagnosis, the median survival is eight months after local resection.

Melanoma can arise throughout the mucosae of the oral cavity – gingiva, buccal/labial mucosa, palate, and/or dorsal tongue. The tonsil and mucosa of the pharynx are rarely involved. The gross appearance of oral melanoma varies from coal black, patchy black and white, pink/red (tumor associated granulation tissue), purple, or white (amelanotic) (Figure 8.3). Oral melanomas have irregular margins and can grow rapidly and become quite large. Melanomas readily invade soft tissues and bone and may be associated with extensive local tissue destruction. Disruption of the dental arcade or pathologic fractures can occur if the melanoma invades the jaw. As a result, surgical resection can be a challenge.

As is true for melanocytoma, melanoma is thought to arise at the epithelial/subepithelial interface of the mucosa (where melanocytes generally reside in normal tissue). *Junctional activity* with the overlying epithelium (nests and packets of neoplastic melanocytes invading the epithelium) is common. Invasion and proliferation within the epithelium is often associated with epithelial acanthosis and rete peg formation, papillary proliferation of the epithelium and ulceration. A *grenz zone* situated between the neoplastic melanocytes and the overlying epithelium is generally not a feature of canine oral melanoma.

Oral melanoma can also be a diagnostic challenge for the pathologist, as amelanotic versions of the tumor are common, and malignant melanocytes demonstrate a broad range of cytologic and architectural features.

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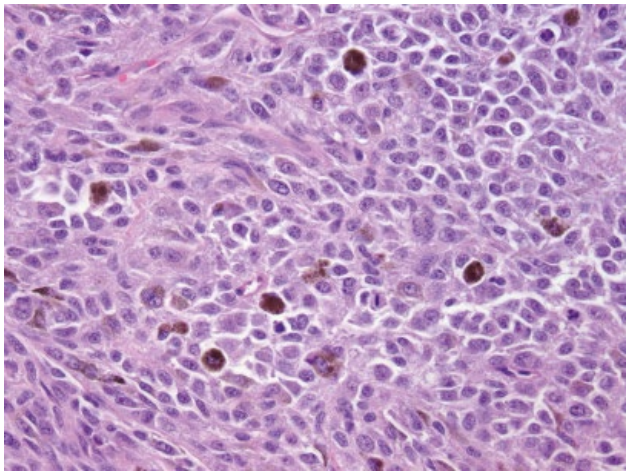


Figure 8.4 Histologic image of a melanoma in the rostral mandible, 12-year-old FS Labrador/shepherd mix. Neoplastic polygonal cells forming a jumbled sheet demonstrate variable melanization, anisokaryosis and 1–2 irregularly sized nucleoli (compare the cytologic features of this melanoma to the melanocytoma in Figure 8.1).

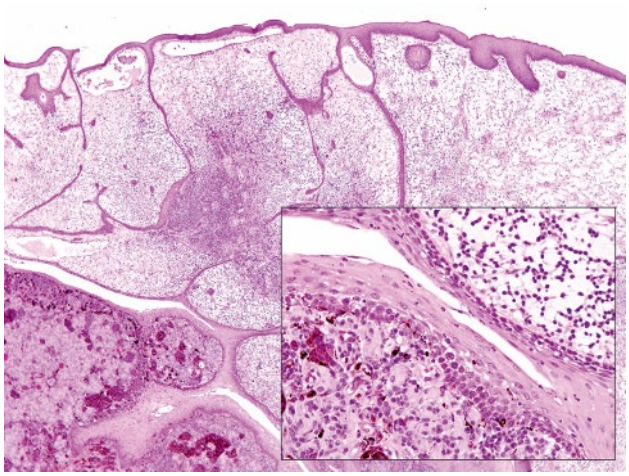


Figure 8.5 Histologic images of a gingival melanoma, 17-year-old FS mixed breed dog. This exophytic mass features hyperplastic epithelium that covers and separates sublobules of neoplastic tissue. Both the histological pattern and amount of pigmentation are variable. Inset – In the solid areas (lower left), the cells are large with indistinct borders. In contrast, neoplastic cells are widely separated and have a dendritic shape where the extracellular compartment is expanded (upper right). Note that the neoplastic cells infiltrate the basal cell layers of the epithelium over both areas.

Canine oral melanoma can histologically overlap with anaplastic sarcomas, carcinomas, lymphomas, and even osteogenic tumors (Figures 8.4 and 8.5). As a result of their neural crest histogenesis, neoplastic melanocytes can masquerade as a variety of cytological shapes: (i) *epithelioid cells* (round to polygonal cells, sometimes mimicking epithelial structures), (ii) *spindloid cells* (resembling fibroblasts), (iii) *a mixture of these two cell types*. A few other, rare melanoma cell types have been reported. Cytoplasmic melanization varies from abundant to inapparent (amelanotic). However, even grossly amelanotic tumors often demonstrate some degree of melanization at the microscopic level. The degree of pigment production is not thought to be a useful predictor of melanoma behavior. Oral melanomas can also demonstrate a variety of architectural cellular arrangements – sheets, streams and organoid clusters which can mimic an epithelial tumor.

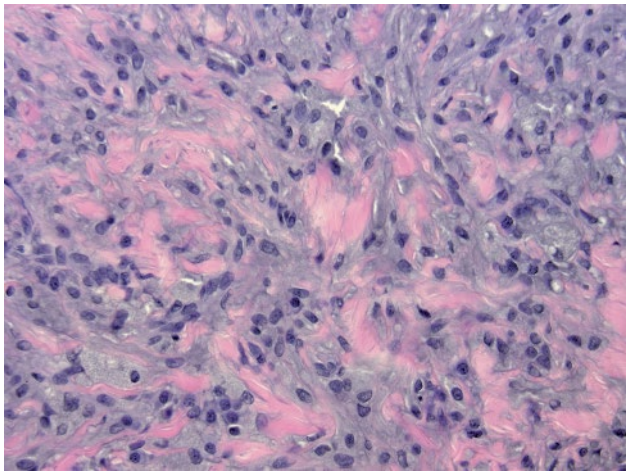


Figure 8.6 Histologic image of a bleached section of a palatal oral melanoma, 10-year-old Irish terrier dog. In heavily pigmented melanocytic lesions, treatment with potassium permanganate ("bleach") facilitates the visualization of nuclear and cytologic details.

Rapidly growing melanomas frequently have extensive areas of necrosis and hemorrhage. Although the neoplastic melanocytes do not produce a matrical product themselves, in some melanomas, osteoid and cartilage have been described within the tumor-associated fibrovascular stroma [7]. This is presumably a result of osseous or chondroid metaplasia and is reminiscent of a mixed mammary or salivary gland tumor. Obviously, these lesions need to be differentiated from bone or cartilage-producing sarcomas.

For the reasons discussed above, the pathologist should be wary of oral melanoma – it should be maintained as a differential diagnosis for any canine oral tumor that *straddles the diagnostic line between an anaplastic sarcoma and carcinoma*. In amelanotic lesions seemingly lacking in melanin pigment, the scattered presence of melanophages concentrating a few cytoplasmic melanin granules can be a useful diagnostic clue. In such a case, special stains like the Fontana-Masson silver stain may reveal the subtle presence of melanosomes that may not be evident in H&E stained sections. In those tumors with an abundance of melanin granules, bleached sections will facilitate the determination of cytological and nuclear details.

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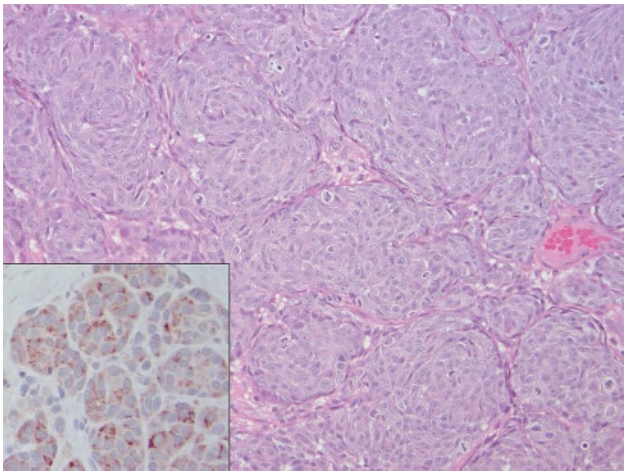


Figure 8.7 Histologic images of an amelanotic melanoma, epithelioid subtype from the oral cavity of a dog. Neoplastic polygonal cells form lobules or organoid structures separated by minimal fibrous stroma. Suspect amelanotic melanomas lacking histological evidence of pigment generally require ancillary testing for confirmation. Inset – positive Melan A immunohistochemistry stain.

Immunohistochemistry assays are an invaluable tool in the diagnosis of canine oral melanoma. A variety of useful antibodies for IHC assays are now available for the diagnosis of canine oral melanoma: S100, Melan A, PNL2 and tyrosinase-related proteins 1 and 2 (Figure 8.7). S100 may be the most sensitive, but it is also the least specific of these antibody stains. Epithelioid melanoma that histologically mimics an anaplastic carcinoma should be cytokeratin negative. Melanophages should not stain with melan A. A Ki-67 IHC stain may provide some useful prognostic information for canine melanoma [6]. As is true of any diagnostic test, none of these IHC assays has 100% sensitivity and specificity. Many investigators feel that anaplastic oral malignancies for which melanoma is a differential may require a panel of antibody stains.

8.1.2.1 Clinical Features

As with most neoplasia, primary treatment is aimed at gaining local control. Whenever possible, the best method for local control is surgical resection of the neoplasia. In the case of melanoma, wide surgical resection with a 2-cm gross surgical margin is indicated. When this is not possible, coarse-fractionated radiation therapy is typically well-tolerated and may slow the growth or shrink the primary tumor. A palliative approach using radiation therapy, pain medications, with or without bisphosphonates (if bone lysis is present) may be considered. The use of immunotherapy with a vaccine may also be considered [8, 9]. The tumor control rate with the commercially available vaccine Oncept (Merial) has been reported to be around 35% (complete response, partial response, and stable disease for at least six weeks) [8]. The use of chemotherapy has been described for melanoma, however, response rates tend to be less than 30% [10].

References

1 Regezi, J.A., Sciubba, J.J., and Jordan, R.C.K. (2008). *Oral Pathology: Clinical Pathologic Correlations*, 5e. St. Louis, Mo: Saunders/Elsevier.

2 Meuten, D.J. (2017). *Tumors in Domestic Animals*, 5e. Ames, Iowa: Wiley.

3 Spangler, W.L. and Kass, P.H. (2006). The histologic and epidemiologic bases for prognostic considerations in canine melanocytic neoplasia. *Vet. Pathol.* 43: 136–149.

4 Esplin, D.G. (2008). Survival of dogs following surgical excision of histologically well-differentiated melanocytic neoplasms of the mucous membranes of the lips and oral cavity. *Vet. Pathol.* 45: 889–896.

5 Ramos-Vara, J.A., Beissenherz, M.E., Miller, M.A. et al. (2000). Retrospective study of 338 canine oral melanomas with clinical, histologic, and immunohistochemical review of 129 cases. *Vet. Pathol.* 37: 597–608.

6 Bergin, I.L., Smedley, R.C., Esplin, D.G. et al. (2011). Prognostic evaluation of Ki67 threshold value in canine oral melanoma. *Vet. Pathol.* 48: 41–53.

7 Maxie, M.G. and Jubb, K.V.F. (2007). *Pathology of Domestic Animals*, 5e. Edinburgh; New York: Elsevier Saunders.

8 Alexander, A.N., Huelsmeyer, M.K., Mitzey, A. et al. (2006). Development of an allogeneic whole-cell tumor vaccine expressing xenogeneic gp100 and its implementation in a phase II clinical trial in canine patients with malignant melanoma. *Cancer Immunol., Immunother.* 55: 433–442.

9 Grosenbaugh, D.A., Leard, A.T., Bergman, P.J. et al. (2011). Safety and efficacy of a xenogeneic DNA vaccine encoding for human tyrosinase as adjunctive treatment for oral malignant melanoma in dogs following surgical excision of the primary tumor. *Am. J. Vet. Res.* 72: 1631–1638.

10 Rassnick, K.M., Ruslander, D.M., Cotter, S.M. et al. (2001). Use of carboplatin for treatment of dogs with malignant melanoma: 27 cases (1989-2000). *J. Am. Vet. Med. Assoc.* 218: 1444–1448.

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8.2 Oral Fibroma/Fibrosarcoma

Although fibrous tissue-based lesions can share substantial histological overlap, these lesions can markedly vary in their biological behavior and long-term prognosis. Many of these lesions are common (at least in the dog) while the underlying pathogenesis remains poorly understood. To make matters more difficult, very few antibody-based reagents or other molecular tools are currently available to assist the pathologist in the diagnosis of fibrous tissue-based lesions in any body system. As a result, a precise morphology-based diagnosis may be difficult or impossible to achieve in every circumstance. Careful communication with the clinician is of utmost importance with this complicated set of oral lesions. In this chapter, we discuss the neoplastic entities *fibroma* and *fibrosarcoma* (FSA). Equally important differentials are the non-neoplastic "benign fibrous gingival lesions" and "proliferative fibro-osseous lesions," which are covered elsewhere in this book.

8.2.1 Oral Fibroma

Oral fibroma is a rarely identified benign tumor in veterinary species. For some reason, in dogs, this benign mesenchymal tumor occurs far less frequently than oral FSA. Similar to cutaneous fibroma, these poorly pigmented, pale, firm, nodular lesions are well-circumscribed with unencapsulated "pushing margins" that do not invade the adjacent soft tissues or jaw bone. As a benign tumor, this lesion does not metastasize.

Fibromas are thought to arise from well-differentiated spindloid fibroblasts and demonstrate *bland cytological features*. In longitudinally cut tissue sections, the fibroblast nuclei are elongated; in transverse sections, they are round or ovoid. Nuclei are often small and heterochromatic. These neoplastic mesenchymal cells form sheets, streams, and bundles separated by variable amounts of pink-staining collagen matrix. Although the density of the cellular and collagenous matrical components varies, the cellularity of oral fibroma is *generally* less, and the matrical collagen content is *generally more,* than that found in FSA. The actual clinical significance of fibroma resides in the ability of the clinician and pathologist to accurately distinguish it from several other (more consequential) differential diagnoses.

Oral fibroma can be grossly and histologically similar to non-neoplastic reactive lesions composed of proliferative fibroblasts (or fibrocytes), including granulation tissue, reparative fibrous tissue (fibroplasia), and/or mature fibrous tissue (fibrosis). Granulation tissue typically has a parallel arrangement of fibroblasts amidst somewhat edematous matrical collagen with numerous interspersed orthogonally oriented small caliber vessels. These reactive fibrous lesions frequently demonstrate some degree of inflammation. However, ulcerated oral fibromas may also be inflamed and even demonstrate a component of reparative fibrosis! In the CCOMP database, 16 cases in dogs are histologically consistent with a fibroma of the oral mucosa and/or submucosa – 11 occurring in the tongue and 5 in the lip. The lingual and labial mucosa are predisposed to injury; therefore, we suspect that some of these lesions are non-neoplastic and resulted from nodular fibrosis subsequent to soft tissue trauma.

Fibroma lesions also need to be distinguished from proliferative fibro-osseous lesions like fibrous dysplasia and ossifying fibroma, and the FEPLO/POF lesion of dogs. In contrast to fibroma, the proliferative fibro-osseous lesions usually contain some quantity of mineralized or unmineralized osteoid (or cementoid) matrix.

Box 8.2 Differential Diagnoses for Oral Fibroma

High/low FSA
Fibrosis/traumatic granuloma
Fibrous dysplasia
Ossifying fibroma
FEPLO/POF

Most importantly, the relatively wide architectural and cytologic latitude of oral fibroma can mimic the histologically low-grade/ biologically high-grade FSA of dogs. The breed of dog, anatomic location/distribution and biological behavior as assessed by diagnostic imaging can be helpful in this regard. Does the diagnosis fit the clinical picture?

8.2.2 Oral Fibrosarcoma in Dogs

FSA is an aggressive malignant neoplasm that occurs in the oral cavity of most veterinary species, but is most often diagnosed in dogs and cats. Although common in dogs, FSA is less often diagnosed than certain other canine oral malignancies including melanoma and squamous cell carcinoma [11].

There are 166 and 127 cases of oral FSA in dogs in the UC Davis and CCOMP pathology databases, respectively. Oral FSA is thought to initiate, in order of occurrence, within the gingiva, hard or soft palate, lip, cheek, and tongue. Maxillary and palatal lesions are more common than mandibular lesions. Just palatal to the maxillary carnassial tooth (maxillary fourth premolar) appears to be a common anatomic site for canine oral FSA. These aggressive lesions often require extensive surgical resections, typically involving maxillectomy or mandibulectomy procedures.

Similar to their cutaneous counterparts, oral FSA are locally aggressive, invasive, and destructive tumors that

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Box 8.3 Differential Diagnoses for Canine Oral Fibrosarcoma

Anaplastic sarcoma
Spindloid amelanotic melanoma
Myxosarcoma
Vascular wall tumor
Peripheral nerve sheath tumor
Granulation tissue/fibrosis/fibroma (for well-differentiated FSA)
FEPLO/POF



Figure 8.8 Gross image of a maxillary fibrosarcoma, six-year-old FS Bernese Mountain Dog. A smooth, pink, firm mass distorts the rostral maxilla/incisive bone buccal and palatal to the incisors. *Source:* Dentistry Oral Surgery Service, University of California, Davis.

often recur after surgical resection but are slow to metastasize to distant anatomic sites. In dogs, FSA occurs in relatively younger animals than melanoma and squamous cell carcinoma (SCC), with a mean age of approximately seven years, and has been described in dogs less than one year of age. The weight of the animal does play some role in the occurrence of oral FSA, as dogs over 23 kg appear to be at greater risk. Golden retrievers, Labrador retrievers, and German shepherds may be overrepresented [12].

Grossly, oral FSA generally lack pigment and are gray to white to pink, smooth swellings or exophytic nodules (Figure 8.8). Oral FSA is highly infiltrative and the lesions are typically fixed and relatively unmovable. They are less often ulcerated than the other two common canine oral malignancies, melanoma, and SCC [11]. Radiographic evidence of osteolysis is common. Metastatic spread occurs late in the pathogenesis of oral FSA. Although many sarcomas tend to metastasize hematogenously (as opposed to lymphatically spread), oral FSA is capable of using either route, spreading to regional lymph nodes and/or the lung.

As is true for fibroma, FSA is comprised of neoplastic, spindloid fibroblasts and variable amounts of interspersed collagenous matrix. FSA can manifest as a well-differentiated neoplasm or as a highly anaplastic sarcoma, and anywhere in between (Figure 8.9). Oral FSA tend to exhibit more exaggerated pleomorphic features relative to fibroma or reactive lesions like fibrosis or granulation tissue. Cytologically, neoplastic fibroblasts are often large, may maintain a fusiform spindle shape, or may be ovoid, stellate or even multinucleate. Cytoplasmic margins may be inapparent. Nuclei are large and may demonstrate anisokaryosis with multiple large nucleoli. Although the numbers vary, mitotic figures are more commonly identified in FSA, as opposed to fibroma. As is true for many

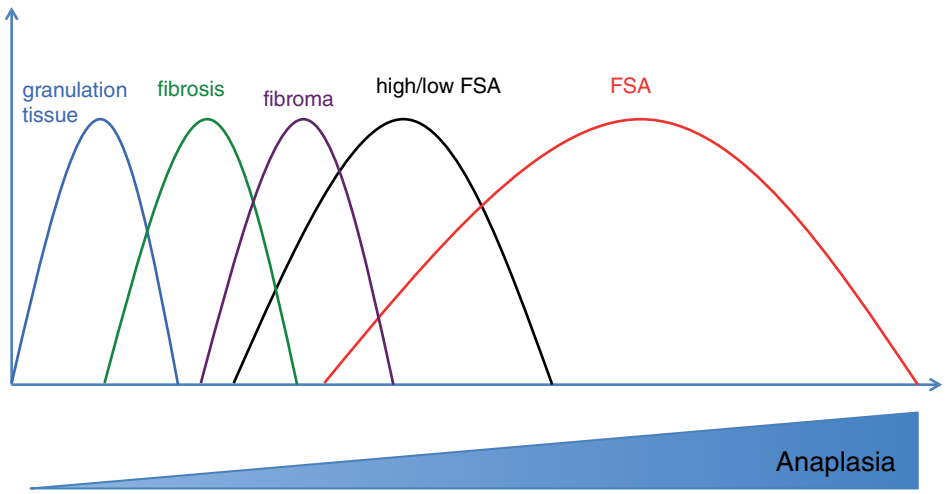


Figure 8.9 Lesion bell curves.

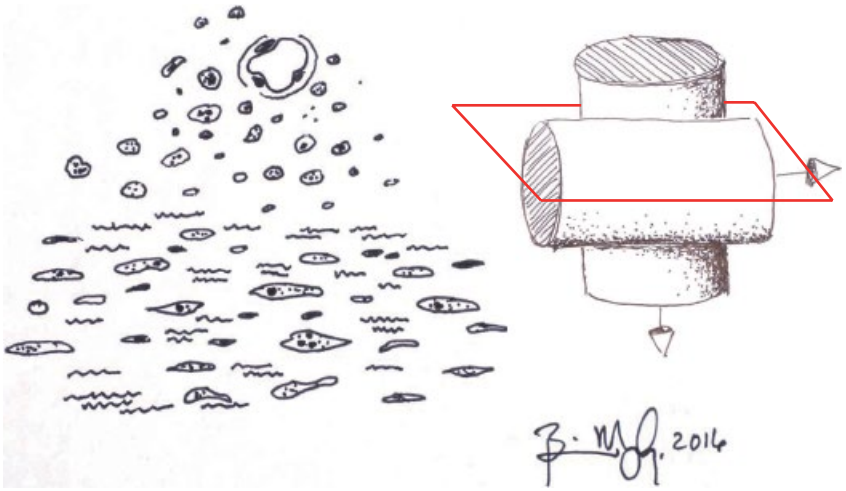


Figure 8.10 Bundles of neoplastic fibroblasts orient to one another in an orthogonal manner.

oral lesions, the final diagnosis should be based upon all of the features of the case including signalment, clinical/gross/surgical appearance, radiographic imaging, anatomic location, and histologic features of the lesion. Pathologists who rely exclusively on microscopic feature for a diagnosis are playing a dangerous game.

All sarcomas arise from transformed mesenchymal cells. Often, these neoplastic mesenchymal cells have a relatively pleomorphic cytology, regardless of histogenesis. In sarcomas that produce a distinct and recognizable extracellular matrix, like osteosarcoma or chondrosarcoma, the diagnosis is relatively straightforward (at least for differentiated tumors). If the sarcoma produces very little extracellular matrix (which is often the case for oral FSA) the diagnosis can become a bit more dicey. The interstitium of FSA may stain pink (collagen) or a bit more basophilic (proteoglycan-rich). FSA is a mesenchymal sarcoma that is on a continuum with myxosarcoma. If the cellular features are not telling, the pathologist must rely on other features of the lesion, like the *architectural arrangement* of the mesenchymal cells.

The microscopic architectural arrangement of the cells can be a very helpful diagnostic feature and best appreciated at low power magnification. Frequently, oral FSA are arranged as tight, parallel bundles of mesenchymal cells oriented orthogonally to adjacent bundles of mesenchymal cells (Figures 8.10 and 8.11). This tendency to form orthogonal bundles is almost pathognomonic for FSA. For some reason, neoplastic fibroblasts have a strong tendency to orient to one another in this manner, which is reminiscent of the 3-axis arrangement of skeletal myocytes in the tongue. Some oral FSA have an *interwoven chevron or herringbone* architectural pattern, recapitulating the structure of dense connective tissue in a ligament or tendon. In the longitudinal plane, the extracellular collagen fibers have an undulating, wavy pattern that is best revealed by stopping down the microscope's condenser to make the image more refractile. Oral FSA can also form diffuse sheets of

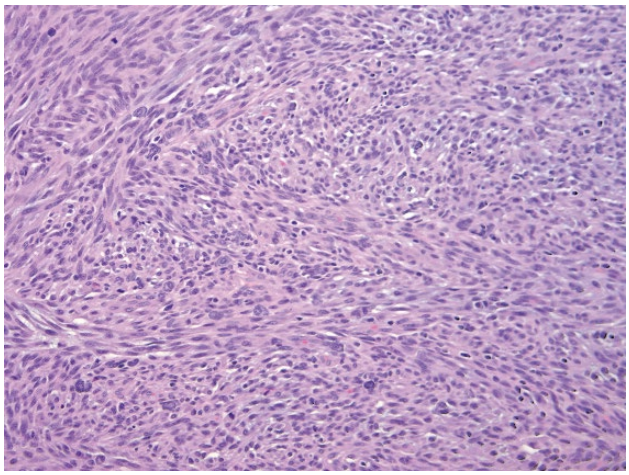


Figure 8.11 Histologic image of fibrosarcoma of the lip, 13-year-old MC Beagle mix dog. Neoplastic fibroblasts are densely packed, have moderate atypia, anisokaryosis, a few mitotic figures, minimal interstitial matrix and are arranged in orthogonal bundles.

mesenchymal cells; it is not uncommon for sarcomas to demonstrate multiple architectural arrangements in different regions of the same tumor. Cellular density often varies throughout the tumor; regions may be edematous, hemorrhagic or necrotic. Although the density varies, FSA tend to have a higher cellularity and a corresponding reduction in the amount of extracellular collagen fibers relative to benign fibrous gingival lesions.

Distinguishing between the neoplasm's edge and the adjacent tissue can be difficult, as neoplastic mesenchymal cells may, and often do, intercalate into the adjacent connective tissue. If the lesion is ulcerated, a layer of granulation tissue and inflammation may partially to completely cover the surface of the tumor. It is important for the pathologist to recognize the degree that secondary inflammation and necrosis can alter the lesion morphology. Differentiating between the reactive mesenchyme of the granulation tissue and the neoplastic FSA can be

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difficult. Non-ulcerated regions may be covered with hyperplastic oral epithelium exhibiting interanastomosing web-like rete pegs. This difficulty in finding the edge of an oral FSA is a real problem, as it complicates the ability of the pathologist to determine the adequacy of surgical excision.

Many of these diagnostic problems would be attenuated if we had sensitive and specific antibodies and immunohistochemical assays in our arsenal that effectively identified specific subsets of fibroblasts and differentiated them from other mesenchymal cells like chondroblasts and osteoblasts. Although excellent reagents exist for the identification of certain mesenchymal cells like melanocytes, myocytes, and leukocytes, this is not currently the case for fibroblasts. Although fibroblasts are assumed to be the cell of origin for oral FSA, this has not been absolutely confirmed by methods other than histomorphology and the tendency of fibroblasts to produce matrical proteins like collagen. Assuming that all spindle-shaped mesenchymal cells that produce collagen are fibroblasts is a gross oversimplification of biology.

8.2.3 Canine Biologically High-Grade/ Histologically Low-Grade Fibrosarcoma

The canine biologically high-grade/histologically low-grade fibrosarcoma (H/L FSA) is an interesting and problematic mesenchymal lesion, first reported in 1994 by Ciekot et al. [13]. H/L FSA has several different synonyms including histologically well-differentiated oral FSA, periosteal FSA or maxillary FSA. This lesion arises from either the maxillary gingiva (most often) or tissues of the mandible; some consider it to arise from the periosteum of the jawbones. H/L FSA occurs most frequently in large breed dogs, the Golden retriever in particular.

The H/L FSA has a deceptively benign histologic appearance that belies its aggressive nature (hence the moniker *biologically high-grade/histologically low-grade FSA*). If the pathologist is not aware of this entity, this aggressive lesion may be misdiagnosed as proliferative fibrous tissue, granulation tissue or benign fibroma. As a result, the differential diagnoses list for H/L FSA is essentially the same as for fibroma. Unlike typical oral FSA, this tumor is paucicellular and the matrix associated with the neoplastic cells is often abundant. The mesenchymal cells demonstrate bland cytological features, a lack of cellular pleomorphism and very few to no mitotic figures (Figure 8.12). Regardless of histologic appearance, the H/L FSA is insidiously invasive, spreading into and effacing the soft and hard tissues of the gums, lips and maxilla or mandible. Osteolysis is typically present. In H/L FSA, the tendency of differentiated fibrous tissue to wrap around and dissect between pre-existing soft tissue elements like skeletal myofibers and the tendency to invade along perivascular fascial planes provides a histologic clue to the invasive nature of this insidious neoplasm. H/L FSA often demonstrates some degree of lymphocytic/plasmacytic inflammation. Loss of bone may also occur as a late change associated with this FSA. It is important to match the clinical aspects of the lesion to the diagnosis!

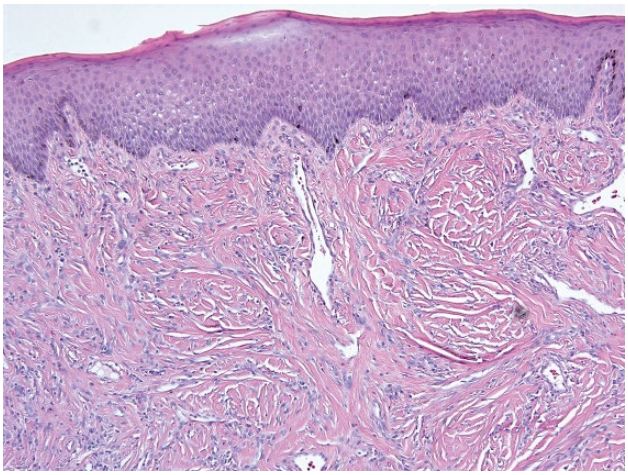


Figure 8.12 Histologic image of a H/L FSA of the mandibular gingiva, four-year-old French Bulldog. Mesenchymal cells with bland cytological features form bundles amidst abundant extracellular collagen matrix. Note the large fiber size of the extracellular collagen.

Frequently, as the lesion is progressively rebiopsied, H/L FSA gradually demonstrates more and more anaplastic features, eventually histologically merging with FSA. Although this tumor rarely metastasizes, achieving a complete surgical resection is difficult. Most dogs with H/L FSA are euthanized not as a result of widespread metastasis but as a result of extensive local tissue spread and destruction. A useful, simple, and widely used grading scheme has been created for non-oral soft tissue sarcomas [14]. Unfortunately, this grading scheme has not been shown to be prognostic in canine oral soft tissue sarcomas.

8.2.3.1 Clinical Features

Given the low metastatic rate of oral FSA, the primary mode of treatment for oral FSA is local control with surgical resection. While case controlled studies directly evaluating the influence of gross surgical margin on recurrence rate of FSA do not exist in dogs and cats, given the reported high recurrence rate of FSA reported in dogs, it is prudent to achieve wide surgical resection with margins of at least 2 cm. Although, oral FSA is generally considered to be radiation resistant, a multimodal approach to treatment that includes wide surgical resection and radiation therapy appears to provide the best survival rates [15–18].

8.2.4 Oral Fibrosarcoma in other Species

In cats, oral FSA are less commonly diagnosed than in dogs, but FSA is still the second most common oral malignancy in cats (after squamous cell carcinoma) [11]. Twenty cases of

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Figure 8.13 Gross image of a maxillary fibrosarcoma, 12-year-old FS DMH cat. A poorly demarcated area of the rostral maxillary gingiva and palatal mucosa is hyperemic and variably eroded with multifocal gingival swellings and patchy loss of palatal rugae. *Source:* H. Lobprise, Main Street Veterinary Dentistry, Flower Mound, Texas.

oral FSA have been diagnosed in the UC Davis Pathology database. Oral FSA in cats occur in anatomically similar sites as dogs, but it is more often found in older animals, with a mean age of approximately 11–14 years. These lesions are also locally aggressive and infiltrative, but slow to metastasize to distant sites. Oral FSA in cats is densely cellular with minimal amounts of extracellular matrix. Fibroblasts are often pleomorphic and multinucleate cells may be present. Feline FSA needs to be differentiated from feline epulides as seen in young cats, fibrous gingival hyperplasia, and inflammatory/fibromatous polyps in the pharynx, eustachian tubes and nasal passages. Lesions arising from the palate/orbital region need to be differentiated from feline restrictive orbital myofibroblastic sarcoma [19].

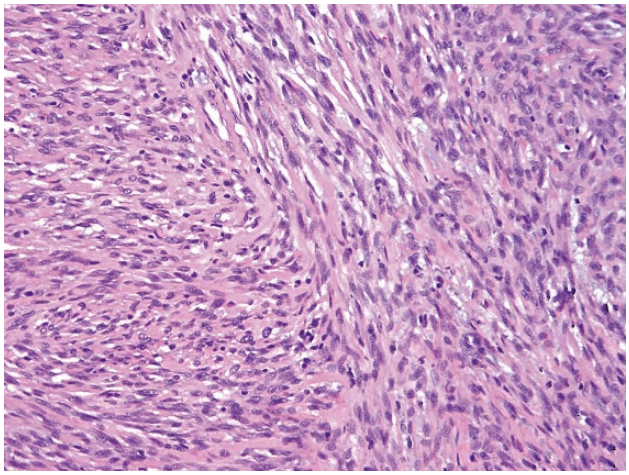


Figure 8.14 Histologic image of a mandibular fibrosarcoma, 13-year-old Quarter horse mare. A 12 × 3 × 5 cm mass along the lingual aspect of the mandible displaced PM 2, 3, and 4. Note the minimal, fibrillar collagenous matrix and the orthogonal architecture of the neoplastic mesenchymal cells.

Low-grade FSA has been identified in the mandible and maxilla of mature sheep and cattle, possibly initiating within the periosteal tissues of cheek teeth (sheep) or incisors (oxen). Oral FSA are very rarely diagnosed in horses; many of the fibro-proliferative lesions of the equine jaws (and nasal bones) have been recently reclassified as ossifying fibroma. There are only three diagnosed cases of oral FSA in horses in the UC Davis pathology database (Figure 8.14).

References

11 Meuten, D. .J. (2017). *Tumors in Domestic Animals*, 5e. Ames, Iowa: Wiley.

12 Gardner, H., Fidel, J., Haldorson, G. et al. (2015). Canine oral fibrosarcomas: a retrospective analysis of 65 cases (1998–2010). *Vet. Comp. Oncol.* 13: 40–47.

13 Ciekot, P. .A., Powers, B. .E., Withrow, S. .J. et al. (1994). Histologically low-grade, yet biologically high-grade, fibrosarcomas of the mandible and maxilla in dogs: 25 cases (1982–1991). *J. Am. Vet. Med. Assoc.* 204: 610–615.

14 Kuntz, C. .A., Dernell, W. .S., Powers, B. .E. et al. (1997). Prognostic factors for surgical treatment of soft-tissue sarcomas in dogs: 75 cases (1986–1996). *J. Am. Vet. Med. Assoc.* 211: 1147–1151.

15 Brewer, W. .G. Jr. and Turrel, J. .M. (1982). Radiotherapy and hyperthermia in the treatment of fibrosarcomas in the dog. *J. Am. Vet. Med. Assoc.* 181: 146–150.

16 Northrup, N.C., Selting, K.A., Rassnick, K.M. et al. (2006). Outcomes of cats with oral tumors treated with mandibulectomy: 42 cases. *J. Am. Anim. Hosp. Assoc.* 42: 350–360.

17 Theon, A.P., Rodriguez, C., and Madewell, B. .R. (1997). Analysis of prognostic factors and patterns of failure in dogs with malignant oral tumors treated with megavoltage irradiation. *J. Am. Vet. Med. Assoc.* 210: 778–784.

18 Forrest, L. .J., Chun, R., Adams, W. .M. et al. (2000). Postoperative radiotherapy for canine soft tissue sarcoma. *J. Vet. Intern. Med.* 14: 578–582.

19 Bell, C. .M., Schwarz, T., and Dubielzig, R. .R. (2011). Diagnostic features of feline restrictive orbital myofibroblastic sarcoma. *Vet. Pathol.* 48: 742–750.

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8.3 Oral Squamous Cell Carcinoma

Oral squamous cell carcinoma (OSCC) is a common and important disease in dogs, cats, and wild/exotic felids. OSCC also occurs in horses, cattle, sheep, goats, rats, hamsters, rabbits, ferrets, hedgehogs, and several other veterinary species, including reptiles. SCC is one of the three most common oral malignancies of dogs, and is the most common oral malignancy in cats. OSCC is a locally invasive, rapidly growing and destructive tumor. Clinically, OSCC can result in ptyalism, dysphagia, trismus, pain, halitosis, tooth loss, oral hemorrhage, pathologic jaw fracture and facial deformity. Unlike oral melanoma, OSCC metastasizes relatively late in the disease course.

OSCC is a malignant tumor of keratinocytes derived from the stratified squamous epithelium of the oral mucosa. Morphologically, the tumor can vary markedly in both gross and microscopic appearance. Well-differentiated OSCC (which does not mean well-behaved!) is generally *not* considered to be a diagnostic challenge for an experienced pathologist. However, in poorly differentiated, spindloid or anaplastic OSCC, identifying the cells as epithelial may present a challenge. It may also be difficult to differentiate the tumor from other similar lesions of the oral cavity. The authors of this textbook have adopted a convention from human oral pathology in choosing to classify all non-odontogenic and non-salivary gland malignant epithelial tumors as squamous cell carcinoma, regardless of whether or not the tumor actually produces keratin.

As SCC is a relatively common and consequential tumor in many animal species, including humans, investigators have long been interested in its etiology. Known risk factors for OSCC in humans include alcohol consumption, tobacco use (smoking), and in some parts of the world, chewing the highly carcinogenic betel nut. Some studies have implicated various human papillomaviruses in OSCC (tonsil). In veterinary species, proposed causes or contributing causes of OSCC are myriad and include chronic exposure to air pollution, tobacco smoke, papillomavirus infections, flea collars, diet, prior radiation exposure, and chronic mucosal and/or periodontal inflammation.

Pathologists who examine human oral biopsy samples pay particular attention to a lesion that is poorly recognized in veterinary oral pathology, epithelial dysplasia. Epithelial dysplasia in human patients, often manifesting grossly as *leukoplakia*, is thought to *precede* both carcinoma in situ and squamous cell carcinoma. As such, its presence is closely monitored by dentists and is reported by pathologists. Whether epithelial dysplasia represents a precursor lesion of more serious oral neoplasms in veterinary species remains relatively unexplored (see below for discussion on sublingual epithelial dysplasia). As effective treatment options for OSCC in veterinary species are presently limited, the early detection of a precursor lesion to OSCC might help save lives.

In OSCC, the amount of tumor-associated inflammation (TAI), along with the presence or absence of perineural invasion (PNI, entrapment or invasion of nerves within the histological section) and lymphovascular invasion (LVI, invasion into lymphatics or vessels) are considered to be important prognostic features of human OSCC [20]. Oral pathologists examining human tissues generally include these observations in their reports. Whether TAI, PNI, and LVI are important in veterinary species with OSCC has yet to be determined.

OSCC can be a devastating disease in humans, cats, and dogs. Multiple investigators have repeatedly made the point that naturally occurring OSCC in the dog and cat are excellent models of human head and neck SCC. Not only do these common oral tumors occur naturally in large bodied, and long-lived companion animals (in comparison to rodent animal models), they occur in similar anatomic sites, and many of the same histologic subtypes have been identified in all three species. As companion animals, dogs, and cats share the same environment with their human caretakers and are presented to veterinarians frequently for oral examinations. OSCC is a very similar disease in humans, cats, and dogs- why aren't we doing more government-sponsored research on OSCC in our companion animal species?

8.3.1 Oral Squamous Cell Carcinoma in Dogs

OSCC, oral melanoma and oral fibrosarcoma are the three most common oral malignancies in dogs. The precise *order of occurrence* of these three malignancies may be dependent upon the epidemiologic methodology of the particular study and/or the geographic location of the dogs in question. In dogs from North America, the apparent order of occurrence is melanoma, followed by OSCC and fibrosarcoma (418, 215 and 166 cases, respectively, in the UC Davis pathology database). However, in the United Kingdom, OSCC is the most common, followed by fibrosarcoma and lastly by melanoma. Even within North America, dramatic differences in the frequency of canine OSCC have been identified between rural and urban settings, with a much higher frequency of canine OSCC in urban settings relative to rural locations. This suggests the possibility of an environmental factor, such as air pollution, playing some role in the etiology of canine OSCC.

Canine OSCC occurs in slightly younger dogs, on average, than the other two most common canine oral malignancies. The mean age of occurrence for nontonsillar/ nonlingual OSSC is eight years, while it is nine years for fibrosarcoma, 10 years for osteosarcoma, and 12 years for melanoma. Tonsillar and lingual SCC both

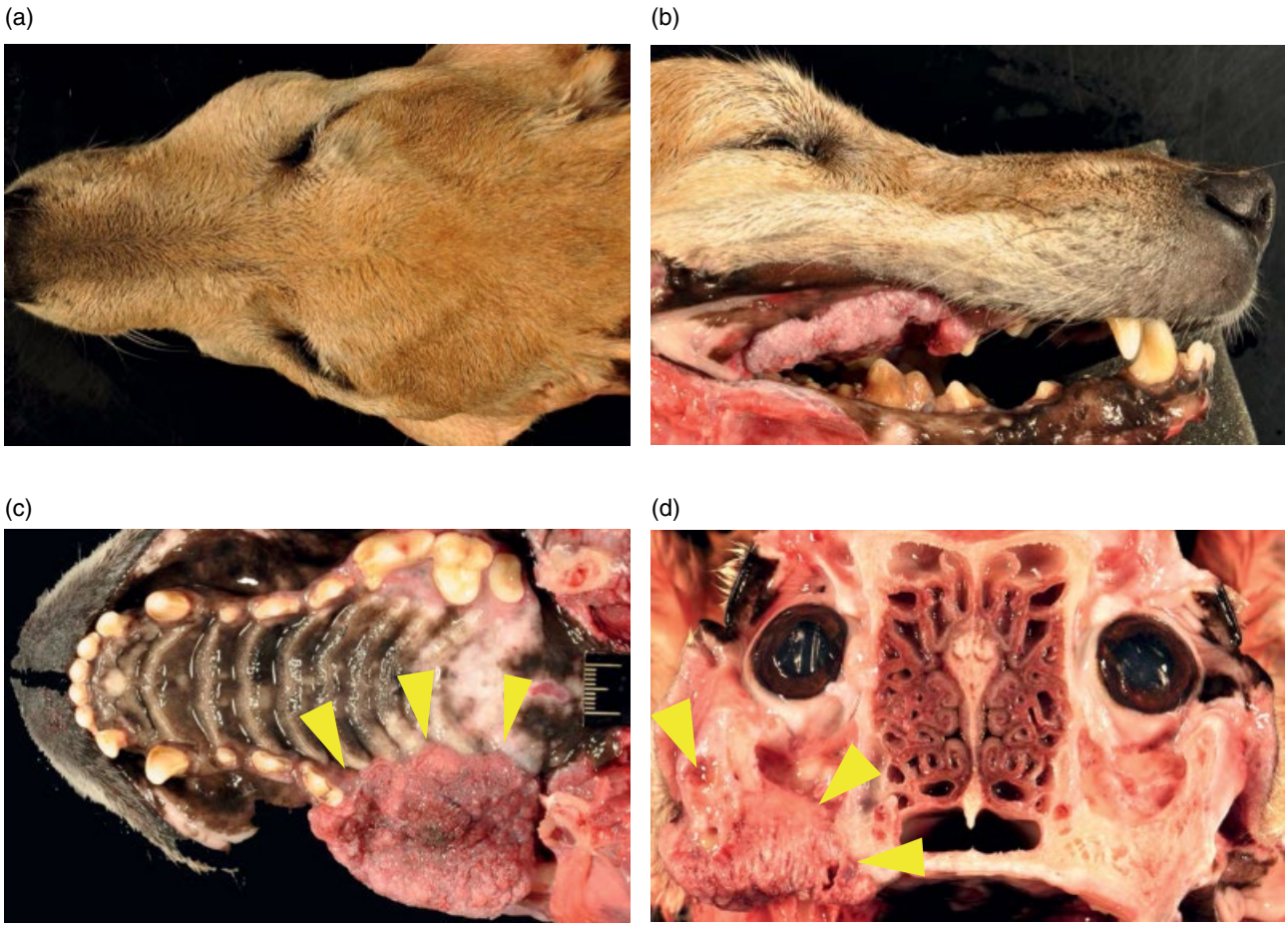


Figure 8.15 Gross image composite of oral squamous cell carcinoma (OSCC) in the right maxilla in a 12-year-old mixed breed dog. The tumor is pink, has a corrugated and roughened surface and replaces maxillary bone on section. Yellow arrowheads delineate the maxillary tumor in c and d. *Source:* R. Zavodovskaya, University of California, Davis.

occur at approximately 9.5 years of age. Large dogs appear to be more frequently affected than smaller dogs. Chronic gingivitis and/or periodontitis have been proposed as etiologic factors initiating or contributing to gingival OSCC formation [21].

OSCC lesions arise from the squamous epithelium of the lip, buccal mucosa, gingival mucosa, mucosa of the palate, crypts of the tonsil, epithelium of the tongue (dorsum, ventrum and base), or the mucosa of the pharynx (Figure 8.15). One of the authors (CB) has seen several cases of sublingual inflammatory/dysplastic lesions in dogs that have eventually transformed into SCC over a time frame of months to years (Figure 8.16). This is similar to what occurs in human OSCC, where some lesions are thought to proceed along a pathway from premalignant state (hyperkeratosis, dysplasia, carcinoma in situ) eventually culminating as OSCC [22].

OSCC occurs most commonly in the tonsils and the oral mucosa of the gums, while OSCC arising from other sites in the oral cavity is less common. Despite its tendency for local tissue destruction, OSCC is relatively slow to metastasize, but given time, eventually spreads to the regional lymph nodes (retropharyngeal, mandibular, cervical), lungs, or to more distant sites. Both the mandible and maxilla are affected in roughly equal measure. Maxillary OSCC can invade the soft tissues and bone of the palate, nasal passages, sinuses, and orbits.

Radiographs of OSCC will reveal a primarily destructive, osteolytic process of the underlying bone with a "moth-eaten" radiolucency and ill-defined borders, which may resemble osteomyelitis radiographically [23]. OSCC manifests grossly in several different ways. It can occur as an exophytic, nodular to multinodular, pink, red, white, or gray mucosal mass. The overlying epithelium may be either intact or ulcerated. In contrast to oral fibrosarcoma, the surface of OSCC is often roughened and papillary/verrucous (wart-like). OSCC can range from friable to firm, or even scirrhous. OSCC can also occur as a thickened, slightly elevated, plaque-like lesion, particularly in SCC of the tonsil or palate. It is also possible for OSCC to infiltrate underlying tissues without

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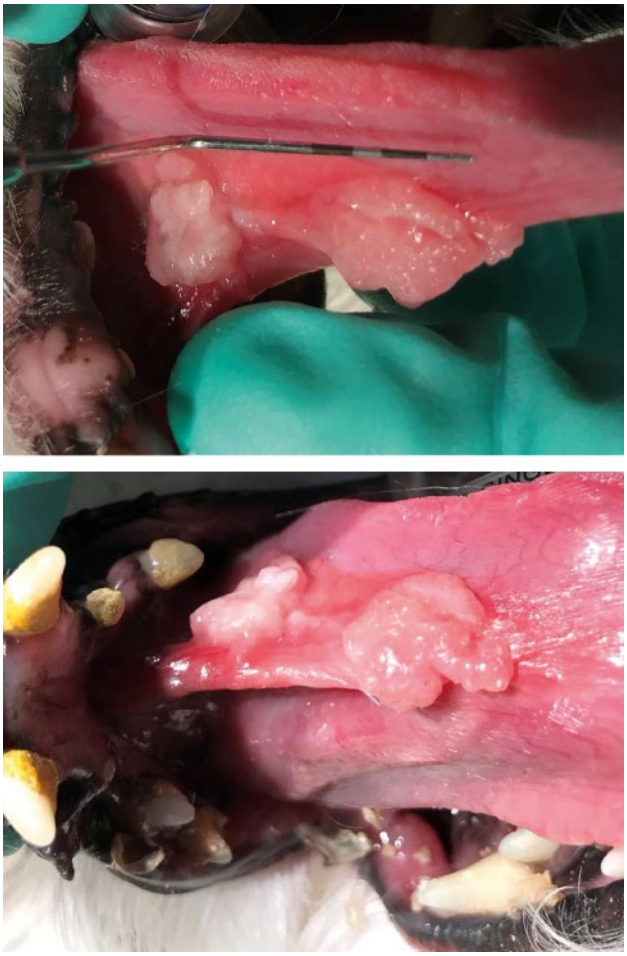


Figure 8.16 Gross images of multiple sublingual squamous cell carcinoma lesions in a dog. Several years previously, these sublingual sites were biopsied and diagnosed as glossitis.

any grossly apparent mucosal abnormality at all. As a result of this vast morphologic variation, differentiating OSCC from other proliferative lesions of the oral cavity by gross morphology alone is diagnostically perilous; some form of biopsy is essential.

Since SCC arises from squamous epithelium, most (but not all) OSCC will demonstrate *some degree of keratinization*, but the degree of keratinization varies greatly. Well-differentiated tumors are comprised of islands and irregular, anastomosing sheets of epithelium, bordered by basal cells that centripetally differentiate into polygonal keratinocytes. The islands of neoplastic epithelium are embedded in an induced fibrous stroma, which varies markedly in volume. It is not uncommon for islands of metaplastic woven bone to be present within the tumor-associated stroma. In some lesions, these bony islands can be numerous and large. Occasionally, osteoidal matrix associated with OSCC lesions (osseous metaplasia) can mimic tumor-associated osteoidal matrix of osteosarcoma.

Neoplastic keratinocytes generally demonstrate numerous spike-like intercellular junctions (desmosomes) – these so-called "prickle cells" are a useful diagnostic feature but should not be confused with the centralized odontogenic epithelial cells of canine acanthomatous ameloblastoma (CAA). Centrally, well-differentiated OSCC tumors often keratinize, forming an aggregate of desquamated or necrotic keratin referred to as a *keratin pearl*. Keratin pearls may be mineralized and/or infiltrated by variably degenerate neutrophils. Precipitous, central epithelial necrosis can create a pseudoglandular appearance known as *comedonecrosis*. Being carcinomas, all SCC *must demonstrate invasion of the basement membrane into the subjacent stroma*. This invasion may manifest as single cells, small clusters of rounded keratinocytes embedded within the fibrous stroma, or alternatively, islands or ribbons of neoplastic epithelium spatially removed from the mucosal surface.

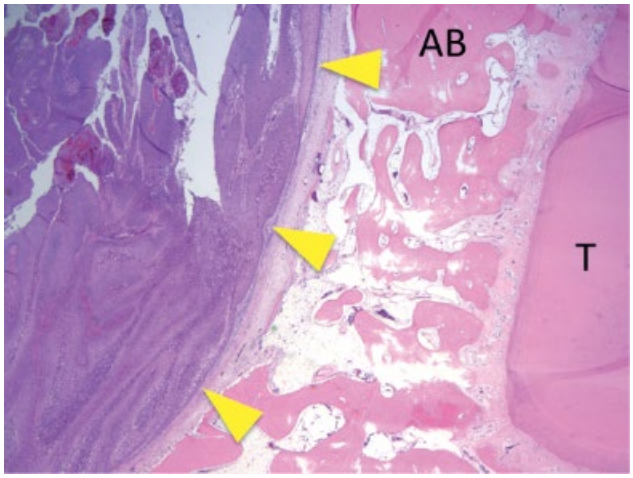
Tonsillar squamous cell carcinoma generally arises from the crypt epithelium, with cords or islands of epithelium invading the underlying lymphoid tissue.

The pathologist needs to be aware that the normal crypt epithelium of tonsillar tissue *is histologically unusual* – the crypt epithelium has an irregular border that appears to lack a basement membrane and may be heavily infiltrated by large numbers of lymphocytes. Some degree of keratinization within the crypt can be a normal finding (squamous metaplasia). A pathologist who is unaware of these features may run the risk of inappropriately diagnosing tonsillar SCC when it is not actually present. As one might expect from its anatomic location, tonsillar SCC tends to metastasize more readily than other forms of OSCC. In one study, 98% metastasized to the regional lymph nodes (via lymphatics) and 63% to more distant anatomic sites (presumably hematogenously). By contrast, in non-tonsillar OSCC, fewer than 15% of dogs have detectable nodal metastases and fewer than 5% of dogs have radiographic evidence of pulmonary metastasis at the time of diagnosis [24]. Due to its high metastatic potential, tonsillar SCC has a worse prognosis than OSCC arising from other anatomic sites.

As OSCC becomes less well-differentiated, the epithelial cells demonstrate progressively more cellular atypia – anisocytosis, anisokaryosis, anaplasia, large nuclear: cytoplasmic ratio, clumped chromatin with multiple nucleoli, increased mitotic figures (prophase/metaphase), and/or bizarre Y-shaped or irregular metaphase spreads. Keratinization may or may not occur within the peripheral rim of basal cells. Less well-differentiated OSCC may organize into thin, 1–3 cell- thick plexiform ribbons; it may occur as isolated individual epithelial cells or cells that are indistinguishable from the stromal fibroblasts (Figure 8.17). The use of cytokeratin and vimentin IHC stains can be useful adjuncts to distinguish between anaplastic keratinocytes and the adjacent

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(a)



(b)

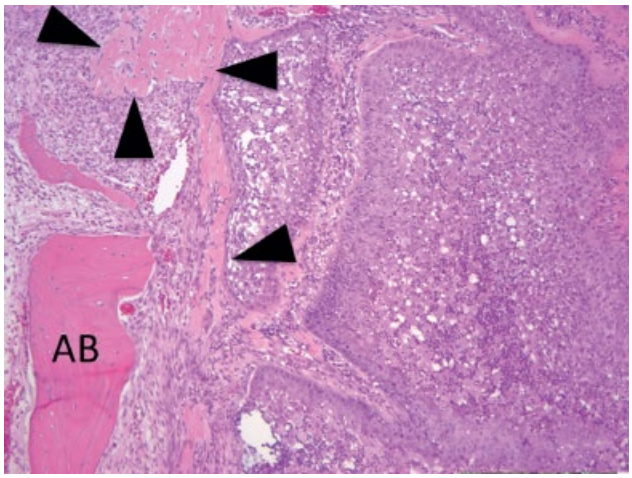


Figure 8.17 Histologic images of an invasive squamous cell carcinoma (papillary subtype), eight-year-old Siberian Husky F/S dog. (a) The OSCC, delineated by yellow arrowheads, invades and replaces the alveolar bone (AB) adjacent to the maxillary PM4 tooth (T). (b) Islands of neoplastic epithelium abut subepithelial ribbons and aggregates of osteoidal matrix that mimic the tumor-associated osteoid of OSA (black triangles). Remnant alveolar bone (AB) is also evident.

mesenchyme. Such IHC stains may also reveal basement membrane invasion by individual or small clusters of neoplastic epithelial cells, especially if the epithelial/subepithelial interface is obscured by inflammation.

OSCC has a tropism for bone. It may destroy periodontal structures resulting in loosening or loss of teeth. Histologically, it is sometimes difficult to determine if the osteolysis is the result of the neoplasm influencing (signaling) osteoclasts or alternatively, is directly mediated by the neoplastic epithelium itself. Bone formation (osteoproliferation) may be a concurrent feature in OSCC lesions. Some degree of inflammation is commonly present in OSCC, both within the neoplastic epithelium

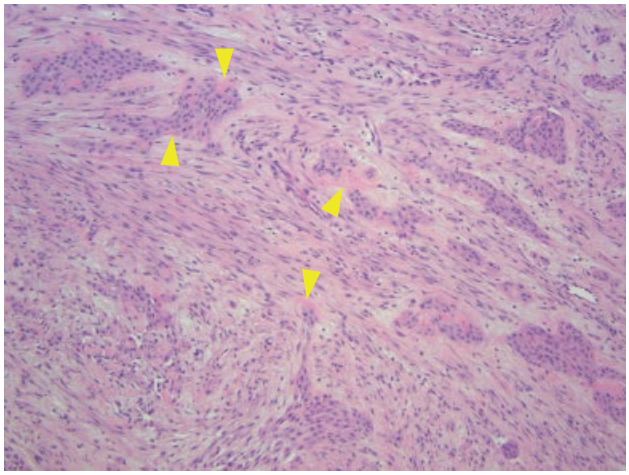


Figure 8.18 Histologic image of a maxillary squamous cell carcinoma, 11-year-old Gordon setter (conventional, poorly differentiated subtype). Irregular islands of neoplastic epithelium are embedded in abundant fibrous stroma (desmoplasia). Note the subepithelial aggregates of eosinophilic material are not keratin, but collagen (yellow arrowheads).

(infiltrating neutrophils) and the subjacent stroma (mixed mononuclear inflammatory cells and neutrophils). The TAI may be the result of surface ulceration, or alternatively, could be a response to neoplasm-associated keratin that is exposed within the tumor-associated stroma.

In human patients, multiple histologic subtypes of OSCC have been described, some of which are associated with predictable biological behaviors (although controversy exists about the true prognostic value of histologic subtyping) [25]. Histologic subtypes identified in humans include conventional SCC (further subdivided into well-, moderately, and poorly differentiated), papillary, basaloid, verrucous, spindle cell, and adenosquamous SCC. All of these OSCC subtypes have been identified in dogs, and occur in a descending order of frequency from well-differentiated, moderately differentiated, poorly differentiated, papillary, basaloid, adenosquamous, and spindle cell (Figure 8.18) [26]. The vast majority of canine OSCC are the conventional (well- and moderately differentiated) subtypes, which fortunately also happen to be the most straightforward tumors to diagnose. In general, the histologic subtype of OSCC cannot be determined from the gross appearance of the lesion alone. Whether the histologic subtype of OSCC in dogs affects prognosis will require further study.

Canine papillary SCC is a distinct subtype of OSCC initially thought to occur only in young animals, but now has been shown to occur in adult dogs as well. Papillary SCC occurs as either (i) an intraosseous, deeply cavitating cyst or cup-like indentation within the jaw bone, lined by neoplastic epithelium forming papillary structures (cavitating pattern), or (ii) an exophytic mass grossly similar to a benign papilloma (non-cavitating

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pattern) [27, 28]. Other important histological features that may be present in papillary SCC is a lack of keratinization, degeneration of apical cells, and abundance of intraepithelial neutrophils.

Although the verrucous subtype has been previously described in dogs, it was grouped along with the papillary subtype [29]. The verrucous subtype, as described in humans, is a plaque-like and less aggressive subtype of OSCC [20]; this subtype was not identified in the 2012 Nemec study, which examined non-tonsillar OSCC in 84 dogs. However, one of the authors, (CB) has diagnosed several lesions analogous to the human verrucous OSCC in the canine tongue.

Box 8.4 Differential Diagnoses for Oral Squamous Cell Carcinoma

Conventional ameloblastoma
CAA
Papilloma (papillary OSCC)
Periodontitis-associated hyperplasia/dysplasia of the gingival sulcal epithelium

Canine OSCC (common) must be differentiated from its principal differentials, namely conventional ameloblastoma (uncommon) and CAA (common). OSCC and CAA can share substantial histologic overlap. In CAA, neoplastic epithelial cells generally remain well-differentiated, tend to form architectural structures consistent with odontogenic epithelium, and may exhibit the cardinal histologic features of odontogenic epithelium (see Odontogenic tumors). As described in the section on odontogenic tumors, tumors that straddle the line between conventional ameloblastoma and OSCC (odontogenic epithelium with cytological/architectural evidence of malignancy) may be most appropriately diagnosed as ameloblastic carcinoma. In dogs with severe periodontitis, the sulcal epithelium adjacent to the tooth crown can demonstrate pronounced hyperplasia and (dyskeratosis) which can histologically mimic OSCC.

DNA from canine papillomavirus-1 (CPV-1) and CPV-17 has been amplified from canine OSCC lesions. However, whether CPV is etiologically associated with the occurrence of OSCC is presently controversial [24, 30, 31]. Studies have come to various conclusions over the presence or absence of CPV-1 DNA, viral RNA, and viral protein within canine OSCC lesions. In human lesions, p16 immunostaining (IHC) has been used as a surrogate marker strongly suggesting an etiology involving human papillomavirus. However, in canine lesions, p16 antigen has been detected in canine OSCC lesions *in the absence of detectable viral DNA*, indicating that p16 may not be an appropriate marker of CPV infection in canine tissues.

8.3.1.1 Clinical Features

As with most invasive tumors, in the absence of metastatic disease, the primary treatment goal of OSCC is achievement of local control via surgical resection. In humans, the appropriate visible width of the surgical margin is regarded to be 1-cm and this guideline has generally been utilized effectively in the dog. However, controlled studies evaluating the true efficacy of various macroscopic surgical margin widths have not been published. Mandibulectomy for SCC in dogs is associated with a 10% recurrence rate and survival times ranging from 19 to 26 months [32]. The combination of surgery and radiation therapy is associated with a median survival time of approximately 34 months [33]. The median survival time for dogs treated with definitive radiation therapy alone is approximately 14 months [33].

8.3.2 Oral Squamous Cell Carcinoma in Domestic Cats

Feline OSCC is the most common oral malignancy of domestic cats, representing 60–70% of all malignant feline oral tumors. The UC Davis pathology database has 190, 20, and 4 cases of feline OSCC, fibrosarcoma, and melanoma, respectively. As is true for canine OSCC, feline OSCC arises from transformed keratinocytes within squamous epithelium throughout the oral cavity (lips to pharynx, including tonsil). Sublingual and lingual sites appear to be particularly common. Historically, feline OSCC has been thought of as a lesion that metastasizes late in the disease course. However, recent investigations have identified a relatively high metastatic rate to the mandibular lymph nodes (35.7%) [34]. It is still true that most cats with OSCC will succumb to the primary disease before the metastatic disease has an opportunity to become clinically relevant [24].

In general, feline OSCC occurs in older cats; the median age of occurrence is approximately 14 years (out of 220 cases of feline OSCC, CCOMP database). Clinical signs include anorexia or hyporexia, weight loss, lethargy, decreased grooming, ptyalism, oral hemorrhage, tooth loss or tooth mobility, halitosis, facial deformity and pathologic fracture (Figure 8.19). OSCC involving the tongue may manifest as a decreased lingual mobility, contributing to hyporexia. The tongue may protrude from the mouth. Lesions in the maxillary arcade or palate may involve the nasal passages or orbit, potentially interfering with respiration or ocular function. Extensive OSCC lesions can invade the skin to cause ulceration while osteolysis +/− osteoproliferation may result in marked facial/head deformities.

The proposed causal or contributory etiologies for this common feline malignancy are a bit different than those identified for dogs. These factors include the use of flea collars, periodontal disease, exposure to tobacco smoke

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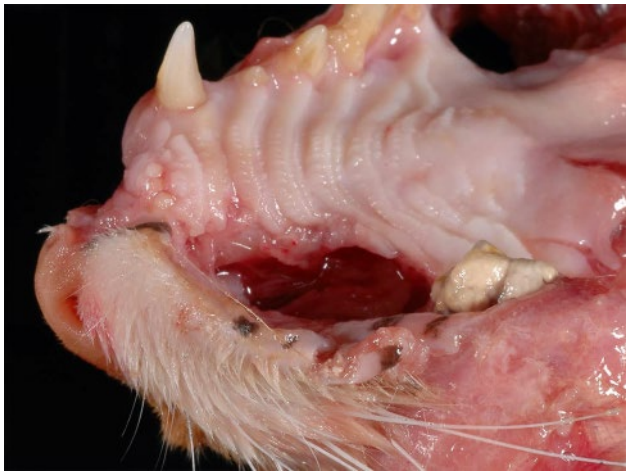


Figure 8.19 Gross image of a destructive maxillary SCC, 17-year-old DSH cat. The maxilla is partially effaced and distorted by the neoplastic process. *Source:* D. Gasper, University of California, Davis.

(concentrated in the mouth as a result of the cat's grooming behavior), and diet. The role of diet is particularly interesting, as cats that frequently consume canned food diets, and tuna in particular, appear to be at greater risk [35]. Whether this is the result of the nutritional content of the diet, presence of a toxin, or rather a diet-related predisposition to periodontal disease, has not been determined. Controversy persists over the role of viruses in feline OSCC. Exposures to feline immunodeficiency virus (FIV), feline leukemia virus (FeLV), and/or feline sarcoma virus (a variant of FeLV) are no longer thought to play an etiologic role in feline OSCC. The role of feline papillomaviruses in OSCC remains unsettled. As for dogs, investigations have rarely identified papillomavirus DNA sequences in feline OSCC lesions. As was found for canine OSCC, elevated p16 levels in feline lesions have not generally been associated with amplifiable papillomavirus DNA.

Feline OSCC, like the canine lesion, manifests grossly in a variety of ways, dependent upon the anatomic site, the depth and size of the lesion, presence of ulceration, necrosis, and the involvement of bone, teeth, nerves, and/or blood vessels. Early lesions may be submucosal or intraosseous, with no visible oral mass. Such lesions may or may not be palpable. Early lesions may be subtle and could be confused with proliferative or ulcerative gingivostomatitis. Small ulcerated and proliferative mucosal lesions may represent "the tip of the iceberg," with grossly inapparent yet extensive bone, muscle, or deep tissue involvement. Mucosal lesions are often irregular, nodular to multinodular, red-gray and friable with ulcerated surfaces that may bleed easily. Feline OSCC lesions can also be fixed to underlying structures like the periosteum of the jaw and may be firm due to desmoplasia and/or osteoproliferation. Lesions on the palate can manifest as ulcerated plaques, which may invade the underlying maxillary/incisive bones. Palatal OSCC may invade the nasal passages, effacing and replacing the palatal bone, nasal turbinates, and mucosa (Figure 8.20).

Histologically, feline OSCC is similar to canine OSCC. Neoplastic islands and cords of epithelium are embedded in an induced fibrovascular stroma, which supplies the tumor with blood. The stroma may be relatively inapparent, or more likely, desmoplastic. Epithelial cells generally demonstrate intercellular desmosomes and tend to keratinize, forming centripetal keratin pearls. While not overtly keratinized (like the stratum corneum), centripetal keratinocytes progressively enlarge, and are brightly eosinophilic with rhomboidal sharp-sided cell margins. In such lesions, sharply delineated, central cyst formation and comedonecrosis may be present *in lieu* of actual keratin pearls. Such structures may have a pseudoglandular appearance. Rare feline lesions may completely lack keratinization and may present a diagnostic challenge. As for canine lesions, CK and vimentin IHC assays may be of assistance.

Ulceration, necrosis and hemorrhage may be present. Any evidence of entrapped or invaded peripheral nerves (PNI) and LVI should be noted in the pathology report. Tumor- associated inflammation, often abundant, is a common finding, involving lymphocytes, plasma cells and neutrophils. Histologic subtypes of feline OSCC, as described for human oral pathology [25], have not been published. Our (unpublished) observations suggest that conventional (well-differentiated), conventional (moderately differentiated), papillary, and basaloid subtypes of OSCC all occur in cats. As has been found for canine lesions, conventional well- and moderately differentiated tumors appear to be the most common (mercifully, for pathologists). Despite the state of differentiation, conventional, well-differentiated feline OSCC can still be highly aggressive and destructive tumors.

Invasion of bone with associated osteolysis is common. The invasion of bone must be differentiated from *metaplastic bone formed within the tumor stroma or on the surface of the preexisting lysed bone*. Osteolytic bone is typically lamellar with scalloped margins, osteoclasts may be present at the bone–tumor interface, and isolated bone fragments may lack evidence of osteocytes and palisading osteoblasts (ischemic bony sequestra). Tumor-associated metaplastic bone or bone formed (plated) on the surface of lysed bone is typically woven, has smooth margins, and may or may not be palisaded by osteoblasts or bone-lining cells. Extensive destruction of the jawbones is often associated with substantial periosteal bone formation (parallel plates of woven bone), which may form a "shell" near the tumor margins. Interestingly, paraneoplastic

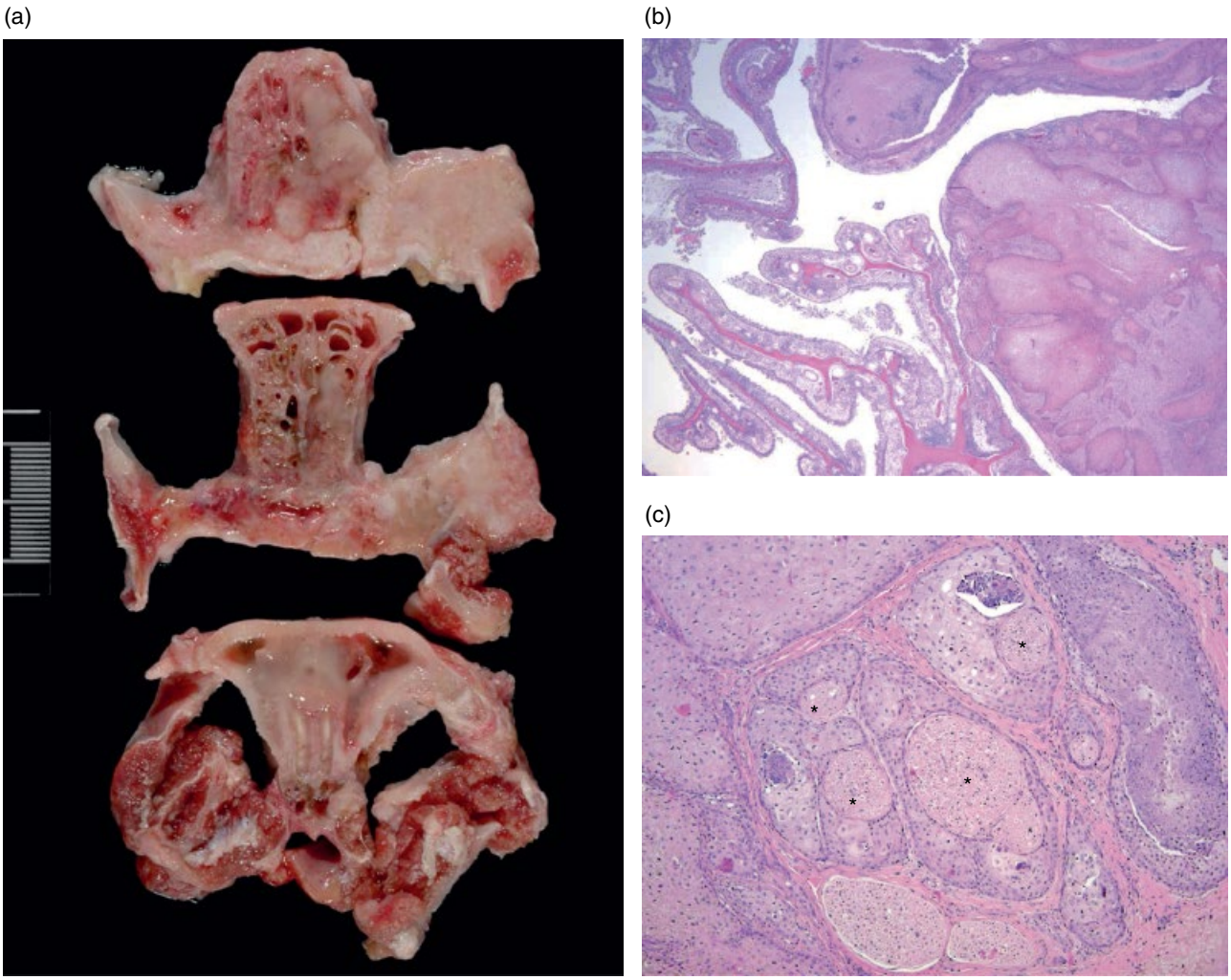


Figure 8.20 Gross and histologic image composite of maxillary/nasal OSCC, 12-year-old DSH cat. (a) Serial, transverse sections through the nasal cavity and maxilla. An infiltrative and destructive lesion partially effaces the maxillary bone and occludes the nasal turbinates. (b) Histologic image- nasal turbinates on the right side of the image are effaced by the neoplastic epithelium and associated stroma. (c) Histologic image- multiple nerves are entrapped by neoplastic epithelium (* perineural invasion, PNI). *Source:* S. Siso, University of California, Davis.

hypercalcemia has been reported in some feline OSCC (tumor production of parathyroid hormone-related peptide, PTHrp).

8.3.2.1 Clinical Features

Surgery, with or without radiation therapy, is the mainstay of locoregional treatment for OSCC in cats. Typical surgical resection guidelines of 1–2 cm are often found in the literature. However, given the typical size of lesion at the time of diagnosis and the poor post-operative adaptation of cats, adequate local control may be difficult. One author (JS) generally attempts a 1 cm surgical margin. Even with treatment, outcomes are generally disappointing with reported median survival times of 3–14 months with longer survival times for tumors located in the mandible and in combination with radiation therapy [36, 37].

8.3.3 Oral Squamous Cell Carcinoma in Horses, Cattle, and Other Species

In horses, OSCC is uncommon, but when present, arises from the gingiva, tongue, larynx, pharynx, and palate of older horses (>10 years of age). As is true for some other species, OSCC in horses is thought to be associated with chronic periodontal disease. Affected horses may present with dysphagia or dyspnea [24]. The lesions can be quite large, are locally destructive and bone invasive, and metastasize late in the disease course to the regional lymph nodes (mandibular, retropharyngeal, cervical). OSCC is often ulcerated, necrotic, gray to white, forming large plaque-like or exophytic lesions grossly similar to other malignant tumors of the equine oral cavity (Figures 8.21 and 8.22). OSCC involving the mandibular or maxillary cheek teeth may result in their loosening



Figure 8.21 Gross image of a mandibular SCC in a horse, 19-year-old Quarter Horse gelding. The tumor forms an ulcerative mass that has expanded the mandible. The caudal cheek teeth are absent. *Source:* M. Drozd, Kansas State University.



Figure 8.22 Gross image of glossal SCC, 20-year-old American Miniature horse. The base and lateral aspect of the tongue are partially effaced by an ulcerated and necrotic mass. *Source:* W. Siniard, University of California, Davis.

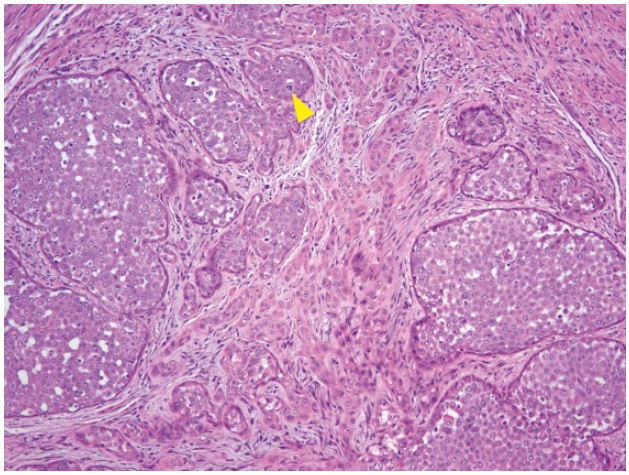


Figure 8.23 Histologic image of a gingival SCC, five-year-old American Paint horse (mandible). Irregular islands and cords of neoplastic epithelium are embedded within abundant fibrous stroma. A mitotic figure is indicated by the yellow triangle. Keratin pearls are not evident in this field.

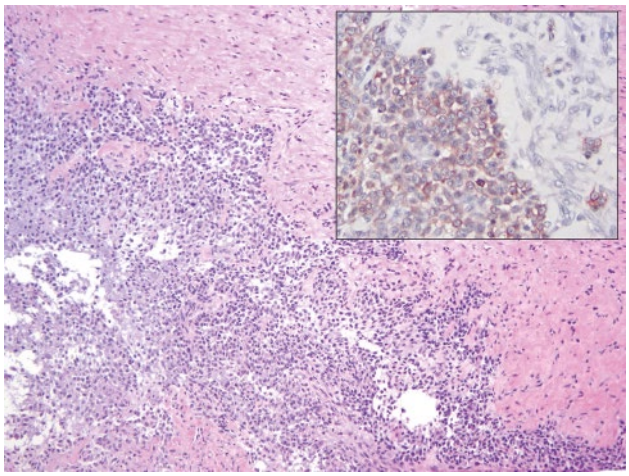


Figure 8.24 Histologic images of a poorly differentiated mandibular OSCC, horse. The tumor is comprised of irregular sheets of partially discohesive polygonal to spindloid cells embedded within fibrous stroma. Inset – neoplastic epithelial cells stain brown (positive reaction), pan CK immunohistochemistry.

or loss. Although papillomavirus has been shown to be associated with the pathogenesis of genital SCC in horses, the role of papillomavirus in equine oral SCC remains to be established.

Some equine OSCC lesions are so poorly differentiated, it is difficult to determine if they have an epithelial or mesenchymal histogenesis (Figure 8.23). These lesions have extensive regions of necrosis, invade and efface soft tissues and bone, and are comprised of polygonal, round or spindle-shaped cells forming irregular sheets. Desmosome intercellular junctions may or may not be evident in thin histologic sections. Although the carcinomas may be associated with fibrous stroma, they generally do not form architectural structures consistent with epithelium. Pan CK and vimentin IHC staining is very helpful in making sense of these highly anaplastic carcinomas.

OSCC occurs in cattle over four years of age, but is generally rare. In some geographic regions, OSCC is more common and is associated with the ingestion of bracken fern and infection with bovine papillomavirus (BPV). Although most BPV-associated papillomas regress, occasionally these lesions persist and transform into SCC. In cattle, papillomavirus lesions are more often identified in the esophagus and rumen than the oral cavity.

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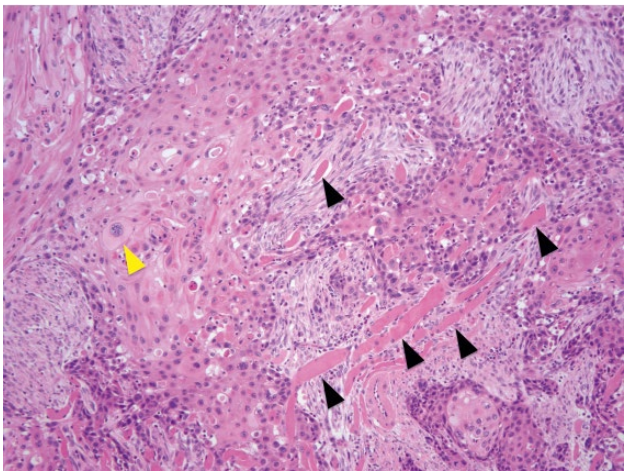


Figure 8.25 Histologic image of a mandibular SCC, African hedgehog. The neoplastic epithelium is moderately anaplastic with prominent anisokaryosis (yellow triangle). Entrapped and atrophied skeletal myocytes are evident within the associated fibrous stroma (black triangles).

It hasn't made it into the peer-reviewed literature as of yet, but SCC of the upper alimentary tract is a fairly common lesion in exotic felids. A search of the pathology database at the University of California, Davis identified multiple cases of oral, laryngeal, and esophageal SCC in multiple species of exotic felids including lions, snow leopards, leopards, Geoffroy's cats and bobcats.

Although production pigs do not tend to live long enough for OSCC to arise, several published and unpublished cases of OSCC have been identified in aged (10–18 year old) companion pigs (Vietnamese pot-bellied pigs, *Sus scrofa*). These tumors arise as ulcerative, plaque-like lesions from the mandible, maxillary alveolus or hard palate. OSCC is commonly identified in the mandibles of older African hedgehogs. As is true for some other species, these carcinomas in hedgehogs tend to be highly destructive, effacing the bony architecture of the jaw and resulting in pathologic fractures and tooth loss. In some sections, very little mandibular bone may remain (Figure 8.25).

References

20 Regezi, J.A., Sciubba, J.J., and Jordan, R.C.K. (2008). *Oral Pathology: Clinical Pathologic Correlations*, 5e. St. Louis, Mo: Saunders/Elsevier.

21 Maxie, M.G. (2016). *Jubb, Kennedy, and Palmer's Pathology of Domestic Animals*, 6e. St. Louis, Missouri: Elsevier.

22 Regezi, J.A., Sciubba, J.J., and Jordan, R.C.K. (2012). *Oral Pathology: Clinical Pathologic Correlations*, 6e. St. Louis, Mo: Elsevier/Saunders.

23 Todoroff, R.J. and Brodey, R.S. (1979). Oral and pharyngeal neoplasia in the dog: a retrospective survey of 361 cases. *J. Am. Vet. Med. Assoc.* 175: 567–571.

24 Meuten, D.J. (2017). *Tumors in Domestic Animals*, 5e. Ames, Iowa: Wiley.

25 Pereira, M.C., Oliveira, D.T., Landman, G., and Kowalski, L.P. (2007). Histologic subtypes of oral squamous cell carcinoma: prognostic relevance. *J. Can. Dent. Assoc.* 73: 339–344.

26 Nemec, A., Murphy, B., Kass, P.H., and Verstraete, F.J. (2012). Histological subtypes of oral non-tonsillar squamous cell carcinoma in dogs. *J. Comp. Pathol.* 147: 111–120.

27 Nemec, A., Murphy, B.G., Jordan, R.C. et al. (2014). Oral papillary squamous cell carcinoma in twelve dogs. *J. Comp. Pathol.* 150: 155–161.

28 Soukup, J.W., Snyder, C.J., Simmons, B.T. et al. (2013). Clinical, histologic, and computed tomographic features of oral papillary squamous cell carcinoma in dogs: 9 cases (2008–2011). *J. Vet. Dent.* 30: 18–24.

29 Head, K.W. and Armed Forces Institute of Pathology (U.S.), American Registry of Pathology., & WHO Collaborating Center for Worldwide Reference on Comparative Oncology (2003). *Histological classification of tumors of the alimentary system of domestic animals*. Published by the. Washington, DC: Armed Forces Institute of Pathology in cooperation with the American Registry of Pathology and the World Health Organization Collaborating Center for Worldwide Reference on Comparative Oncology.

30 Luff, J., Rowland, P., Mader, M. et al. (2016). Two canine papillomaviruses associated with metastatic squamous cell carcinoma in two related Basenji dogs. *Vet. Pathol.* 53: 1160–1163.

31 Munday, J.S., French, A., and Harvey, C.J. (2015). Molecular and immunohistochemical studies do not support a role for papillomaviruses in canine oral squamous cell carcinoma development. *Vet. J.* 204: 223–225.

32 Kosovsky, J.K., Matthiesen, D.T., Marretta, S.M., and Patnaik, A.K. (1991). Results of partial mandibulectomy for the treatment of oral tumors in 142 dogs. *Vet. Surg.* 20: 397–401.

33 LaDue-Miller, P. and Page, T. (1996). Radiotherapy of canine non-tonsillar squamous cell carcinoma. *Vet. Radiol. Ultrasound* 37: 74–77.

34 Bilgic, O., Duda, L., Sanchez, M.D., and Lewis, J.R. (2015). Feline oral squamous cell carcinoma: clinical manifestations and literature review. *J. Vet. Dent.* 32: 30–40.

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35 Bertone, E.R., Snyder, L.A., and Moore, A.S. (2003). Environmental and lifestyle risk factors for oral squamous cell carcinoma in domestic cats. *J. Vet. Intern. Med.* 17: 557–562.

36 Marconato, L., Buchholz, J., Keller, M. et al. (2013). Multimodal therapeutic approach and interdisciplinary challenge for the treatment of unresectable head and neck squamous cell carcinoma in six cats: a pilot study. *Vet. Comp. Oncol.* 11: 101–112.

37 Fidel, J.L., Sellon, R.K., Houston, R.K., and Wheeler, B.A. (2007). A nine-day accelerated radiation protocol for feline squamous cell carcinoma. *Vet. Radiol. Ultrasound* 48: 482–485.

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8.4 Oral Papilloma

Oral papillomas are benign, generally self-limiting, exophytic, papillary lesions of the mucosal epithelium that are organized around variably proliferative cores of fibrovascular tissue. Colloquially, these lesions have been referred to as *warts*, and occur as solitary, or more frequently, as multifocal masses; the disease is called *oral papillomatosis*. Oral papillomatosis occurs in the labial mucosa, gingiva, buccal mucosa, tongue, palate, pharynx, and esophagus. Dogs and cattle are most frequently affected; these lesions are less often identified in cats (including exotic felids), horses and other species. Fifty-nine cases of canine oral papillomas are in the UC Davis pathology database. Oral papillomatosis lesions seem to be more common in some geographic regions, but overall, they tend to be uncommon.

Severe oral papillomatosis is rare, but when present, may interfere with mastication, swallowing, and even respiration. Affected animals are often, but not always, young. Some authorities subdivide oral papillomas into virus-associated papillary lesions (*viral papilloma*) and virus-independent papillary lesions (*squamous papilloma*). Some have argued that viral papillomas are non-neoplastic/hyperplastic lesion, while squamous papillomas represent benign neoplasms [38].

It is the opinion of the authors of this text that most oral papillary lesions arise as a result of an infection with a (typically) host-specific *papillomavirus*. If the investigator is sufficiently perseverant, *some evidence of an association with papillomavirus can be identified* – histologic, ultrastructural identification of viral particles, immunohistochemical detection of viral antigen, amplification and sequencing of viral nucleic acids (PCR), or in situ hybridization to detect viral DNA. Otherwise, a presumptive diagnosis may be based on characteristic histologic changes that papillomavirus is known to induce (more on this below). In the last several decades, much has been learned about the biology and diversity of papillomaviruses. This highly diverse group of viruses forms complex pathogenic and apathogenic relationships with its host species; we still have much to learn.

8.4.1 Oral Papillomas in Dogs

Canine oral papillomatosis, most often occurring in puppies less than a year of age, is generally thought to result from an infection with canine papillomavirus 1 (CPV-1). Canine papillomaviruses are highly diverse – 17 different canine papillomaviruses have been described to date, and this diversity is likely to increase. It is quite possible that oral papillomatosis in dogs may involve papillomavirus types other than CPV-1. These lesions may be solitary,



Figure 8.26 Clinical image of multiple papillomas in the labial mucosa of a young dog. *Source:* H. Lobprise, Main Street Veterinary Dentistry, Flower Mound, Texas.

but are more often multifocal, proliferative, *verrucous* (wart-like) lesions that are pale, gray, white, or the color of the mucosa (Figure 8.26). The papillomas progressively enlarge and may become roughened, firm, and often are grossly reminiscent of cauliflower florets. The base of the lesion may be broad and sessile or narrow and pedunculated. Less often, some papillomas in the oral cavity manifest as smooth or rough, flattened, plaque-like lesions of focally thickened epithelium.

The lesion incubation period is approximately one–two months, and lesions progress from small, indiscernible foci of epithelial hyperplasia to grossly evident papillary proliferations. Histologically, the proliferative epithelium of the papilloma is often severely acanthotic, keratinized, and typically organized into numerous *papillary frond-like structures that tend to be pointed*. Each frond has a thin fibrovascular core of tissue providing a critical blood supply to the overlying epithelium. Papillary fronds generally orient in a manner perpendicular to the adjacent mucosal surface, but they don't necessarily separate into individual finger-like structures. In some papillomas, the overlying proliferative keratin serves to fuse the papillary projections into a single, coherent structure.

Importantly, the neoplastic epithelium *does not* invade through the basement membrane into the underlying fibrovascular stroma. Lesions demonstrating overt stromal invasion are better classified as the papillary subtype of squamous cell carcinoma (SCC). Basal epithelial cells are proliferative, jumbled (dysplastic), and have increased numbers of mitotic figures (Figures 8.27 and 8.28). The papillomavirus replicates in the upper layers of the mucosal epithelium, the stratum spinosum and stratum granulosum. The stratum granulosum is often thickened and disorganized (dysplastic) – these cells generally

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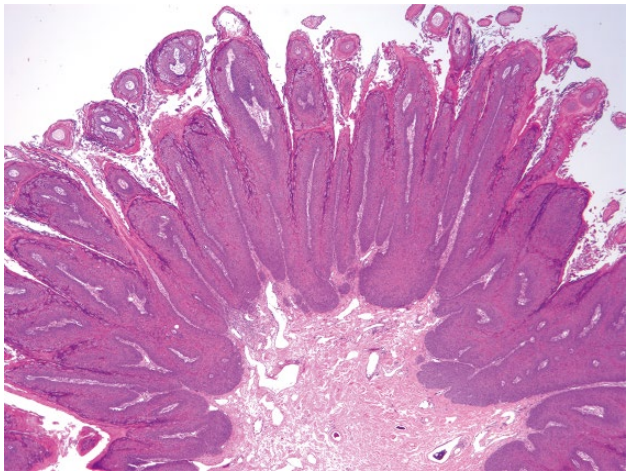


Figure 8.27 Histologic image of the frond-like architecture of an oral papilloma, seven-year-old Poodle dog. Note the radiating epithelial projections oriented around thin fibrovascular cores.

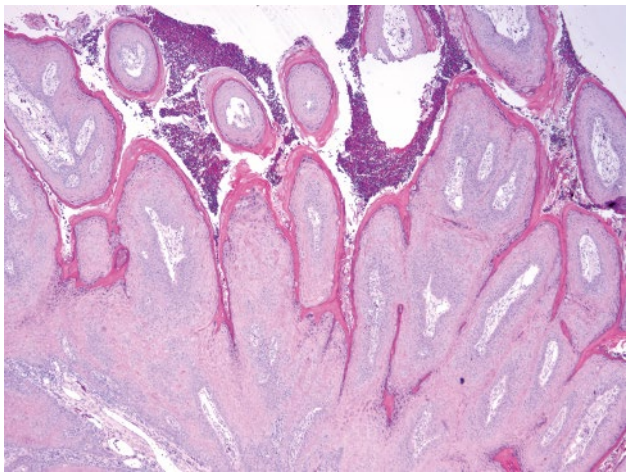


Figure 8.28 Histologic image of an oral papilloma, 14-year-old German shorthair pointer dog. Epithelial projections often fuse into short club like structures.

contain many variably sized, basophilic keratohyaline granules. Rare to uncommon, scattered, and transient intranuclear inclusions are most often evident in keratinocytes at the interface between the stratum corneum and upper stratum spinosum/stratum granulosum; rarely, a few intracytoplasmic inclusions may also be present. Large, mature papilloma lesions (or *regressing lesions*, see below) are less likely to demonstrate inclusions. Virion assembly, expression and shedding occur in the degenerating keratinocytes of the stratum corneum.

The papillomavirus-infected keratinocytes may also develop into diagnostically useful cells called *koilocytes*. Koilocytes are enlarged and degenerate keratinocytes in the upper epithelial layers that have watery, poorly staining cytoplasm or a perinuclear cytoplasmic halo (ballooning degeneration) with a small smudged or vesiculate eccentric nucleus. Viral cytopathology may also manifest as cells containing increased quantities of finely granular gray-blue cytoplasm [38]. The presence of intralesional viral cytopathology (with or without viral inclusions), dysplasia, and/or associated lymphocytic inflammation are provocative clues of a papillomavirus etiology (see Figures 8.29–8.31).

Animals affected with oral papillomatosis typically experience spontaneous, immune-mediated recovery, which generally takes one–two additional months. During the recovery phase (lesion regression), the papillary "fingers" open up and atrophy. Lesion regression is mediated by the host's adaptive immune system, CD4 and

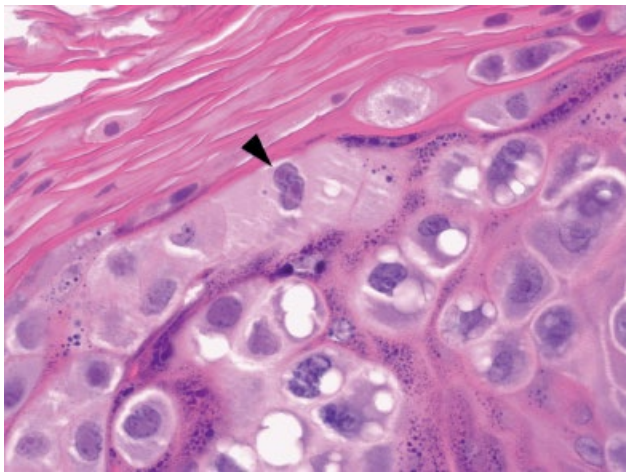


Figure 8.29 High magnification histologic image of an oral papilloma, seven-year-old Poodle dog (same case as Figure 8.27). The black arrowhead indicates the intranuclear viral inclusion bodies (papillomavirus). Note degenerative cytologic features (vacuolated cytoplasm) in multiple epithelial cells.

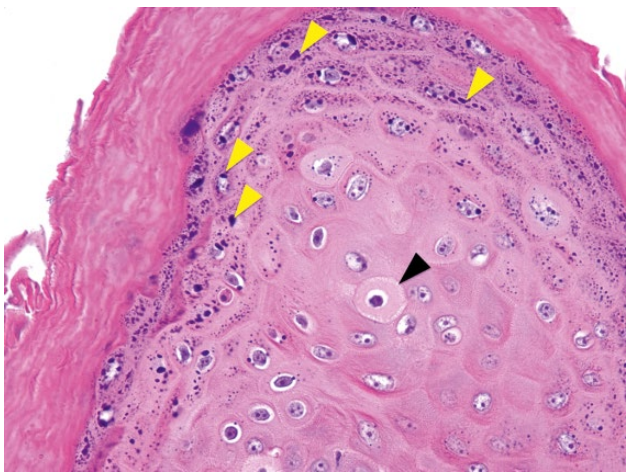


Figure 8.30 Cytological features typical of viral papillomas, 14-year-old German Shorthair pointer dog (same dog as Figure 8.28). Note the presence of a koilocyte (black arrowhead) and numerous keratohyaline granules (yellow arrowheads).

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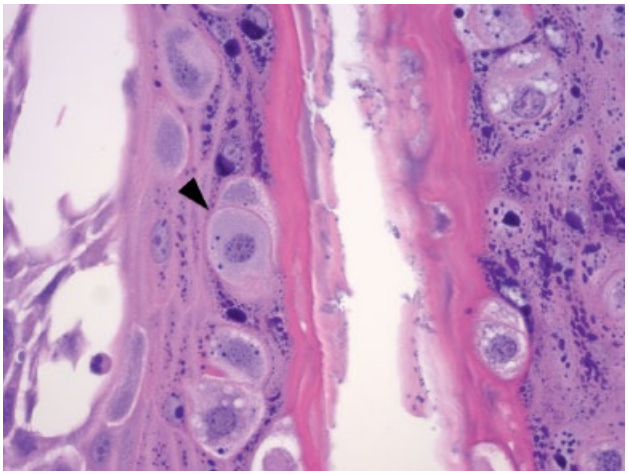


Figure 8.31 Cytological features typical of viral papillomas, three-year-old Great Dane dog. Scattered epithelial cells have vacuolated cytoplasm. A single cell has increased quantities of finely granular gray-blue cytoplasm and small numbers of keratohyaline granules (black arrowhead).

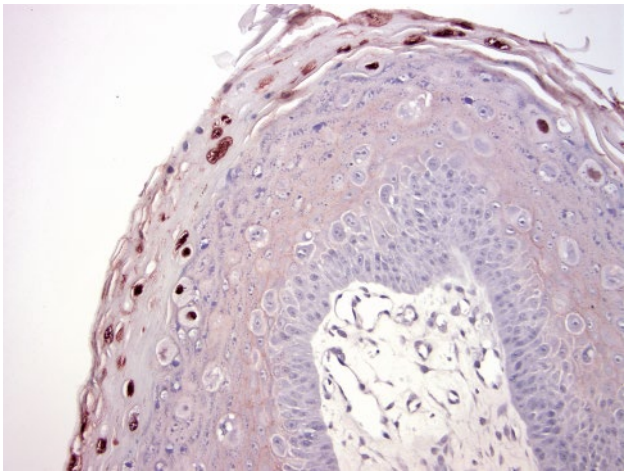


Figure 8.32 Immunohistochemistry for the detection of papillomavirus antigen, three-year-old Great Dane dog (same dog as Figure 8.31). Abundant brown granular material in the lesional stratum granulosum and stratum corneum indicates the presence of papillomavirus antigen in these epithelial cells (bovine papillomavirus IHC).

CD8 T lymphocytes, resulting in a durable immunity to reinfection [39]. In a manner similar to canine cutaneous histiocytosis, infiltrating lymphocytes may be present within the subepithelial stroma of regressing papilloma lesions.

This durable immunity is perhaps the reason that oral papillomatosis is typically a disease of young animals, as the "educated and wise" immune system of the adult animal is generally capable of blocking viral (re-)occurrence. Cases of clinically severe papillomatosis suggest the possibility of immunosuppression, and not generally a virulent viral variant. IgA deficiency in Beagle dogs has been associated with fulminant oral papillomatosis and dogs with X-linked severe combined immunodeficiency are at risk for developing cutaneous papillomas.

Oral papillomas occasionally occur in older dogs. While some lesions have characteristic features of a viral etiology, adult dogs are more likely to have lesions that lack overt histologic evidence of an association with papillomavirus (presence of viral cytopathology, associated lymphocytic inflammation and/or viral inclusions). Classically, such lesions have been referred to as *squamous papilloma,* and the suggestion has been made that these lesions have a virus-independent etiology. Considering that papillomavirus inclusions are often difficult to find and may only be transiently detectable, it seems plausible that *squamous papilloma* lesions in older dogs may actually be occult viral lesions. IHC assays to detect virions (electron microscopy), viral proteins and/or techniques to demonstrate viral nucleic acid (in situ hybridization, PCR assays) may be warranted. Antibody to bovine papillomavirus cross-reacts with CPV-1 and is used in IHC assays with canine tissues (Figure 8.32). It is important to note that IHC detection of papillomaviruses is only possible when viral replication is present [38]. PCR assays may be falsely negative if a variant papillomavirus is undetectable by agent-specific assays.

Box 8.5 Differential Diagnoses for Oral Papilloma

SCC, papillary
Mucosal hyperplasia, papillary
Feline naso-oropharyngeal polyps

Rarely, papillomas can undergo malignant transformation, although most cases of canine SCC *do not arise* from papillomavirus-induced benign lesions [40]. A few well-documented cases of malignant transformation of papillomavirus-associated lesions have been described, but this area of investigation is highly controversial (see Section 8.3 on oral squamous cell carcinoma).

8.4.1.1 Clinical Features

Specific therapy for canine oral papillomatosis is generally unnecessary as most lesions spontaneously regress over a 4–8 week period. However, in some cases, lesion regression may take as long as 12 months [41]. However, in severe cases in which the lesions interfere with mastication or respiratory efforts, surgical intervention may be required. Traditional surgical excision, cryosurgery, and electrosurgery have all been advocated to various degrees. In such cases, owners should be advised that continued development of lesions may be seen after surgery. Viral capsid-based and autologous vaccines have been attempted, however, both failed to result in faster lesion regression. Additionally, azithromycin has been

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shown to result in faster lesion regression compared to untreated dogs [42].

8.4.2 Oral Papillomas in Felids

Oral papillomatosis has been infrequently reported in domestic cats. This is interesting, in that SCC is the most common feline oral malignancy (by far). This suggests that oral papillomatosis is either *not* a precursor lesion to SCC, or that papillomatosis rarely "progresses" to SCC. Either way, a pathogenic connection between feline oral papillomatosis and SCC is, at best, tenuous. Unlike dogs, papillomavirus infections in cats typically *do not* result in verrucous proliferative lesions. Multifocal, well-demarcated, plaque like lesions on the ventral surface of the tongue have been described several times in older cats. These incidental lesions, which may spontaneously resolve, are associated with hyperplastic folded epithelium forming keratin-filled cup-like structures on the ventral surface of the tongue. An association with papillomavirus has been demonstrated (koilocytes, papillomavirus antigen [IHC] and viral DNA) [43].

A variant of papilloma lesion, the fibropapilloma, has been described in young cats (distinct from feline epulis), along with cattle and other animals. In contrast to the prototypical canine wart-like lesion, the bulk of the fibropapilloma lesion is stromal, characterized by prominent streams of benign-appearing fibroblasts with few mitoses [44]. The overlying epithelium is not greatly thickened but does send deep branching epithelial rete pegs into the underlying fibrous mass. Koilocytes and intranuclear inclusions are not a feature of fibropapilloma. If the epithelium ulcerates, the lesion can become inflamed and edematous; it also may be mistaken for a fibroma. Feline fibropapillomas also need to be differentiated from nasopharyngeal inflammatory polyps.

Multiple species of wild felids (African lions, Canada lynx, others) have had documented evidence of solitary or multiple oral papillomas with evidence of papillomaviral infection. In these lesions, intralesional papillomavirus DNA, viral antigen, or virion structures consistent with papillomavirus have been demonstrated. The relationship of oral papillomatosis lesions to oral SCC in felids remains speculative.

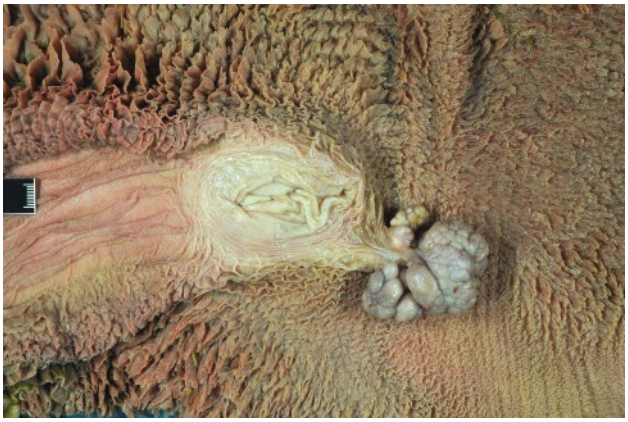


Figure 8.33 Pedunculated fibropapilloma in the rumenal mucosa of a six-year-old Holstein cow. *Source:* A. Michel, University of California, Davis.

8.4.3 Oral Papillomas in Cattle and Other Species

Oral papillomatosis in cattle is the result of an infection with bovine papillomavirus [39]. These lesions are often characterized as fibropapillomas, however multifocal verrucous papillomas grossly and histologically similar to those found in dogs have been described in calves. In some geographic regions, there appears to be a strong connection between the grazing of bracken fern and oral papillomatosis in cattle. Although these papilloma lesions in cattle can occur on the lips or within the oral cavity, they are more frequently identified arising from the mucosa of the esophagus or rumen (Figure 8.33).

Papillomas arising from the lips, oral cavity or esophagus of both young and mature horses have been described infrequently. Congenital, verrucous papillomas have been described in five fetal and neonatal foals on the lips and skin. Although the lesions demonstrated koilocytes, immunohistochemical assays for papillomavirus antigen were negative. In horses, infection with *bovine papillomavirus* is the cause of the very common cutaneous sarcoid lesion, which to the authors knowledge has not been reported to occur in the oral cavity.

Fibropapillomas, associated with a unique papillomavirus, have been reported to occur on the lips of llamas.

References

38 Meuten, D.J. (2017). *Tumors in Domestic Animals*, 5e. Ames, Iowa: John Wiley & Sons.

39 Maxie, M.G. (2016). *Jubb, Kennedy, and Palmer's Pathology of Domestic Animals*, 6e. St. Louis, Missouri: Elsevier.

40 Luff, J., Rowland, P., Mader, M. et al. (2016). Two canine papillomaviruses associated with metastatic squamous cell carcinoma in two related Basenji dogs. *Vet. Pathol.* 53: 1160–1163.

41 Sancak, A., Favrot, C., Geisseler, M.D. et al. (2015). Antibody titres against canine papillomavirus 1 peak around clinical regression in naturally occurring oral papillomatosis. *Vet. Dermat,* 26 (57–59): e19–e20.

VetBooks.ir

42 Yagci, B.B., Ural, K., Ocal, N., and Haydardedeoglu, A.E. (2008). Azithromycin therapy of papillomatosis in dogs: a prospective, randomized, double-blinded, placebo-controlled clinical trial. *Vet. Dermat.* 19: 194–198.

43 Munday, J.S., Fairley, R.A., Mills, H. et al. (2015). Oral papillomas associated with Felis catus papillomavirus type 1 in 2 domestic cats. *Vet. Pathol.* 52: 1187–1190.

44 Head, K. W., Armed Forces Institute of Pathology (U.S.), American Registry of Pathology, & WHO Collaborating Center for Worldwide Reference on Comparative Oncology. (2003). Histological classification of tumors of the alimentary system of domestic animals. Published by the Armed Forces Institute of Pathology in cooperation with the American Registry of Pathology and the World Health Organization Collaborating Center for Worldwide Reference on Comparative Oncology, Washington, DC.

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8.5 Oral Lymphoma

Lymphoma is a malignant round cell tumor derived from various lineages of neoplastic lymphocytes. The term *lymphosarcoma* is an antiquated term and *malignant lymphoma* is now considered to be redundant, in the same manner that *malignant melanoma* is redundant. The concept of malignancy is implicit within the term *lymphoma*.

There are many different types of lymphoma, each with its own particular biological behavior (indolent or aggressive), etiology, and common anatomic sites of occurrence. Although lymphoma occurs in many different veterinary species, oral lymphoma most often occurs in dogs and cats and less often in horses, cattle, and goats (Figure 8.34). Oral lymphoma can initiate within the oral mucosa (mucosa-associated lymphatic tissue, or MALT), bones of the jaw, or lymphoid tissues of the tonsil. Oral lymphoma can also directly extend into the oral cavity from a lymphoma lesion in an adjacent structure, such as the nasal cavity, lip or as metastatic spread from a distant anatomic site. Oral lymphoma is rarely a solitary lesion; the presence of oral lymphoma suggests the possibility of lesions elsewhere in the alimentary tract, skin, lymph nodes, or distant sites. This possibility should be communicated to the submitting clinician (providing the clinician did not suggest this possibility to the pathologist in the first place).

The etiology of lymphoma is multifactorial, but begins with one or more genetic aberrations in a lymphocyte's genome. These aberrations include the functional loss of one or more tumor suppressor genes, increased functionality of proto-oncogene products (conversion of a proto-oncogene into a functional oncogene), inhibition of apoptosis regulatory mechanisms, or less commonly, genetic injury to systems of DNA repair. In human pathology, multiple lymphoid tumors are associated with a predictable chromosomal translocation event, often resulting in the constitutive activation of a signaling molecule like tyrosine kinase. Chromosomal translocation may result in the loss of the normal regulatory mechanism of a proto-oncogene. This results in an unregulated and constitutively active signaling molecule driving cellular growth. Chromosomal translocations are particularly common in lymphocytes as a result of their peculiar biology – their unique and transient ability to rearrange their genome in order to generate immune molecule diversity (VDJ recombination). In human lesions, specific lymphoid translocations have actually become genetic signatures of particular lymphoid tumors. In veterinary species, most of the putative chromosomal translocation events have yet to be discovered.



Figure 8.34 Gross images of mandibular lymphoma in a 13-year-old Boer goat. In addition to the bone lesion, the goat was affected by multicentric B cell lymphoma involving most of the lymph nodes (inset photo). There is also a focus of necrosuppurative osteomyelitis apical to one of the cheek teeth (tooth root abscess). *Source:* V.S. Chen, University of California, Davis.

As lymphoma is a type of round cell tumor, the clinician and pathologist should consider a differential list of mucosa-associated round cell lesions: lymphoma, plasma cell tumor, mast cell tumor, histiocytoma, cutaneous histiocytosis (dogs and cats), melanoma, neuroendocrine tumors, and transmissible venereal tumor (TVT, dogs in geographically appropriate locations). Non-neoplastic lesions like reactive lymphoid hyperplasia or dysplasia should also be considered as differentials. Lymphoid hyperplasia (physiologic antigen-associated proliferation of lymphoid tissue) typically occurs in a follicular pattern and needs to be differentiated from follicular lymphoma. Multifocal lymphoid hyperplasia of the pharyngeal and laryngeal mucosa is common in horses and cats. Dogs are more likely to have hyperplastic tonsils.

To the non-specialist, a suspect lymphoma lesion may appear to be a daunting sea of round blue cells. Knowledge of the patient history and signalment, intercurrent clinical signs and lesions, anatomic location, gross features, microscopic features (H&E staining), and the judicious use of special stains (such as toluidine blue to reveal occult mast cell granules), may all facilitate a preliminary diagnosis. However, a morphologically and phenotypically precise diagnosis may require a

Box 8.6 Differential Diagnoses for Oral Lymphoma

Plasmacytoma
Mast cell tumor
Melanoma
Histiocytoma
Cutaneous histiocytosis
Neuroendocrine tumor (carcinoid)
Transmissible venereal tumor (TVT)
Hyperplastic lymphoid tissue
Ectopic lymphoid tissue (cats and horses)
Canine chronic ulcerative stomatitis (CCUS)
Gingivitis/stomatitis/periodontitis

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Table 8.1 Leukocyte antigens for lymphoma diagnostics.[a]

Formalin fixed tissue		
CD18	(D/C/H)	pan leukocyte
CD45	(D)	pan leukocyte
CD3	(D/C/H)	T lymphocyte
CD20	(D/C/H)	B cell/T cell (rare)
CD79a	(D/C/H)	pan B cell
Mum1	(D/C/H)	plasma cell
CD204	(D/C/H)	macrophage
CD11d	(D)	macrophage
Iba-1	(D)	histiocytes
Frozen or fresh tissue		
CD4	(D/C)	CD4 lymphocyte
CD8	(D/C)	CD8 lymphocyte

[a] Leukocyte antigens useful in the diagnosis of canine, feline, and equine lymphomas

panel of immunohistochemical stains and may even require other ancillary diagnostics such as *clonality testing* and/or *flow cytometry*.

A diagnosis of "lymphoma" is not monolithic, as the neoplastic lymphocytes comprising the lesion can be parsed into ever-smaller subsets. Lymphoma lesions are classified by a variety of different criteria – anatomic distribution (localized, multicentric, alimentary, epitheliotropic), perceived behavior (high grade, low grade), architectural pattern (diffuse, follicular, T-zone), cytologic features (centrocyte, centroblast, immunoblast), and lymphocyte subset (T cell, B cell, non-T/non-B). To add to the diagnostic complexity, it is not uncommon for reactive, non-neoplastic, differentiated lymphocytes to *infiltrate* lymphoma lesions as part of the immune response. Such "inflamed lymphomas" can be a real diagnostic challenge.

Neoplastic lymphocytes are fragile and tend to degrade (autolyze) relatively quickly in postmortem tissues. Inappropriately aggressive biopsy techniques can also induce artifactual changes that may obfuscate the pathologic diagnosis. Some assays utilized for parsing out lymphoma lesions require the use of *snap-frozen tissues*, as formalin fixation may obscure or destroy (coagulate) critical diagnostic proteins like CD4 or CD8 which may be used for immunophenotyping lymphoid lesions. High-quality lesional DNA, available in fresh or frozen tissues, may also be needed for *clonality testing*. However, diagnostically useful DNA samples can usually be obtained from formalin-fixed, paraffin-embedded lesions. Lymphoma classification has become its own subspecialty (immunopathology); because of this, a precise morphologic immunopathologic diagnosis is beyond the scope of this textbook.

8.5.1 Canine Oral Lymphoma

Oral lymphoma accounts for approximately 5% of all canine oral tumors. Epitheliotropic T cell lymphoma is most common and grossly presents as bright red erosions/ulcers of the mucosa that can progress to solid mass lesions, particularly in the tissues of the tongue or cheek. Histologically, these lesions are associated with single to clusters to sheets of neoplastic T cells within the mucosal epithelium (Pautrier's microabscesses) [45]. Epitheliotropic T cell lymphoma (mycosis fungoides) can arise within the oral mucosa as an isolated lesion, or more often, may be associated with multiple cutaneous lesions. Information provided by the clinician on the patient's intercurrent diseases is critical to establishing the most accurate diagnosis. Canine lymphoma lesions (typically T cell lymphomas) may secrete PTHrp (pseudohyperparathyroidism), which is often associated with hypercalcemia. If hypercalcemina is present, tests are available to identify the presence of PTHrp in the serum.

Mucosal lymphoma manifests as a focal to diffuse swelling of the mucosa of the lips, tongue or pharynx. Histologically, mucosal lymphoma is comprised of variably dense arrays of round cells reminiscent of lymphocytes lacking an induced stroma or tumor cell-associated matrix (Figure 8.35). Depending upon the diagnosis, the neoplastic cells may be either monotonously homogeneous or demonstrate anaplastic features. Mucosal lymphomas arising from MALT are often B cell tumors and may have preserved follicular architecture (marginal zone lymphoma). Such lymphomas may progress to diffuse large B cell lymphomas. It is rare for canine B cell lymphomas to be confined to the oral cavity [46].

Lymphoma of the tonsil can occur unilaterally or bilaterally – it must be differentiated from squamous cell carcinoma of the tonsil and hyperplastic lymphoid tissue (reactive and everted follicular tissue). Tonsillar lymphoma can occur as an isolated tumor or as a component of multicentric lymphoma. In cases of suspected tonsillar lymphoma, the regional lymph nodes should be closely examined (palpated/imaged) and either aspirated for cytological examination or biopsied for histological examination (see Figure 8.36).

A diagnosis of lymphoma can often be established from the morphologic features with or without additional immunodiagnostics. The architectural arrangement of the cells (sheets, nodules, follicles), size of the nuclei, mitotic rate, and other cytologic features (presence of large nucleoli) facilitate the classification and grade of the particular type of lymphoma. The interested reader is referred to one of the many available immunopathology texts that specifically deal with lymphoma diagnostics.

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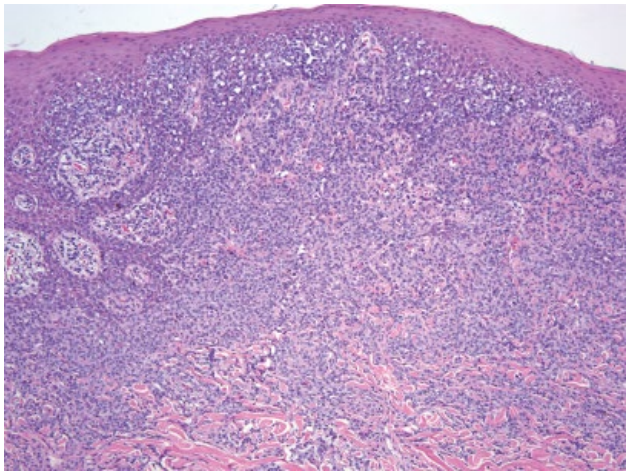


Figure 8.35 Histologic image of epitheliotropic lymphoma in the lip of an 11-year-old mixed-breed dog. Sheets of neoplastic round cells infiltrate both the subepithelium and mucosal epithelium, often obscuring the junctional interface. The neoplastic round cells were positive for CD3 expression (via immunohistochemistry) and were determined to be have a clonal T cell receptor expression pattern (via clonality testing). *Source:* P. Moore, University of California, Davis.

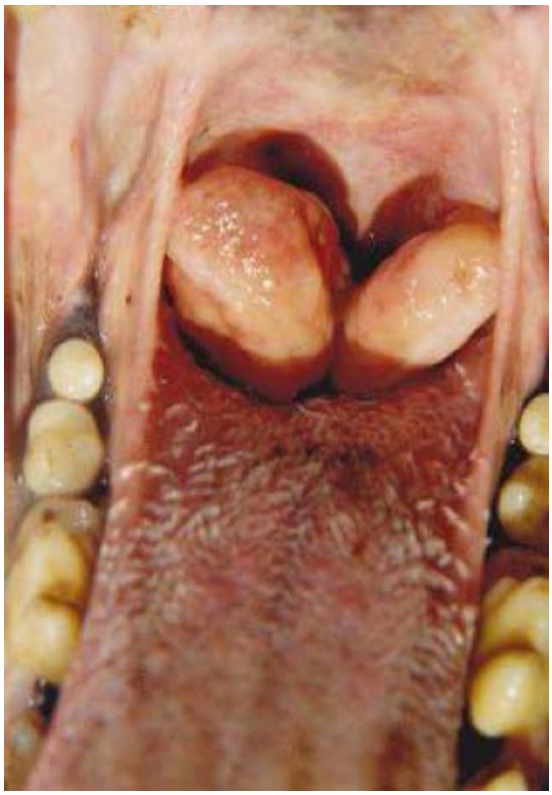


Figure 8.36 Gross image of tonsillar lymphoma, 13-year-old intact male dog. This dog had multicentric lymphoma. *Source:* A. Loretti.



Figure 8.37 Gross image of lingual/sublingual lymphoma, eight-year-old cat. A large mass distorts the tongue and sublingual region. Note: the lesion has been incised. *Source:* S. McGraw, University of California, Davis.

8.5.2 Feline Oral Lymphoma

Lymphoma is the fourth most common malignant oral tumor of cats [46], and lesions arising in the gingiva or tongue appear to be more common than those arising from the tonsil or pharynx. As is true for dogs, feline oral lymphoma most often occurs as a component of systemic disease. Gross lesions may be red and ulcerated and as a result, be associated with secondary, often suppurative, inflammation (Figure 8.37). Although oral lymphoma can occur in animals younger than a year, these tumors are more often identified in older cats (mean age of 9.5 years).

As is true for canine oral lymphoma, MALT-derived lymphomas are often of B cell origin. Oral extranodal lymphomas are reportedly more common in cats infected with the retroviruses feline immunodeficiency virus (FIV) and/or feline leukemia virus (FeLV). Lymphoma of the feline oral mucosa needs to be differentiated from feline chronic gingivostomatitis (FCG). Fortunately, the presence of abundant plasma cells in FCG generally facilitates the appropriate diagnosis (Figure 8.38). However, FCG can be associated with hyperplastic lymphoid nodules, which may generate confusion in small biopsy specimens.

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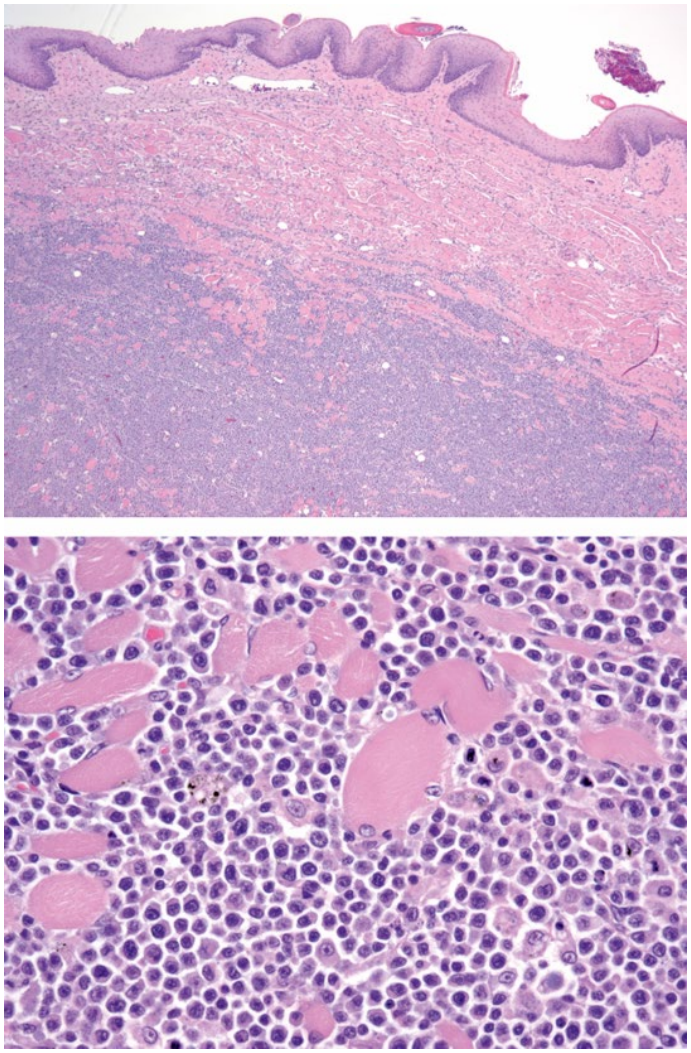


Figure 8.38 Histologic images of lingual/sublingual lymphoma in a cat. A mass comprised of neoplastic round cells infiltrates the subepithelium and skeletal muscle of the tongue. The tumor is composed of large lymphoblasts forming sheets without an associated matrix. Note the isolated myocytes and lack of plasma cells. This is the same lesion as depicted in Figure 8.37.

8.5.3 Oral Lymphoma of Ruminants

Bovine lymphoma occurs sporadically in calves without an infectious etiology (sporadic juvenile lymphoma). Sporadic juvenile lymphoma typically manifests as multicentric lymphoma. In adult animals, infectious bovine lymphoma (enzootic bovine leukosis) is the result of an infection with the retrovirus bovine leukemia virus (BLV). BLV infections, most often associated with the proliferative but non-neoplastic disorder *persistent lymphocytosis* (~30% of infected animals), are also associated with lymphocyte transformation and solid lymphomas. BLV causes a persistent lifelong infection, which can progress to multicentric lymphoma in a subset of adult cattle (1–3% of infected animals). The primary target cell of BLV infection is the B lymphocyte, although monocytes and macrophages can also be infected. Contrary to the name, BLV is generally not associated with leukemia.

References

45 Moore, P.F., Affolter, V.K., Graham, P.S., and Hirt, B. (2009). Canine epitheliotropic cutaneous T-cell lymphoma: an investigation of T-cell receptor immunophenotype, lesion topography and molecular clonality. *Vet. Dermatol.* 20: 569–576.

46 Meuten, D.J. (2017). *Tumors in Domestic Animals*, 5e. Ames, Iowa: John Wiley & Sons.

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8.6 Neuroendocrine Carcinoma (Carcinoid)

Neuroendocrine carcinoma, or *carcinoid*, has rarely been identified in the oral mucosa of dogs and cats. These neuroendocrine tumors are generally considered to be low to moderate-grade malignancies that may arise from lip, gingiva, esophagus, or sinonasal tissues. More often, these tumors occur in the gastric/intestinal mucosa, the pancreatic/hepatic parenchyma or lung [47]. In humans, neuroendocrine carcinomas of the head are rare, but most often occur in the nasal cavity or nasal sinuses [48]. These tumors are rarely identified in animals – a search of the CCOMP and UC Davis pathology databases yielded no cases of neuroendocrine carcinoma in veterinary species.

Mucosal carcinoids, at least initially, are slow-growing and arise from the diffuse mucosa-associated neuroendocrine tissues, structures associated with the regulation of alimentary physiology. These tumors have been previously known by several different names including argentaffinoma, enterochromaffin cell tumor, and "apudoma" (amine precursor uptake and decarboxylation). Carcinoids may or may not be endocrinologically active.

Histologically, many carcinoids have a distinct *neuroendocrine* architecture. They are comprised of populations of ovoid, polygonal to spindloid cells forming *solid sheets or nests separated by a delicate fibrovascular stroma* (Figure 8.39). The tumor architecture is reminiscent of neuroendocrine tissues such as the pars distalis of the pituitary gland, the chief cells of the parathyroid gland and the chromaffin cells of the adrenal medulla. These tumors can also be arranged as rosettes or acini, or in cord-like architectural structures. The neoplastic cells are generally small and have ovoid, central nuclei with euchromatin. Some lesions may have multinucleate cells. Interstitial amyloid may be present in some lesions. As is true of most neuroendocrine lesions, distinguishing between benign and malignant lesions histologically can be difficult. Cytologic anaplasia and mitotic figures may be present in aggressive lesions, although local infiltration/invasion, microscopic evidence of vascular invasion and/or distant metastasis are more consistent with malignancy.

Carcinoids have intracytoplasmic, membrane-bound dense-core neurosecretory granules, which are pathognomonic for tumors of neuroendocrine origin. The granules are demonstrable by electron microscopy or by light microscopy with silver stains like Cherukian-Schenk or Fontana-Masson. More often, the diagnosis of carcinoid is confirmed by having ruled out other neuroendocrine tumors and by one or more positive immunohistochemical stains like neuron-specific enolase (NSE) and/or chromogranin A. Some carcinoids also stain for one or more specific secretory products like serotonin, synaptophysin, or somatostatin.

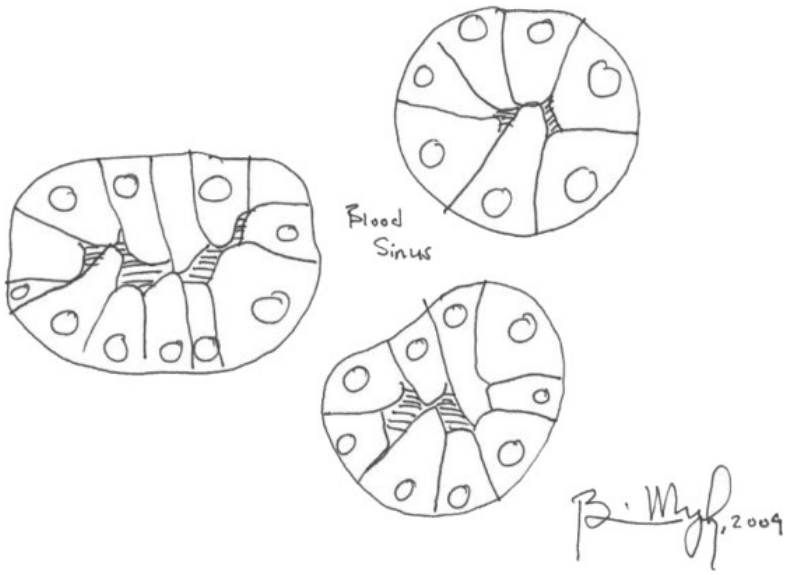


Figure 8.39 Packeting architecture of neuroendocrine tumors.

References

47 Meuten, D.J. (2017). *Tumors in Domestic Animals*, 5e. Ames, Iowa: John Wiley & Sons.

48 Barnes, L., Universitäts Spital Zürich. Departement Pathologie, International Academy of Pathology et al. (2005). *Pathology and Genetics of Head and Neck Tumours*. Lyon: IARC Press.

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8.7 Granular Cell Tumor

Granular cell tumors (GCT) are uncommon, benign tumors of dogs, cats, and horses, and arise from the oral cavity mucosa and elsewhere. Oral GCT have been most often identified in the tongue of older dogs (often sublingual), but can also occur in the mucosae of gum, lip, palate, and tonsil. At UC Davis and CCOMP, the majority of oral GCT lesions in dogs have been identified in the tongue (Figure 8.40). Like oral mast cell tumor, oral GCT can occur multifocally. The oral distribution for cats is similar to that of the dog; oral GCT have not been reported in horses. In horses, GCT are most often identified in the lung. In general, GCT are slow-growing tumors. Although recurrence may be a concern, they may be treated with conservative excision. Considered to be a benign neoplasm, rarely, GCT have been reported to metastasize and have also been associated with bone lysis.



Figure 8.40 Gross image of sublingual canine GCT. *Source:* University of Wisconsin-Madison.

GCT are generally small lesions (0.5–2 cm diameter) but can grow up to 7 cm in diameter. Grossly, GCT are firm, raised, red, and smooth to granular. The overlying mucosal epithelium may be ulcerated and GCT are typically white on section. Histologically, GCT are unencapsulated and comprised of dense sheets or nests of large, round to polygonal shaped cells with small round nuclei amidst minimal reticular stroma. In general, GCT are not invasive, although the lesion margins may be indistinct. In alignment with the lesion name, the neoplastic cells are filled with innumerable, variably sized, eosinophilic cytoplasmic granules and have round to oval nuclei with few mitotic figures. Nuclei can be central or eccentric (Figure 8.41). The cytoplasmic granules are PAS positive and diastase resistant, are not acid fast, and do not stain purple with metachromatic stains like toluidine blue or giemsa. Criteria for malignancy include evidence of necrosis, spindle-shaped cells, large nucleoli, increased mitotic activity, high nuclear to cytoplasmic ratio, and pleomorphism [49]. GCT may have a fibrous to inapparent stroma. Rare GCT have been associated with a collagenous stroma that mimics osteoid, arranged in trabeculae-like structures. This osteoid-like stroma is fibrillar and lacks palisading osteoblasts and embedded osteocytes.

The histogenesis of GCT has been controversial. Formerly known as *myoblastoma*, GCT were thought to arise from a variety of cells or tissues including skeletal muscle, smooth muscle, Schwann cells, basal cells, histiocytes, or fibroblasts. It is currently thought that GCT have a neural crest origin, like melanomas. The results of immunohistochemical studies have varied, but most of these tumors express S100 and vimentin and are negative for cytokeratin expression. IHC assays often provide little additional information [50], but may be helpful to rule out other differential diagnoses (see below). Recent ultrastructural investigations (electron microscopy) suggest

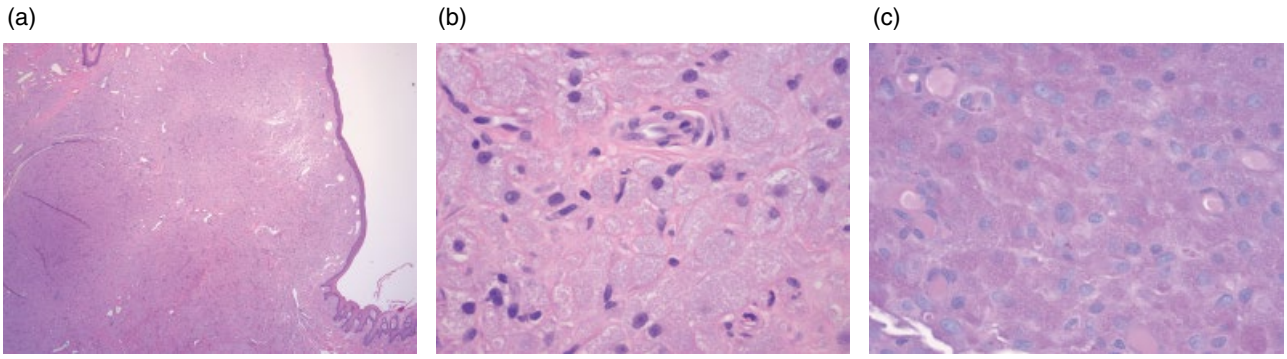


Figure 8.41 Histologic images of a lingual granular cell tumor, eight-year-old Labrador Retriever dog. (a) The lingual granular cell tumor (GCT) is elevated from the tongue surface is unencapsulated and comprised of sheets of round to polygonal cells. (b) The GCT is comprised of round to polygonal cells with moderate anisokaryosis distended with eosinophilic cytoplasmic granules. (c) The cytoplasmic granules are PAS positive (purple-staining).

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that the cytoplasmic granules are autophagosomes or autophagolysosomes (secondary lysosomes) [51].

Box 8.7 Differential Diagnoses for Oral Granular Cell Tumor

Rhabdomyoma
Oncocytoma
Liposarcoma (well-differentiated)
Melanoma
Histiocytic foam cell nodules

GCT need to be differentiated from rhabdomyoma and oncocytoma, all three of which exhibit some degree of cytoplasmic granularity and can be difficult to distinguish between on the basis of histologic features alone. Rhabdomyoma occurs in the canine larynx and oncocytoma develops most frequently in the salivary gland [50]. Rhabdomyoma should stain appropriately with markers of myogenic lineage and ultrastructurally exhibits myoblast-specific features. The cytoplasmic "granules" in oncocytoma and rhabdomyoma lesions are mitochondria (*not* the autophagolysosomes of GCT) and as such, should be ultrastructurally discernible. A note of caution: GCT may stain positively for desmin with IHC and oncocytoma can stain positively with PAS.

To add to the diagnostic complexity, a relatively newly described oral lesion in miniature Dachshund dogs shares some histological overlap with GCT [52]. These lesions, *histiocytic foam cell nodules* (HFCN), are thought to be inflammatory aggregates of histiocytic foam cells with vacuolated cytoplasm and occurred multifocally in the ventral and lateral surfaces of the tongue (see Tumor like proliferative lesions in the oral mucosa). HFCN is PAS negative and positive for the macrophage scavenger receptor CD204.

References

49 Rallis, T.S., Tontis, D.K., Soubasis, N.H. et al. (2001). Immunohistochemical study of a granular cell tumor on the tongue of a dog. *Vet. Clin. Pathol.* 30: 62–66.

50 Meuten, D.J. (2017). *Tumors in Domestic Animals*, 5e. Ames, Iowa: John Wiley & Sons.

51 Suzuki, S., Uchida, K., Harada, T. et al. (2015). The origin and role of autophagy in the formation of cytoplasmic granules in canine lingual granular cell tumors. *Vet. Pathol.* 52: 456–464.

52 Katou-Ichikawa, C., Izawa, T., Sasai, H. et al. (2016). Multiple histiocytic foam cell nodules in the tongue of miniature Dachshund dogs. *Vet. Pathol.* 53: 625–628.

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8.8 Mast Cell Tumor

Oral mast cell tumors (MCT) occur in dogs and cats, but rarely so. Eighteen and five oral MCT have been identified in the CCOMP database for dogs and cats, respectively. This rarity is in contrast to the high incidence of MCT in the haired skin of dogs. Oral MCT are extremely rare in horses and cattle [53]. Oral MCT are round cell tumors that arise from the lip (both from the lip mucosa and the mucocutaneous junction), buccal mucosa, gingiva, tongue, and hard palate; they can also occur at multiple sites concurrently. MCT represent approximately 6% of canine oral tumors. Labrador and golden retrievers appear to be overrepresented. Due to nominal understanding of the biological behavior of oral MCT, local invasiveness into bone and, thus, key radiologic features are unknown. Differential diagnoses for oral MCT include other round cell tumors in addition to several inflammatory conditions. Oral MCT may or may not be part of a systemic disease process. Mast cells are round cells that exfoliate readily; as a result, cytology performed from fine-needle aspirates may provide valuable diagnostic information with minimal associated morbidity or cost (although aspirating an oral lesion may require anesthesia). One should bear in mind that aspirates of MCT can be difficult to differentiate from eosinophilic granuloma lesions (see below for discussion on feline eosinophilic granuloma).

Box 8.8 Differential Diagnoses for Oral Mast Cell Tumor

Lymphoma
Plasmacytoma
Melanoma
Histiocytoma
Cutaneous histiocytosis
Neuroendocrine tumors (carcinoid)
Eosinophilic granuloma
Other stomatidides featuring mast cell proliferation

MCT are unencapsulated, and have variably distinct lesional margins. The neoplastic mast cells do not produce a matrix. Neoplastic mast cells infiltrate through the pre-existing subepithelial connective tissue. Tumors are comprised of variably dense sheets and/or cords of (typically) granulated round cells. The cytoplasmic granules are metachromatic and stain purple with toluidine blue or Giemsa stains (note that in Romanovsky-stained slides the granules may not be evident). Variable numbers of infiltrating eosinophils are generally associated with MCT and this can be a useful diagnostic feature. In poorly granulated MCT, the presence of interspersed eosinophils (even a few) provides a diagnostic clue as to the identity of the tumor. Normal oral mucosa and gingiva have resident mast cells that may become abundant and prominent during inflammatory reactions, but should still remain individualized and scattered. Because mast cells are so cytologically striking, the pathologist is cautioned to avoid over-interpreting inflammatory lesions featuring proliferative mast cells. As always, the morphologic diagnosis should fit the clinical features of the case (see Figure 8.42).

Oral MCT seem to demonstrate a more aggressive clinical course than those arising from haired skin. In a retrospective study of 33 dogs with oral MCT, approximately 55% had cytological evidence of mast cells in the regional lymph nodes [54]. However, since lymph node involvement was determined cytologically, it is possible that the number of cases with actual *lymph node metastasis* was overestimated. Nonetheless, dogs with cytologic evidence of mast cells in regional lymph nodes had a poorer overall outcome. As is true for cutaneous MCT, the mitotic index appears to be highly predictive of outcome for dogs with oral MCT. Oral MCT with a mitotic index of >5 per 10 high power fields had a significantly reduced overall survival time. Unfortunately, the grading schemes developed for MCT of the haired skin [55, 56], do no apply to oral MCT.

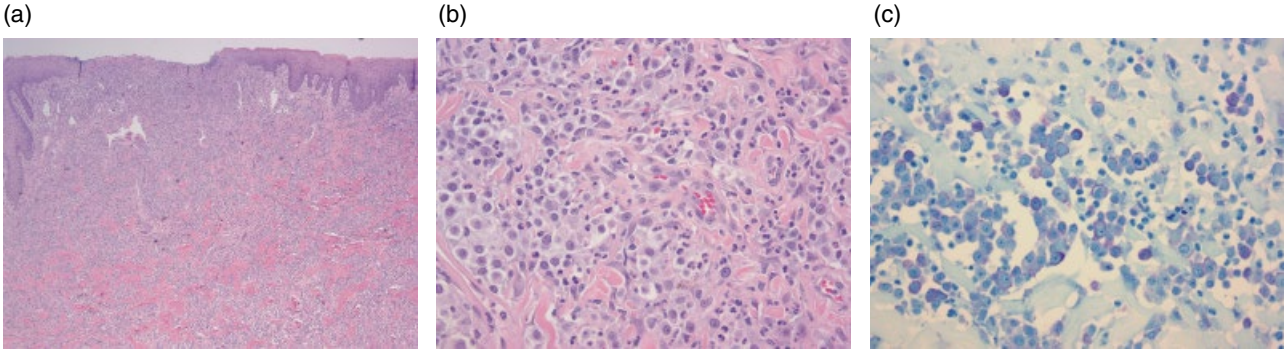


Figure 8.42 Histologic images of a mast cell tumors (MCT) in the lip of a five-year-old Standard Poodle dog. (a) The lip is expanded by an ulcerated mass comprised of round cells forming sheets and cords. (b) The round cells have variable numbers of cytoplasmic granules and are interspersed with infiltrating eosinophils. (c) The cytoplasmic granules stain metachromatically (purple) with toluidine blue stain.

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Although, the aggressive biological behavior of oral MCT may suggest that a more vigorous surgical approach to local tumor control is necessary, current recommendations are the same as for cutaneous MCT; wide surgical excision of 2 cm gross clinical margins with radiation therapy and/or chemotherapy as needed.

In cats, MCT have been rarely described in the lip (mucocutaneous junction), buccal mucosa, soft palate and sublingual region. Eosinophilic granuloma (EG, often arising from the lip) is a relatively common lesion in cats and should always be maintained as a differential for the much less common oral MCT. Although both EG and MCT have variable numbers of eosinophils and mast cells, EG generally demonstrate more necrosis, collagenolysis, and degranulation of both the mast cells and eosinophils. Grossly, EG can also be markedly destructive (e.g. rodent ulcer). A histology-based grading scheme that accurately predicts outcome for feline MCT has proven difficult to develop.

References

53 Meuten, D.J. (2017). *Tumors in domestic animals*, 5e. Ames, Iowa: Wiley.

54 Elliott, J.W., Cripps, P., Blackwood, L. et al. (2016). Canine oral mucosal mast cell tumours. *Vet. Comp. Oncol.* 14: 101–111.

55 Patnaik, A.K., Ehler, W.J., and MacEwen, E.G. (1984). Canine cutaneous mast cell tumor: morphologic grading and survival time in 83 dogs. *Vet. Pathol.* 21: 469–474.

56 Kiupel, M., Webster, J.D., Bailey, K.L. et al. (2011). Proposal of a 2-tier histologic grading system for canine cutaneous mast cell tumors to more accurately predict biological behavior. *Vet. Pathol.* 48: 147–155.

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8.9 Plasmacytoma

Oral plasmacytoma, or extramedullary plasma cell tumor, is a relatively common mucosal tumor that arises from the oral tissues of dogs and cats and is derived from differentiated, immunoglobulin-producing B cells (plasma cells). In an academic study, oral plasmacytoma represented 5.2% of all canine oral neoplasms and was the sixth most common oral tumor in dogs presented to Texas A&M University [57]. These tumors occur in the lips, gingiva, tongue, palate, and pharynx of older dogs. Although oral plasmacytoma may have a predisposition for the mucocutaneous junction of the lips, the majority of canine oral plasmacytoma cases in the last 10 years at UC Davis have been identified in the gingiva and tongue. A few cases have been identified in the laryngeal mucosa of cats at UC Davis.

Plasmacytomas are slow-growing benign mucosal tumors and are biologically distinct from bone marrow-associated plasma cell tumor (multiple myeloma). Multiple myeloma has a more malignant and antibody-productive disease course, often resulting in a systemic monoclonal gammopathy. A detectable monoclonal gammopathy is generally absent in oral plasmacytoma, and no relationship between oral plasmacytoma and the development of multiple myeloma has been documented in dogs [58]. Complete surgical excision appears to be curative.

Box 8.9 Differential Diagnoses for Oral Plasmacytoma

Lymphoma
Melanoma
Mast Cell Tumor
Histiocytoma
Cutaneous histiocytosis
Neuroendocrine tumors
Transmissible venereal tumor (in geographically appropriate locations)

Because plasmacytomas are round cell tumors, they share similar differential diagnoses with lymphoma and melanoma. Grossly, plasmacytomas are 1–2 cm in diameter, may be ulcerated, and occur as either sessile or pedunculated masses. Oral plasmacytoma is generally a solitary tumor, although multifocal lesions have been reported in dogs [59]. Plasmacytomas have relatively distinct margins and are not encapsulated. Less often, plasmacytomas arising from the gingiva have been known to locally invade the underlying bone, requiring *en bloc* resection of bone (and possibly teeth) to achieve complete excision.

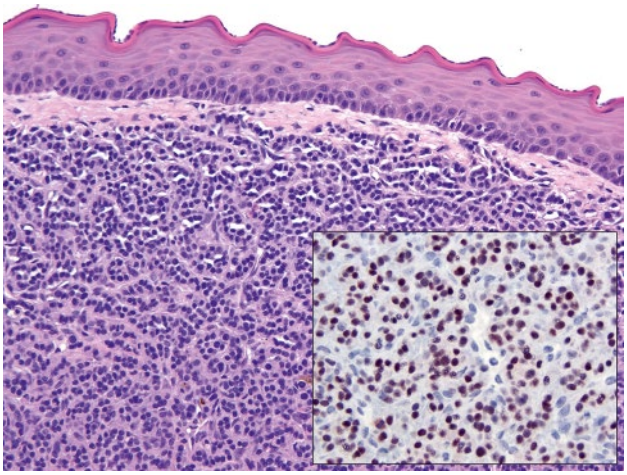


Figure 8.43 Histologic image of a well-differentiated oral plasmacytoma, 10-year-old FS Cocker spaniel dog. This oral plasmacytoma was a large mass in the oropharynx attached by a stalk near the lingual aspect of tooth 410. The tumor is composed of sheets and cords of round cells. Inset is a microscopic image of the same lesion stained for MUM1 expression (immunohistochemistry). *Source:* J. Anderson.

Although plasmacytomas are comprised of differentiated B cells (plasma cells), neoplastic plasma cells in some of these tumors can exhibit marked pleomorphism and anisocytosis. Large multinucleate cells are often present in plasmacytoma lesions, and the numbers of mitotic figures are variable. At the lesion periphery, or scattered within the population of pleomorphic cells, are variable numbers of differentiated, ovoid plasma cells. These "classic" plasma cells have eccentric nuclei, a perinuclear clear zone (Golgi apparatus), and *clock-faced* nuclei (so-called plasmacytoid features). Extracellular deposition of AL amyloid, sometimes extensive, may be present in plasmacytoma lesions. Although CD79a (pan B cell antigen) is often utilized in the diagnosis of plasmacytoma, the immunohistochemical reagent of choice for the diagnosis of oral plasmacytoma is multiple myeloma 1/interferon regulatory factor 4 (MUM1/irf-4), as it is a relatively sensitive and specific antibody for the detection of differentiated plasma cells. Nuclear staining reflects meaningful expression of MUM1 (Figure 8.43). It is important to be aware that some lymphomas may also express MUM1.

References

57 Wright, Z.M., Rogers, K.S., and Mansell, J. (2008). Survival data for canine oral extramedullary plasmacytomas: a retrospective analysis (1996–2006). *J. Am. Anim. Hosp. Assoc.* 44: 75–81.

58 Smithson, C.W., Smith, M.M., Tappe, J. et al. (2012). Multicentric oral plasmacytoma in 3 dogs. *J. Vet. Dent.* 29: 96–110.

59 Meuten, D.J. (2017). *Tumors in Domestic Animals*, 5e. Ames, Iowa: Wiley.

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8.10 Vascular Tumors

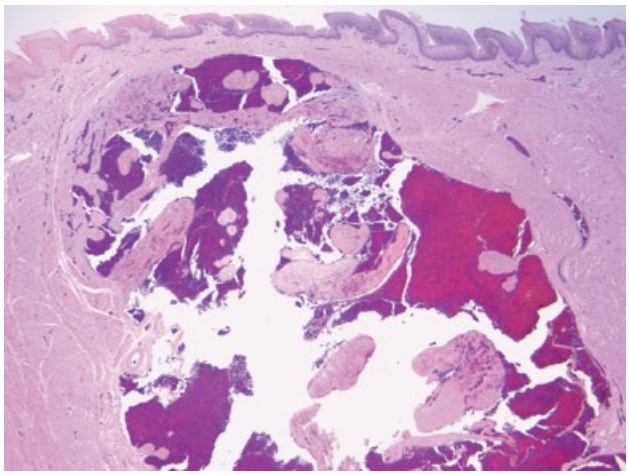
Vascular lesions of the oral cavity are occasionally identified in dogs, cats, horses, and cattle. These lesions can be either congenital or acquired; the etiology of these lesions is most often unknown. Although proliferative vascular lesions can arise from either blood or lymphatic vessels, in the oral cavity, vascular tumors most often arise from the endothelium of blood vessels. Vascular lesions are variably circumscribed, and manifest as a red, blue to purple plaque, raised nodule, coalescent cluster of nodules, or bosselated mass (numerous round protuberances). Dark red to purple vascular tumors can be mistaken for melanin-containing lesions like melanoma (and vice-versa). Multifocal vascular lesions in the oral cavity could represent ecchymoses, multifocal tumors, metastatic hemangiosarcoma (HSA) or angiomatosis (disseminated hemangioma lesions). Digital compression (diascopy) results in the blanching of lesions with blood-filled vascular spaces [60]. Lesions characterized by extravascular blood, such as ecchymoses, do not blanch when compressed. Cytology of these lesions is most often unrewarding; a definitive diagnosis most often requires incisional/excisional biopsy and histological examination.

8.10.1 Hemangioma and Vascular Malformations

Oral hemangiomas are uncommonly diagnosed in dogs and calves. The pathology databases of CCOMP and UC Davis each have but a single case of oral hemangioma in the past 10 years (both of these lesions were in dogs and were lingual). Hemangioma is a benign, proliferative, generally well-circumscribed, unencapsulated, non-invasive lesion comprised of well-differentiated endothelial cells forming variably sized vascular channels ("a ball of well differentiated neoplastic capillaries"). Vascular spaces may contain blood or fibrin thrombi. Direct arteriovenous communications are possible. Neoplastic vessels often include both small capillaries as well as large, cavernous sinuses, and are lined by a single layer of differentiated endothelial cells without a surrounding smooth muscle coat (see Figure 8.44).

An attempt should be made to differentiate between hemangioma and a variety of vascular malformations (hamartoma) and systemic angiomatosis. A *venous varix*, or varicosity, is a type of acquired vascular malformation that is a focal dilation of a single vein [60]. Young animals are more likely to have a vascular hamartoma and multifocal lesions may suggest angiomatosis [61]. Vascular malformations are often poorly circumscribed and are comprised of a mix of arteries, veins, and capillaries. These lesions blanch with diascopy and may be associated with a palpable thrill. Systemic angiomatosis has also been referred to as multicentric hemangioma; it occurs in multiple organs concurrently. At the microscopic level, it may not be possible to absolutely distinguish between these benign and dysplastic/proliferative vascular lesions. The diagnosis of the submitting clinician may provide some guidance.

(a)



(b)

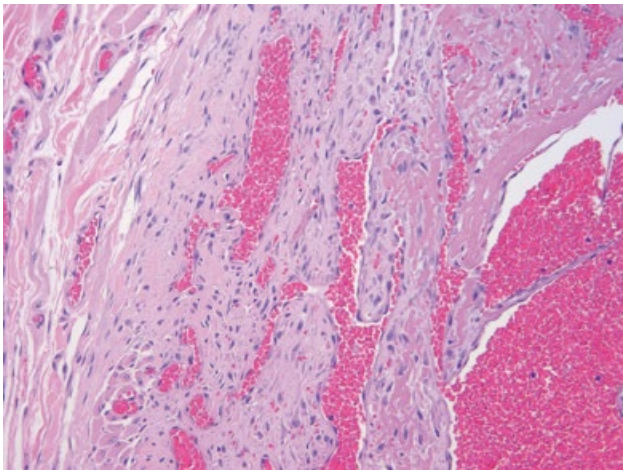


Figure 8.44 Histologic images of a glossal hemangioma, 13-year-old FS Labrador retriever dog. Note the blood filled sinuses lined by a single layer of well-differentiated, flattened endothelial cells. (a) Low and (b) high magnification.

8.10.2 Hemangiosarcoma

Oral HSA is an aggressive malignant tumor of endothelial cells that has been identified in dogs, cats, cattle, and horses. Although uncommon, these lesions are most frequently diagnosed in older dogs. Oral HSA arises from the tongue, gingiva, palate, lip, or jaws; the oral component of HSA can be part of systemic metastases originating from more classically affected tissues like the

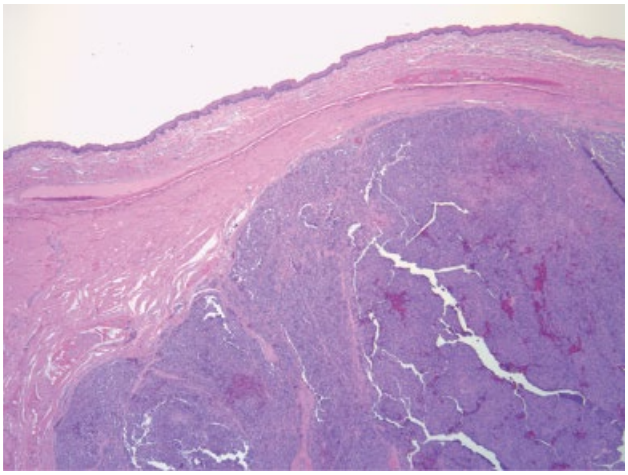
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spleen, liver, or heart. The UC Davis and CCOMP databases suggest that the tongue may be a predisposed anatomic site. As HSA is a malignant, endothelial cell-derived tumor, these lesions are capable of distant metastasis. In a study of 20 cases of lingual HSA in dogs, most of the tumors were small, occurred on the ventral lingual surface, and were associated with a median overall survival time of 533 days [62]. In this study, factors significantly associated with increased survival included small tumor size and absence of clinical signs of an oral mass at the time of diagnosis.

Injury or ulceration of mucosal HSA lesions often leads to bleeding. The lesions are variably well-demarcated and are unencapsulated. The neoplastic endothelium forms capillary-like spaces and cavernous sinuses that are often filled with blood or variably organized thrombi. The neoplastic endothelial cells do not produce their own matrix and are often arranged in multiple, crowded layers lining blood-filled spaces. Neoplastic endothelial cells can exhibit a degree of anaplasia – they are plump and spindloid, with bulging nuclei that often project into the vascular space. Mitotic figures may be numerous, and hemorrhage and necrosis may be present (see Figure 8.45).

Poorly differentiated HSA lesions that fail to demonstrate well-formed vascular structures can be a diagnostic challenge. In some regions of the tumor, the neoplastic endothelium may form extensive sheets and streams indistinguishable from an undifferentiated sarcoma. Antibodies to Factor VIII or CD31 (PECAM, platelet endothelial cell adhesion molecule) are often helpful in revealing their endothelial origin. The endothelium of normal vessels in the section, which are almost always present, provide a useful in-section positive control.

(a)



(b)

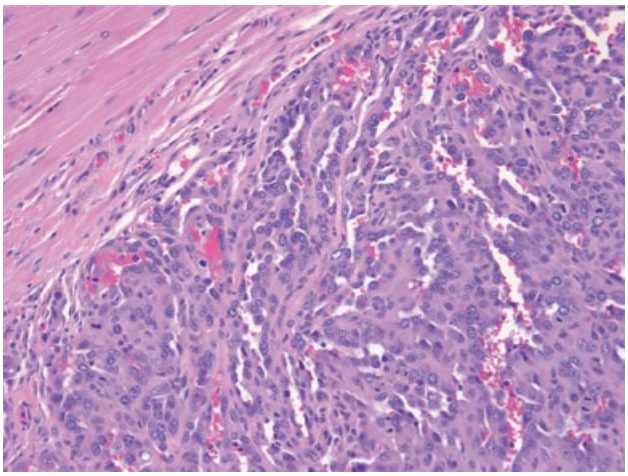


Figure 8.45 Histologic images of a glossal hemangiosarcoma (HSA), 12-year-old MC Catahoula dog. The tumor infiltrates into the skeletal muscle of the tongue. Blood-filled clefts are lined by plump endothelial cells projecting into the luminal space. (a) Low and (b) high magnification.

References

60 Regezi, J.A., Sciubba, J.J., and Jordan, R.C.K. (2008). *Oral Pathology: Clinical Pathologic Correlations*, 5e. St. Louis, Mo: Saunders/Elsevier.

61 Meuten, D.J. (2017). *Tumors in Domestic Animals*, 5e. Ames, Iowa: Wiley.

63 Burton, J.H., Powers, B.E., and Biller, B.J. (2014). Clinical outcome in 20 cases of lingual hemangiosarcoma in dogs: 1996–2011. *Vet Comp. Oncol.* 12: 198–204.

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9

Tumors of the Jaw

9.1 Maxillofacial Osteosarcoma

Maxillofacial osteosarcoma (OSA) is an aggressive bone tumor that is most often diagnosed in adult, large-breed dogs, and less often in cats. Although most frequently diagnosed in dogs, OSA of the mandible and maxilla is *still less common* than melanoma, squamous cell carcinoma and fibrosarcoma [1]. Between 20 and 25% of all canine OSA lesions arise from the axial skeleton; of these tumors, 50% occur in the jawbones, hard palate, and/or craniofacial bones. OSA has also been described in other veterinary species, but rarely so. When OSA does occur in horses, cattle, and sheep, it is most often in the mandible.

Osteosarcomas most often arise within the medullary region of the bone (*central OSA*). Peripheral osteosarcomas arising from the periosteum have been described as *juxtacortical OSA*. Whether or not juxtacortical OSA occurs in the maxillofacial skeleton of veterinary species is controversial at present. If they do occur, they are rare. Another category of OSA described in human oral pathology and recently reported in dogs, is the *central low-grade OSA*. These less aggressive sarcomas are discussed further below.

Although the diagnosis of OSA can be relatively straightforward, this is not always the case. A brief review of some basic aspects of bone biology may be in order. Multipotent mesenchymal stromal cells inhabit a niche within the skeletal periosteum and endosteum. These cytologically bland, spindle-shaped, mesenchymal cells can be observed within the cambium layer of normal, quiescent periosteum. These amazing cells are capable of differentiating into multiple lineages including fibroblasts, chondroblasts, and of course, osteoblasts. When a bone fracture occurs, it is fortunate that these multipotent stromal cells *lie in wait,* as they are the architects of bone repair. The choreographed differentiation into these different cell types, along with the expression of their associated protein products, result in the production of the stabilizing fracture callus.

9.1.1 Tumor-Associated Osteoidal Matrix

Osteosarcoma is an aggressive type of sarcoma that includes *a population of malignant osteoblasts*. The OSA diagnosis is dependent upon accurately identifying these malignant osteoblasts. Malignant osteoblasts may be the predominant mesenchymal population in the tumor (as in osteoblastic OSA), or they may represent only a minor subset of the total neoplastic population. Regardless, whether or not malignant osteoblasts are present is important, because these cells are considered to have the greatest potential for metastatic spread. The osteoblastic component of the sarcoma is expected to produce some amount of osteoidal matrix. The presence of osteoid serves as the principal diagnostic feature of OSA; it signifies that osteoblasts are present in the tumor. This *tumor-associated osteoidal matrix* (TAOM) may or may not mineralize (hydroxyapatite deposition), resulting in the production of tumor-associated bone. Rapidly replicating malignant osteoblasts frequently *do not mineralize* the osteoid that they produce, as cellular replication is their modus operandi.

Despite the histologic diversity of OSA lesions (and they do demonstrate a wide breadth of diversity), if TAOM is present, *the presence of malignant osteoblasts is inferred*. As such, a lesion lacking identifiable TAOM does not fulfill the diagnostic criterion of OSA. If pathologists could precisely and directly identify osteoblasts within the sarcoma population, we would not need to rely on TAOM. Unfortunately, immunohistochemical assays are not currently capable of reliably identifying mesenchymal cells in the osteoblastic lineage. However, there is at least one relatively sensitive and specific means of identifying osteoblasts, but it involves cytologic smears of the suspect tumor made *prior to formalin fixation*. This simple and inexpensive test involves staining the cytologic smears with a low-cost reagent (BCIP/NBT stain) to colorimetrically reveal the presence of osteoblasts producing the enzyme alkaline phosphatase (AP). Interested readers are encouraged to read and implement this useful ancillary test for OSA diagnosis [2].

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Note – it is important to realize that the BCIP/NBT assay identifies the presence of AP-producing osteoblasts, and *not* specifically malignant osteoblasts!

In some lesions, TAOM may represent a proverbial needle in the haystack, and is the reason that multiple regions of the tumor may need to be carefully reviewed. Lesions with a paucity of TAOM may concurrently have abundant fibrous or cartilaginous matrix, blood-filled sinuses, or numerous multinucleate giant cells. Any and all of these ancillary lesional features may serve to obscure the presence of TAOM, and obfuscate the diagnosis of OSA.

So what does TAOM look like? This is one of the diagnostic features that pathologists, through experience, will *know when they see it*. As the positive identification of TAOM is the crucial diagnostic feature, suspect OSA lesions with deposits of purple-staining extracellular matrix (representing either mineralized osteoid or proteoglycan-containing chondroid matrix) should have the paraffin-embedded tissue block face decalcified and another slide cut and stained (see Appendix). Removal of the suspect hydroxyapatite minerals through decalcification will facilitate a more accurate microscopic observation of the matrix.

In H&E-stained tissue sections, osteoidal matrix is pink, as are a number of other biomaterials that might be present: aggregated strands of collagenous protein (birefringent), keratin (associated with keratinocytes), fibrin (lacking birefringence), dentin, cementum (mosaic cementing lines/spheroidal islands), and even chondroid matrix *lacking proteoglycan molecules* (round to oval-shaped lacunae containing large, entrapped chondrocytes). Although all of these materials are morphologically similar, they have subtle structural, tinctorial, or physical relationships with certain cells that generally allow them to be differentiated from osteoid. Although stains like Goldner's trichrome are touted as a means to identify osteoidal matrix, we have not found them to be reliable means of doing so.

Since special stains to distinguish between physiologic osteoid and TAOM do not currently exist, how does one distinguish physiologically normal ostoidal matrix (osteoid produced by non-neoplastic osteoblasts) and TAOM? Pathologic fractures are often associated with OSA lesions, as a result of structural destabilization of the bone. In these lesions, two concurrent processes may be present – (i) hyperplastic osteoblasts producing physiologic osteoid and bone (fracture callus), and (ii) sarcoma cells producing TAOM. Is the osteoidal matrix in question associated with a reactive or neoplastic process? The interrelated processes of fracture repair and the destructive/productive characteristics of OSA may spatially intermingle. OSA is not the only tumor that destroys bone; to mistake the presence of physiologic osteoid for TAOM may mean getting the diagnosis wrong – e.g. diagnosing an OSA when the tumor is really a fibrosarcoma. *This type of error matters* as the prognosis and treatment plans may be quite different for different kinds of sarcomas.

Both TAOM and physiologic osteoid stain pink with H&E stains, are comprised of collagen proteins (mostly collagen I) and therefore demonstrate a degree of birefringence, revealed through polarization. Both of these matrices aggregate in an extracellular location and have a finely fibrillar to amorphously homogeneous structure. Although TAOM shares these histologic features with physiologic osteoid, it often demonstrates a number of specific features, which can help to distinguish it. The cells embedded in TAOM are very likely neoplastic and should demonstrate the same or similar cytologic features that the surrounding sarcoma cells do. In TAOM, the osteocyte lacunae are haphazardly scattered and irregularly clustered, they may be larger than the physiologic lens-shaped lacunae of normal osteoid/bone. In contrast to physiologic osteoid, TAOM may be arranged as thin strands or haphazardly and poorly delineated spicules, TAOM may take on a delicate lace-like pattern. Unlike physiologic osteoid, TAOM has less of a tendency to cross-link into *structurally sound assemblies*. Bear in mind that the purpose of osteoblasts is to build bone, while the purpose of neoplastic osteoblasts is to replicate. Reactive osteoblasts (non-neoplastic) tend to interlink the osteoidal trabeculae, and they often form prominent palisades along the surface of the matrix. Despite these clues, definitively identifying TAOM in histologic sections can be challenging, even for experienced pathologists.

9.1.2 Central Osteosarcoma

Central maxillofacial OSA is an aggressive malignancy that is histologically and behaviorally similar to OSA of the appendicular skeleton. These tumors are more common than peripheral OSA (periosteal and parosteal) and have a consistently greater potential for metastatic spread. Central OSA arises from the medullary cavity of the mandible, maxilla, nasal bones, zygomatic arch, or other facial bones, likely arising from within the endosteal envelope. There are 67 cases of canine central maxillofacial OSA in the UC Davis pathology database. Central OSA of the appendicular skeleton is generally considered to be a high-grade tumor, rapidly metastasizing to the lungs. While central OSA of the axial skeleton has only a marginally better prognosis, central OSA of the mandible is reported to progress more slowly and have a decreased tendency to metastasize.

Central OSA rapidly effaces both bone and adjacent soft tissues, potentially resulting in a host of clinical signs similar to the clinical features associated with

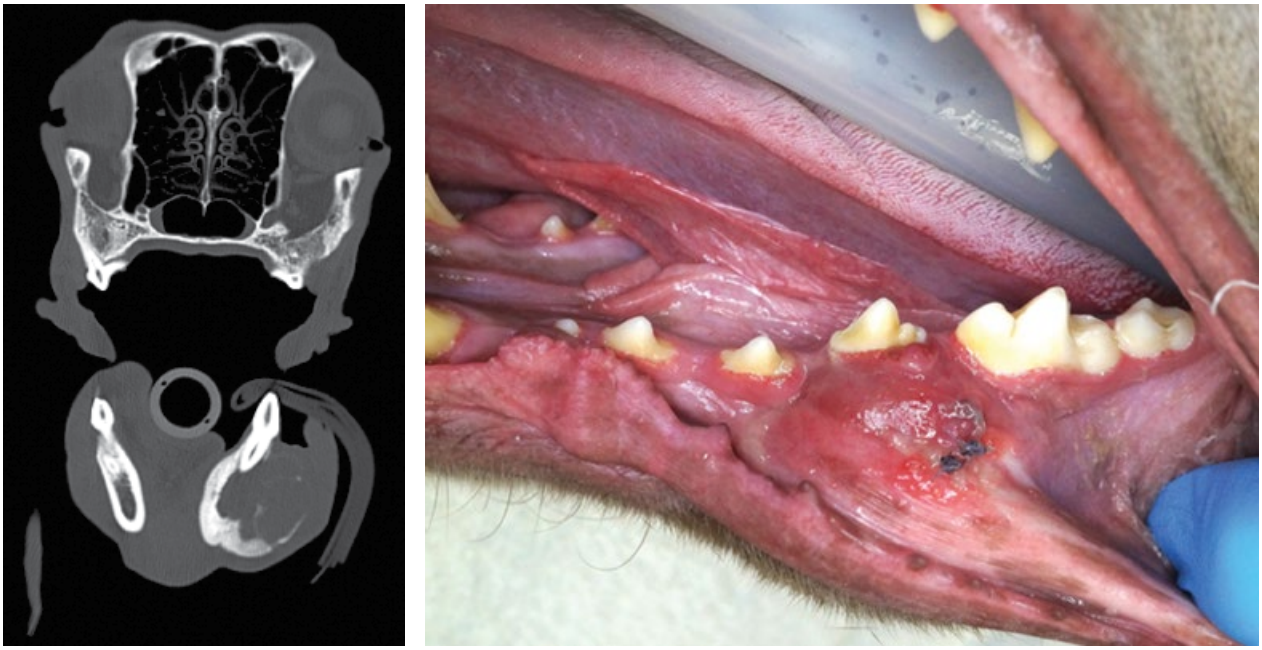


Figure 9.1 CT and gross images of a mandibular osteosarcoma, eight -year-old MN Labrador retriever dog. The incisional biopsy site is evident on the gross image (right) while bone lysis is evident in the CT image (left). *Source:* J. Soukup, University of Wisconsin-Madison.

the three other aggressive malignancies of the canine jaw – melanoma, squamous cell carcinoma, and fibrosarcoma. These signs include distortion of the contour of the jaw or face by a firm mass, oral ulceration, hemorrhage, loosening or loss of teeth, and jaw fractures. Central OSA in the maxillary jaw or palate can invade and destroy the nasal cavity and/or craniofacial bones, resulting in the obstruction of nasal airflow and/or epistaxis. Although OSA of the maxilla and mandible do not metastasize as readily as those arising at other sites, they are still pneumotropic tumors, capable of hematogenously spreading to the lung. OSA generally does not initially metastasize to the regional lymph nodes.

9.1.3 Osteosarcoma Subtypes

There are a variety of ways of categorizing central OSA lesions. Most pathologists favor a scheme based upon the predominant matrix that the tumor cells produce, along with other histologic features. In this scheme, there are six histologic subtypes of OSA – osteoblastic (osteoblasts predominate), fibroblastic (fibroblast-like spindle cells arranged in patterns reminiscent of fibrosarcoma), chondroblastic (extensive regions of chondroblastic differentiation with chondroid matrix deposition), giant cell (large numbers of intermixed multinucleate cells), telangiectatic (endothelium-like sarcoma cells form blood-filled cavities and sinuses reminiscent of hemangiosarcoma), and poorly differentiated OSA (neoplastic cells are anaplastic). Osteoblastic OSA is further subdivided into *productive* (abundant TAOM) or *non-productive* (minimal TAOM). In practice, most OSA demonstrate a variety of subtypes depending upon where you look (so-called mixed or combined type OSA). Whether every one of these OSA subtypes exists in maxillofacial central OSA is controversial. In humans, central OSA of the mandible are generally either subtyped as chondroblastic, osteoblastic, or fibroblastic.

Regardless of whatever else they produce, all of the OSA subtypes *must demonstrate TAOM* to qualify as an OSA; this point cannot be overstated. As is typical of other sarcomas, central OSA lesions often demonstrate a mix of two or more of these subtypes. By convention, the morphologic diagnosis should specify the *predominant subtype*. If there is no predominant subtype, the tumor should be referred to as a *combined type of central OSA*. Properly assigning an OSA subtype based upon minimalistic core biopsy findings can be problematic.

Central maxillofacial OSA varies markedly in gross features and imaging characteristics. The gross appearance of central OSA is often dependent upon the predominant histologic subtype. Chondroblastic OSA produces cartilage matrix; grossly these lesions may be glistening, bluish-white, or gelatinous on section and are often indistinguishable from chondrosarcoma. Telangiectatic OSA is hemorrhagic and may be indistinguishable from medullary hemangiosarcoma. All of these OSA lesions can be osteoproductive, lytic, or more often, both osteoproductive and lytic. Very often,

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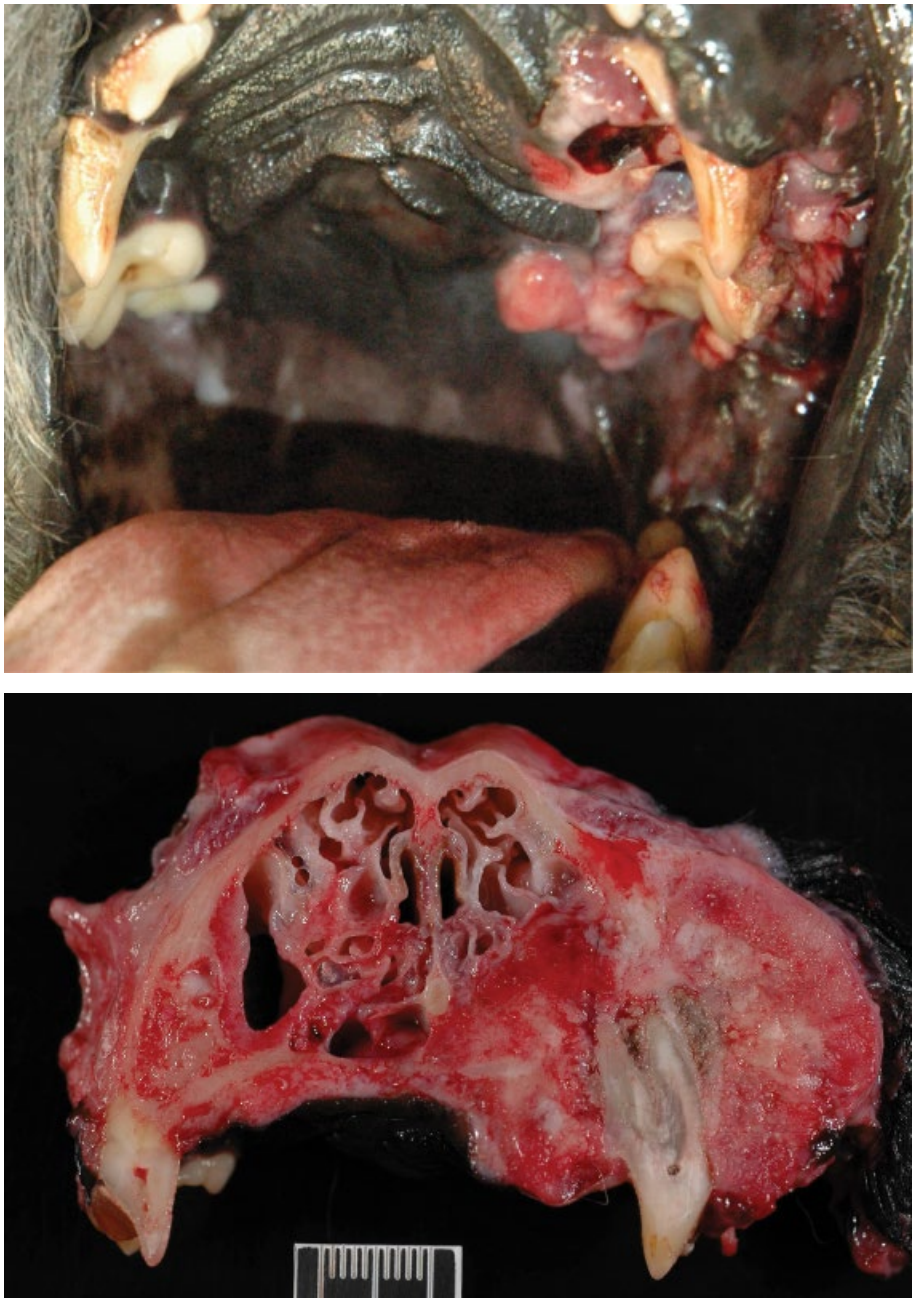


Figure 9.2 Gross images of a maxillary central OSA, chondroblastic variant, two -year-old MC miniature schnauzer. An ulcerated mass is evident in both the buccal mucosa of the palate and labial mucosa (intraoral gross image). On a postmortem cross section of the maxilla, the neoplastic mass involves the buccal and palatal maxillary bone, nasal passage and alveolar bone of the maxillary carnassial tooth (lower image). *Source:* J. Vilches-Moure, University of California, Davis.

reactive/reparative bone will be present along with the tumor-associated bone (see Section 9.1.1 on TAOM).

Microscopically, central OSA also varies greatly from subtype to subtype. Giant cell OSA is associated with large numbers of multinucleate giant cells, while fibroblastic OSA has architectural and cytologic features of fibrosarcoma. The neoplastic cells in telangiectatic OSA may look like endothelial cells, in osteoblastic OSA, they are plump, spindle to angular polygonal cells with eccentrically positioned, hyperchromatic nuclei. OSA lesions may be associated with substantial bone production and/or bone lysis. Extensive regions of necrosis and hemorrhage may be evident, especially in the telangiectatic subtypes. Most importantly,

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the common features across all central OSA lesions are (i) streams or sheets of neoplastic mesenchymal cells architecturally and cytologically consistent with sarcoma, and (ii) the presence of TAOM. If these two criteria are fulfilled, and the tumor arises from the medullary cavity of the bone, the lesion is a central OSA. It is the authors' contention that at present, immunohistochemistry has limited utility for the diagnosis of OSA. Antibodies to osteonectin, osteocalcin, and other osteoid-associated proteins often cross-react with the matrix of other normal and neoplastic tissues, reducing the assay's specificity. However, antibodies directed to CD31 (platelet–endothelial cell adhesion molecule-1, PECAM) or factor VIII can facilitate the differentiation of neoplastic endothelium in hemangiosarcoma from the telangiectatic OSA.

Box 9.1 Differential Diagnoses for Maxillofacial Osteosarcoma

Chondrosarcoma
Fibrosarcoma
Hemangiosarcoma
Anaplastic sarcoma
Fracture callus
Ossifying fibroma
Fibrous dysplasia
Fibrous osteodystrophy
Periosteal proliferation (hypertrophic osteopathy)
Craniomandibular osteopathy (lion jaw)

The precise histologic subtype is somewhat academic as many of these lesions are actually combined subtypes and studies have not conclusively determined an association between subtype and prognosis. There is, however, some evidence that the telangiectatic subtype may have a worse prognosis, while the fibroblastic subtype may have a more favorable prognosis relative to other histologic subtypes.

In addition to OSA subtypes, several histologic grading schemes have been proposed. These schemes, based upon nuclear and cytoplasmic features of the neoplastic cells, have not gained wide acceptance by veterinary pathologists.

9.1.4 Central Low-Grade Osteosarcoma

This uncommon variant of OSA arises from the jaw and is relatively well-described in humans. This tumor is both histologically and behaviorally less aggressive than central OSA. Histologically, central low-grade OSA (LG-OSA) is characterized by relatively bland spindle cells demonstrating minimal atypia, occasional mitotic figures, and interspersed spicules of osteoid, bone, and/or cartilage (Figure 9.4). It is less cellular than central OSA, and may resemble low-grade fibrosarcoma. Unlike fibrous dysplasia, it has an invasive, poorly delineated, intramedullary growth pattern associated with cortical bone destruction and penetration into the adjacent soft tissues. In time, this lesion may be capable of transforming into central OSA.

In dogs, this tumor has been reported as a differential for proliferative fibro-osseous lesions of the jaw, namely ossifying fibroma (OF) and fibrous dysplasia (FD)

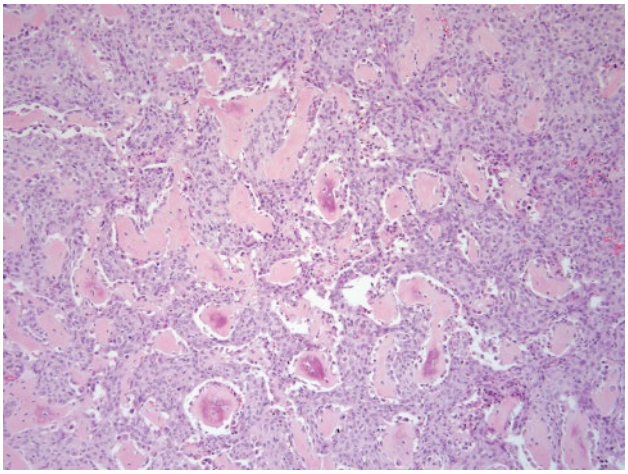


Figure 9.3 Histologic image of a central osteosarcoma of the maxilla (osteoblastic, productive subtype), dog. Numerous unlinked islands of osteoid are interspersed amidst sheets of neoplastic polygonal cells.

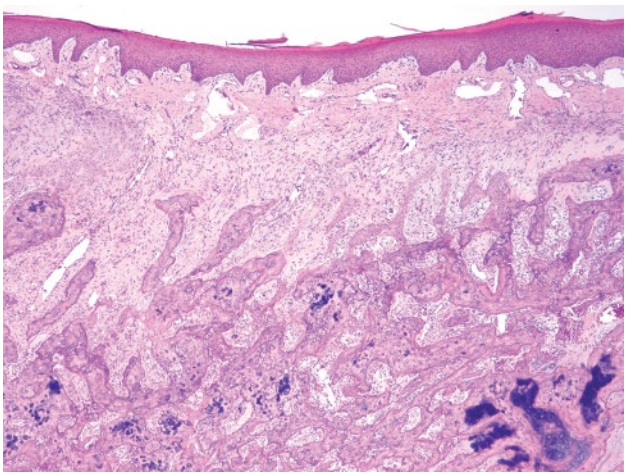


Figure 9.4 Histologic image of a central low-grade osteosarcoma of the maxilla, dog. Polygonal cells with bland cytologic features surround interlinking trabeculae comprised of osteoid and/or chondroid matrix.

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(see Chapter 10: Tumor-like proliferative lesions of the oral mucosa and jaws) [3]. The imaging features of central LG-OSA are suggestive of a more aggressive lesion than OF or FD. LG-OSA has been described as a lytic lesion with mixed opacity and ill-defined margins. Radiographically, it is characterized as an aggressive bony lesion demonstrating elements of both bone lysis and cortical thinning. Some lesions demonstrate a "sunburst" or spiculated periosteal reaction.

Histologically, the canine lesion consists of dense collagenous stroma comprised of spindloid mesenchymal cells with some nuclear pleomorphism and variable numbers of mitotic figures. Islands of cartilage and irregular trabeculae of mineralized bone are distributed throughout the stroma. The neoplastic stromal cells may invade osteonal canals. Soltero-Rivera and co-authors make the point that LG-OSA *must be diagnosed in conjunction with radiographic imaging results and clinical suspicion*, that is, the diagnosis should not be based upon histologic findings alone.

9.1.5 Peripheral Osteosarcoma

There are two types of *peripheral* (synonym *juxtacortical*) OSA – periosteal and parosteal OSA [4]. These peripheral bone tumors both arise from the periosteal surface of the bone and are thought to have a more favorable prognosis relative to central OSA. However, they are both poorly documented in veterinary species. In order for veterinary pathologists and clinicians to diagnose these lesions, they must pay particular attention to the lesion's anatomical association with bone. Imaging features can play a key role in the diagnosis.

9.1.6 Parosteal Osteosarcoma

Parosteal OSA arises from the outer fibrous layer of the periosteum [5]. These slow-growing, radiodense, well-differentiated tumors are purported to have a much less aggressive behavior than central OSA or periosteal OSA. In humans, the clinical course is longer with a higher survival rate. Parosteal osteosarcomas are comprised of differentiated osseous, fibrous, or cartilaginous tissues and concurrently demonstrate TAOM. A radiolucent line (or "cleavage plane") corresponding to the periosteum may be identifiable between the tumor and bone cortex in radiographic studies. In human lesions, parosteal OSA has a bland histologic appearance and is comprised of spindle cells with minimal atypia and rare mitotic figures and interspersed irregular trabeculae of woven bone. This histologic appearance raises the differentials of osteoma, bony exostosis, or osteochondroma.

Parosteal OSA is a surface tumor – a firm, smooth to multinodular, slowly enlarging bony mass which may interfere with function and eventually result in some degree of disfigurement. Parosteal OSA may invade the associated cortical bone late in the disease process. In human patients, the majority of these tumors occur in the appendicular long bones. Parosteal OSA is poorly documented in veterinary species but has been described in dogs, cats, horse, pig, and cow. This juxtacortical tumor has been described arising from the surface of the mandible of a cat. Whether its rarity in veterinary species reflects the true incidence of occurrence or is the result of poor recognition by clinicians, radiologists, and pathologists is not currently known.

9.1.7 Periosteal Osteosarcoma

Periosteal OSA arises from the periosteal cambium layer of the bone and can demonstrate gross and histologic features consistent with osteoblastic, fibroblastic, and/or chondroblastic differentiation [5]. By definition, the periosteal OSA lesion must also demonstrate the presence of TAOM histologically. Periosteal OSA reportedly has a behavior, histology, and prognosis that is *intermediate between the more aggressive central OSA and the less aggressive parosteal OSA*. As such, periosteal OSA has a reduced tendency for metastasis, relative to central OSA, but tends to penetrate the adjacent cortical bone more readily than parosteal OSA. Late in the disease course, distinguishing between a periosteal and central OSA might be difficult. In humans, periosteal OSA is diagnosed much less frequently than parosteal OSA. Periosteal OSA has rarely been identified in the jaws. In humans, periosteal OSA histologically resembles the chondroblastic subtype of central OSA.

Periosteal OSA in veterinary species is poorly documented, but has been described in a dog, cat, and horse. Whether a maxillofacial form of periosteal OSA actually exists in veterinary species has not been conclusively determined. As is true for parosteal OSA, the diagnosis is highly dependent upon recognition of a periosteal origin by the pathologist. This requires that the pathologist and clinician communicate regarding the pertinent supporting imaging features, or, that the pathologist pays close attention to the gross specimen, radiographic images, or imaging report supplied by the clinician.

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References

1 Farcas, N., Arzi, B., and Verstraete, F.J. (2014). Oral and maxillofacial osteosarcoma in dogs: a review. *Vet. Comp. Oncol.* 12: 169–180.

2 Barger, A., Graca, R., Bailey, K. et al. (2005). Use of alkaline phosphatase staining to differentiate canine osteosarcoma from other vimentin-positive tumors. *Vet. Pathol.* 42: 161–165.

3 Soltero-Rivera, M., Engiles, J.B., Reiter, A.M. et al. (2015). Benign and malignant proliferative fibro-osseous and osseous lesions of the oral cavity of dogs. *Vet. Pathol.* 52: 894–902.

4 Regezi, J.A., Sciubba, J.J., and Jordan, R.C.K. (2008). *Oral Pathology: Clinical Pathologic Correlations*, 5e. St. Louis, MO: Saunders/Elsevier.

5 Meuten, D.J. (2017). *Tumors in Domestic Animals*, 5e. Ames, Iowa: John Wiley & Sons.

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9.2 Osteoma

Osteoma is an uncommon, slowly progressive, benign, well-differentiated bone tumor that has been described in dogs, cats, horses, cattle, and small ruminants, and rarely in other veterinary species. Osteomas arise most often from the craniofacial bones of the skull – the maxilla, mandible, sinonasal bones, and bones of the face and cranium; embryologically, these bones are created through the process of intramembranous ossification [6]. The relevance of this observation to lesion pathogenesis (if any) remains ambiguous. Osteomas can also occur in other sites like the pelvic bones, and must be diagnostically differentiated from osteochondroma, a dysplasia of endochondral ossification initiating at the physis.

Box 9.2 Differential Diagnoses for Osteoma

Ossifying fibroma
Fibrous dysplasia
FEPLO/POF
Bony exostosis/periosteal hyperplasia
Multilobular sarcoma of bone
Craniomandibular osteopathy (dogs)
Low grade osteosarcoma
Osteochondroma
Feline osteochondromatosis

Osteomas can arise from the periosteum (peripheral or *periosteal osteoma*), endosteum (central or *endosteal osteoma*), or within the soft tissues themselves (*extraskeletal osteoma*). The etiology of osteoma in veterinary species is unknown. These slowly proliferative bony masses are generally not painful and may result in little more than a firm swelling along with some degree of disfigurement. However, large osteomas can markedly interfere with the processes of breathing or jaw function.

There is some diagnostic confusion regarding the pathogenesis and categorization of this lesion. There is appreciable morphologic overlap with the lesions *ossifying fibroma* and *fibrous dysplasia* (see Chapter 10, Tumor-like proliferative lesions of the oral mucosa and jaws) [7]. All three of these proliferative fibro-osseous lesions arise from the membranous bones of the skull. Some pathologists even consider these lesions to represent different stages of the same entity. Some have argued that osteoma is not actually a true neoplasm, but rather a hamartoma or even an unexplained, chronic hyperplastic/ dysplastic process resulting in a focal bony exostosis. Given small biopsy specimens, differentiating histologically between osteoma and other bone-containing lesions can be problematic (see Box 9.2). Clinical information such as the signalment, lesion history and imaging features should be carefully considered before rendering a diagnosis.

In general, osteomas are monostotic, slowly progressive, smoothly contoured, broad-based, or pedunculated (mushroom-shaped) lesions, arising from either

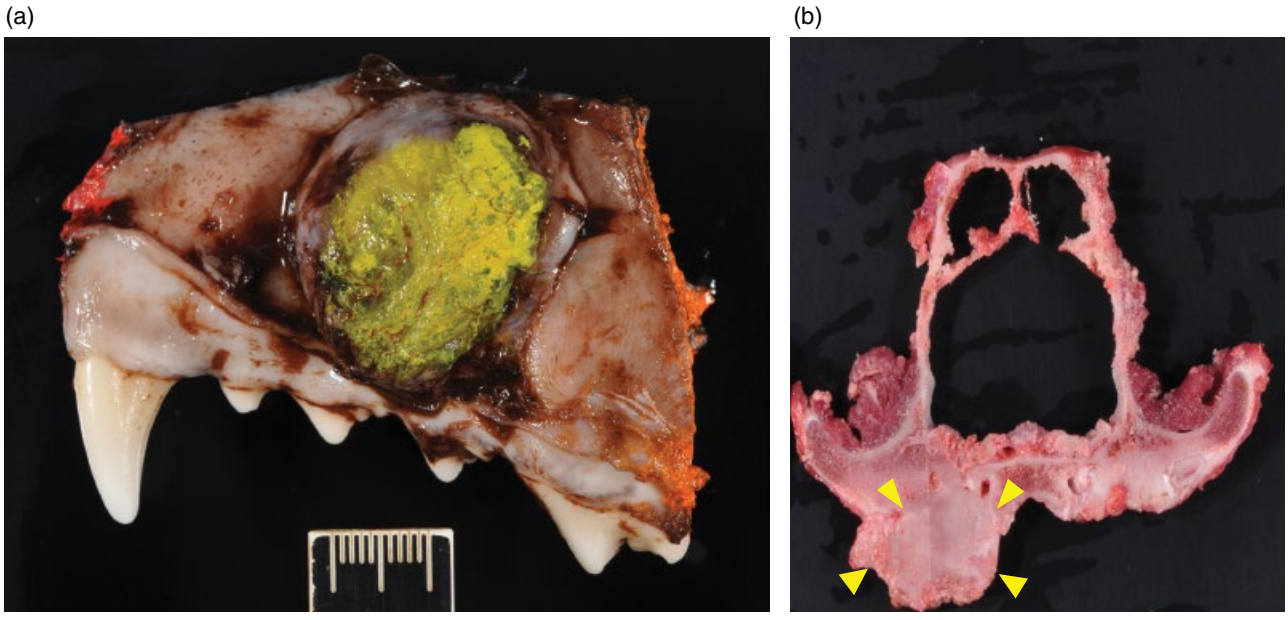


Figure 9.5 Gross images of osteomas. (a) Gross image of a maxillary osteoma, three-year-old Rottweiler dog. *Source:* Dr. R. Zavodovskaya, University of California, Davis. (b) Gross image of an osteoma of the tympanic bone (yellow arrowheads), one year old Coonhound dog. *Source:* E. LaDouceur, University of California, Davis.

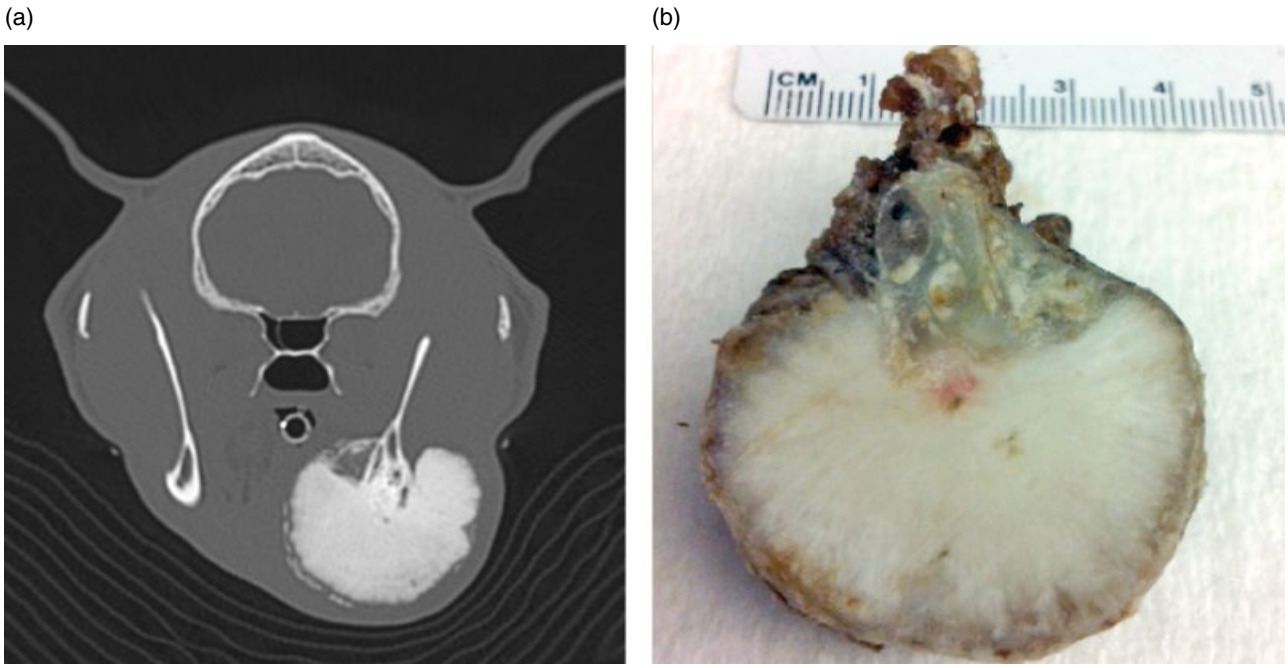


Figure 9.6 CT and Gross images of osteomas. (a) CT image of a mandibular osteoma, seven-year-old DSH cat (University of Wisconsin-Madison). (b) Gross image of a mandibular osteoma, resected surgical specimen, seven-year-old DSH cat (University of Wisconsin-Madison).

the periosteum or endosteum of the craniofacial bones. Grossly, osteomas blend smoothly into the adjacent bone tissue (Figure 9.6). Although osteomas may initially be indistinguishable from a bony exostosis, as they mature they can become massive and increasingly sclerotic. Sectioning of osteoma specimens for pathologic examination often requires the use of a saw. As a result of the bone density and mineralization, the decalcification process for osteomas may be prolonged. Sectional shattering and fragmentation of osteoma lesions is common, and should not be exclusively blamed upon the histotechnologist! It is desirable to attempt to obtain as thin a section of the suspected osteoma as possible *prior to* decalcification (see Appendix).

Osteoma lesions are often microscopically similar to, and may be indistinguishable from, periosteal hyperplasia (hypertrophic osteopathy). These well-differentiated and highly organized lesions initiate as thin spicules of woven bone arising from the parent periosteum (or endosteum) of the craniofacial bones. The proliferative bony spicules have numerous embedded osteocytes and are lined by palisading polygonal to cuboidal osteoblasts, separated by moderate amounts of intertrabecular loose fibrovascular connective tissue or adipose tissue. Less commonly, the intertrabecular space can contain aggregates of hematopoietic cells. With time, the bony spicules become thicker by appositional bone growth, progressively interconnecting into a more rigid

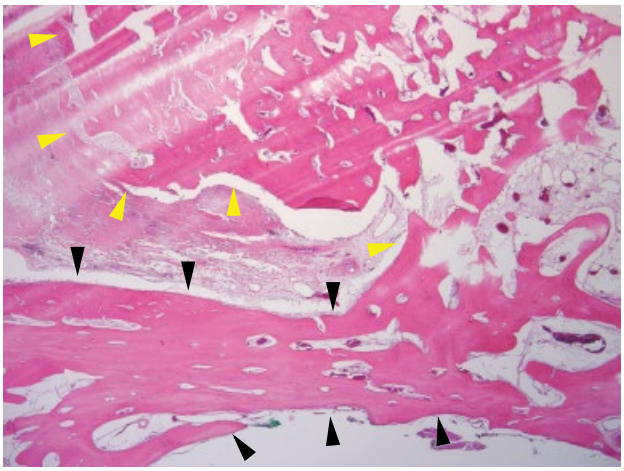


Figure 9.7 Histologic image of a canine maxillary osteoma, three-year-old Rottweiler dog. Black arrowheads denote the parent maxillary bone while yellow arrowheads denote the pedunculated osteoma (same lesion as Figure 9.5a).

sheet-like osseous array. These anastomosing spicules of woven bone are gradually replaced by increasingly dense and compact lamellarized bone. Eventually, this stage of the osteoma lesion (the lesion core) mimics dense cortical bone (see Figures 9.7 and 9.8).

If one carefully examines a complete osteoma lesion in cross-section, a *vector of time* can often be traced from the initial periosteal origin, now associated with older,

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lamellarized cortical bone, gradually transitioning out to a newly deposited, finger-like lesion periphery. Between these two extremes, the osteoma is comprised of anastomosing plates of trabecular bone exhibiting a combination of woven and lamellar features. The peripheral bone is often comprised of more slender spicules of cancellous woven bone arranged in a perpendicular manner to the outer lesional margin. This outer margin of the lesion may be capped with a smooth, periosteal cambium-like layer of proliferative mesenchymal cells. In some osteoma lesions, an outer *false cortex* of intermixed woven/lamellar bone may be identified subjacent to the periosteal layer (see Figure 9.9).

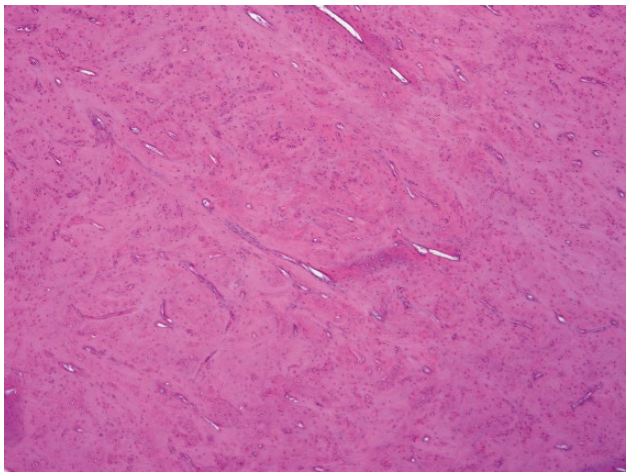


Figure 9.8 Histologic image of a mandibular osteoma, horse. Mature mandibular osteoma comprised of a compacted sheet of principally woven and lesser amounts of lamellar bone. Haversian systems (osteons) are not evident.

In time, mature osteoma lesions may cease to grow, eventually achieving some form of permanent and static quiescence. In these mature lesions, the proliferative cambium layer is absent and the entire lesion may be replaced by compact, lamellar bone with minimal intertrabecular connective tissue. These mature osteoma lesions may be histologically indistinguishable from bony exostoses (e.g. *buccal exostoses* in the human jaws). Although this described pathogenesis of spicules of woven bone gradually transitioning into compact lamellar bone *requires the presence of osteoclasts* (bone remodeling), they are rarely identified histologically within osteoma lesions. Osteomas do not invade and destroy the cortex of the parent bone (although they may blend into it) and do not "evolve" into osteosarcomas.

A recent review of oral and maxillofacial osteomas in seven cats reported on five osteomas arising from the mandible, one from the maxilla and one within the nasal passage [8]. The affected animals ranged from 1 to 23 years of age. Osteomas arose as either endosteal or periosteal lesions with a wide variety of gross appearances, from broad-based to pedunculated osteomas; a single case in a one-year-old cat was characterized as a diffuse bony swelling of the entire right mandible caudal to the canine tooth. Oddly, this patient also had persistent deciduous dentition and unerupted permanent teeth.

Feline osteoma must be differentiated from feline osteochondromatosis, an aggressive, quasi-neoplastic disease process that is distinct from osteochondromatosis of dogs and horses. Although the pathogenesis of feline

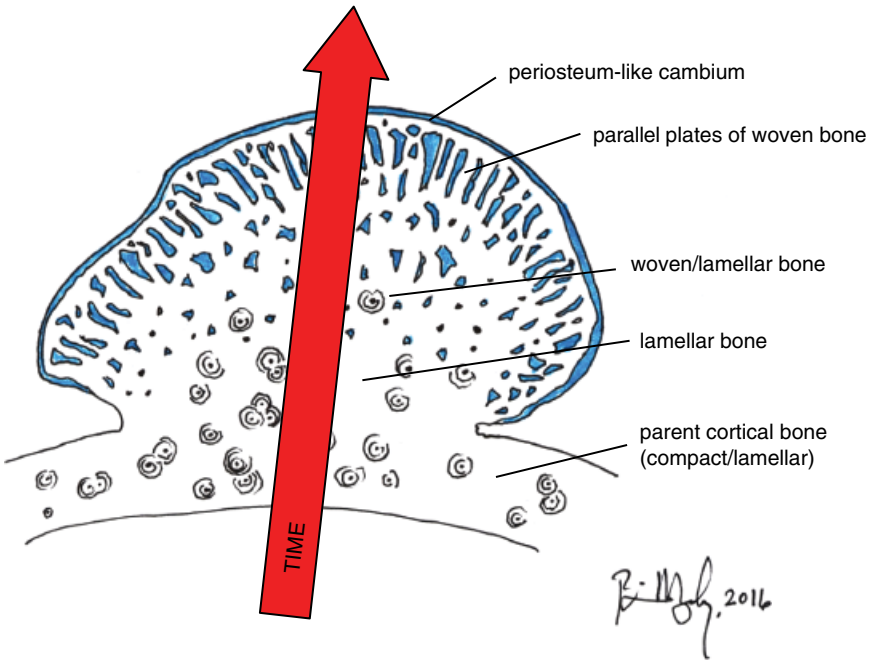


Figure 9.9 Osteoma diagram.

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osteochondromatosis is unsettled, it is closer to a sarcoma than to dysplasia. For some unexplained reason, feline osteochondromatosis has become rare – no cases have been identified in the University of California database in the past 25 years.

References

6 Maxie, M.G. (2016). *Jubb, Kennedy, and Palmer's Pathology of Domestic Animals*, 6e, vol. 3. St. Louis, MO: Elsevier.

7 Meuten, D.J. (2017). *Tumors in Domestic Animals*, 5e. Ames, Iowa: John Wiley & Sons.

8 Fiani, N., Arzi, B., Johnson, E.G. et al. (2011). Osteoma of the oral and maxillofacial regions in cats: 7 cases (1999–2009). *J. Am. Vet. Med. Assoc.* 238 (11): 1470–1475.

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9.3 Multilobular Sarcoma of Bone

Multilobular sarcoma of bone (MLSB) is a histologically unique and interesting tumor that is anatomically constrained and becomes progressively more malignant over time (see Box 9.3). Generally arising from the flat bones of the skull, MLSB is a tumor of dogs that has occasionally been diagnosed in cats and very rarely in other species like the horse, ferret, and African wild dog (*Lycaon pictus*). In dogs, MLSB is uncommon and appears to be a disease of middle-aged to older, medium- to large-breed dogs. In a study of 39 dogs diagnosed with MLSB, the median weight was 29 kg [9]. Nevertheless, MLSB has also been described in both young and small-breed dogs. In a search of the UC Davis veterinary pathology database, MLSB was diagnosed 32 times in dogs over the past 10 years, twice in cats and once in a horse.

Box 9.3 Multilobular Sarcoma of Bone, Differential Diagnoses

osteosarcoma
chondrosarcoma
ossifying fibroma
fibrous dysplasia

MLSB demonstrates a progressively malignant disease course and a degree of histologic plasticity, and shares some microscopic features with certain orthopedic lesions of humans. As a result, MLSB has acquired a rather large and confusing set of synonyms (Box 9.4). The name *MLSB* is favored by the authors, as this name (i) accurately identifies the malignant nature of the lesion, (ii) specifies the osseous origin, (iii) references the characteristic multilobular architectural pattern and (iv) intentionally *does not* specify cartilage and/or bone matrix, as *either or both* of these matrices may be present in MLSB. The term MLSB also avoids the confusion of assigning the name of a similar but not identical bone tumor of humans.

Box 9.4 Multilobular Sarcoma of Bone (Synonyms)

Multilobular tumor of bone
Multilobular osteosarcoma
Multilobular chondrosarcoma
Multilobular osteochondrosarcoma
Multilobular chondroma
Multilobular osteoma
Chondroma rodens
Cartilage analogue of fibromatosis
Calcifying aponeurotic fibroma

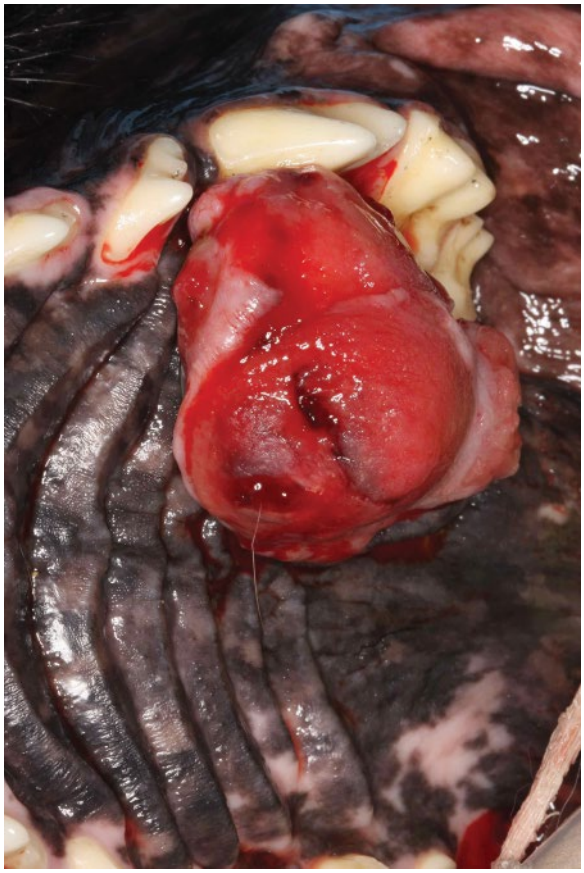


Figure 9.10 Gross image of a palatal multilobular sarcoma of bone (MLSB), nine-year-old FS Newfoundland dog. *Source:* Dentistry Oral Surgery Service, U.C. Davis.

Anatomically, MLSB most often arises from the flat bones of the head – the maxilla (especially the rostral or caudal palate), incisive bone, mandible, occipital bone, zygomatic process, orbit, or tympanic bulla; it has rarely been reported at other anatomic sites [10] (Figure 9.10). MLSB occurs more frequently in the maxilla than in the mandible. The flat bones of the skull and mandible have an intramembranous embryologic origin, suggesting the possibility that this relatively unique embryology may have something to do with the lesional pathogenesis. Investigators have hypothesized that MLSB arises from the periosteum of bones formed through intramembranous ossification, or alternatively, arises from the suture lines (syndesmoses/synostoses) separating the flat bones of the skull (personal communication, Dr. Roy Pool). A pathogenesis involving the suture lines/syndesmoses of the skull is intriguing, as it may account for the

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Figure 9.11 Gross image of adrenal gland with metastasis of a multilobular sarcoma of bone (MLSB), 10-year-old Border collie dog. *Source:* H. Aina, U.C. Davis.

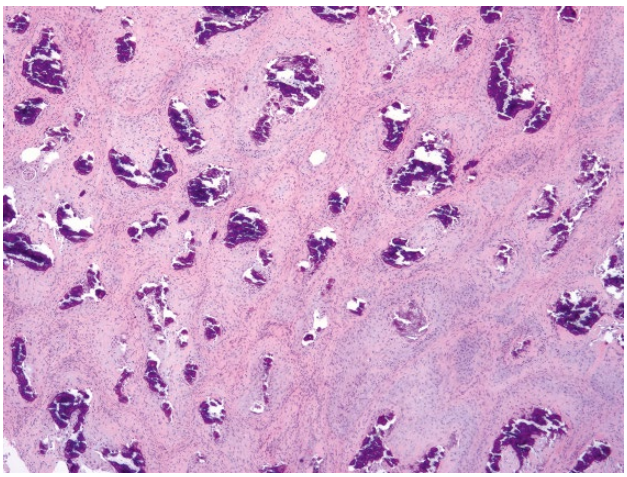


Figure 9.12 Histologic image of a well-differentiated multilobular sarcoma of bone (MLSB), 11-year-old Labrador retriever dog, mandible.

majority of the common anatomic sites (e.g. symphysis of the mandible and the incisive-maxillary syndesmosis) as well as the classic tri-laminar histologic appearance of MLSB (see below).

Clinically, MLSB is characterized (at least initially) as a firm, slowly progressive and expansile growth. Clinical signs are dependent upon the anatomic location of the lesion and include neurologic deficits, ocular signs/exophthalmos, dyspnea, trismus, malocclusion, and pain. MLSB initially compresses, rather than invades, adjacent structures, often resulting in pressure atrophy. Given sufficient time, MLSB will eventually transition into a highly aggressive, locally infiltrative and metastatic sarcoma, spreading to the lungs or other distant anatomic sites (Figure 9.11). Metastatic lesions may also be slowly progressive; dogs with pulmonary metastases can remain free of clinical signs for a year or more. Approximately 50% of resected MLSB tumors recur. However, complete surgical resection can provide good long-term disease remission.

Radiographically, MLSB often has a sharply demarcated, lobulated "popcorn ball" appearance with limited lysis of the adjacent bone. Grossly, MLSB manifests as a hard, 2–10 cm diameter, unmovable mass firmly fixed to the underlying periosteal bone surface. If the lesion projects into the oral cavity, it is often pink to red, multinodular, and may be ulcerated (Figure 9.10). The tumor is typically covered with a membrane of fibrous tissue (encapsulated or pseudoencapsulated), forming an expansile and compressive mass that may extend into the oral cavity, nasal passage, or calvarium. At least initially, adjacent soft tissues (e.g. brain) are compressed but not invaded. On section, MLSB consists of numerous, small, gritty, grayish white to yellow nodules separated by a network of fibrous tissues.

Classic MLSB lesions are comprised of innumerable, variably sized and shaped contiguous nodules (or lobules), each nodule exhibiting a *trilaminar histologic appearance* (Figures 9.12 and 9.13). The nodules are organized around a central focus of variably differentiated and variably mineralized immature bone or cartilage (or sometimes a mixture of both). MLSB lesions tend to exhibit a matrix that is either predominantly bone (bony variant) or predominantly cartilage (cartilaginous variant). If the lesion is heavily mineralized, the fragmented and mineralized matrix can obscure the identity of the underlying matrix. Although decalcifying the face of the paraffin block may assist in identifying the nature of the matrix (see Appendix), whether it is bone or cartilage is diagnostically irrelevant. Surrounding the central focus of matrix is a cuff of plump neoplastic round to polygonal mesenchymal cells (Figure 9.13). These cells are often hyperchromatic and may resemble primitive (fetal) osteoblasts. The individual nodules are separated from one another by streams of fibrous tissue, resulting in the characteristic, trilaminar appearance and the multilobular architecture of the tumor. A transect line bridging two adjacent central bone foci demonstrates the bone-fibrous joint-bone

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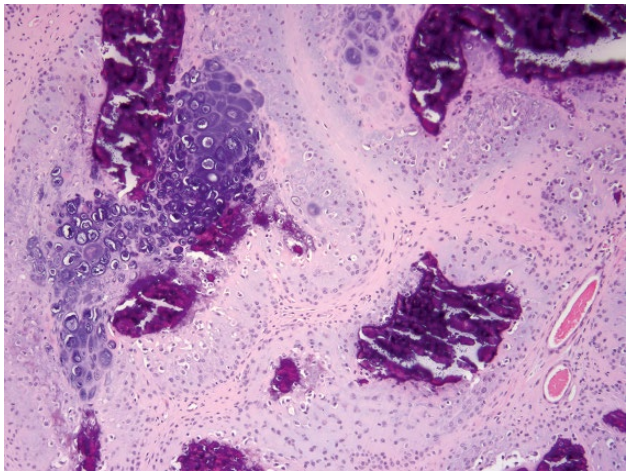


Figure 9.13 Histologic image of a well-differentiated multilobular sarcoma of bone (MLSB), 10-year old Portuguese water spaniel dog, dorsal calvarium.

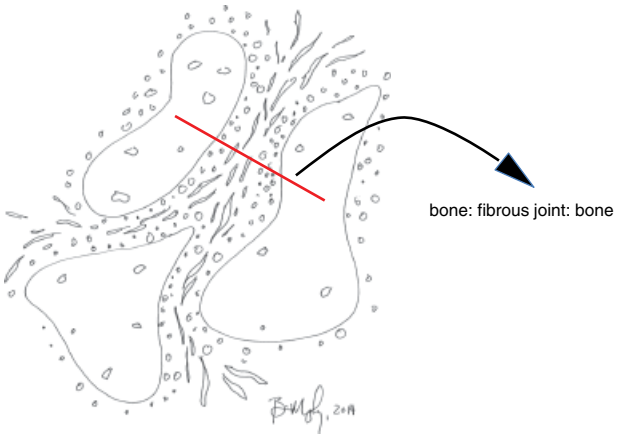


Figure 9.14 Architecture of multilobular sarcoma of bone (MLSB).

structure that recapitulates the syndesmosis joint (Figure 9.14). Vessels typically travel through the fibrous tissue band between lobules, but can also extend into the central matrical islands that are undergoing endochondral ossification.

In some MLSB lesions, the "classic" trilaminar architecture is abrogated by the loss of the nodular architecture and increased cellular pleomorphism. Some tumors may have regions demonstrating extensive, relatively uninterrupted sheets of cartilage, focally mimicking chondrosarcoma (Figure 9.15). A grading scheme based on the overall MLSB lesion size and organization, number of mitotic figures, cellular pleomorphism, and necrosis has been devised (Table 9.1). This grading scheme has been shown to predict time to metastasis, time to recurrence, and survival time (all decreased for grade II and III MLSB lesions).

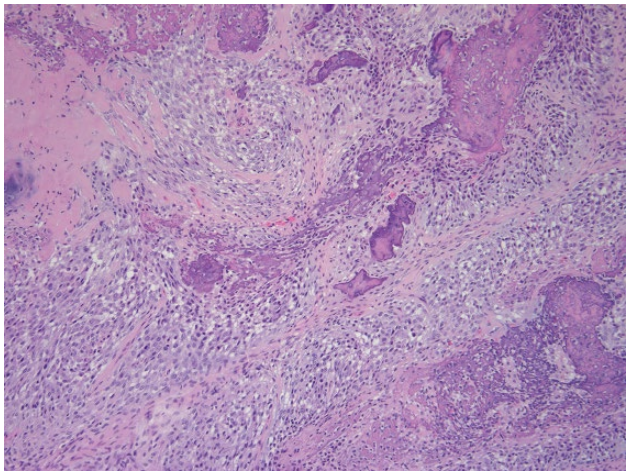


Figure 9.15 Histologic image of a poorly differentiated multilobular sarcoma of bone (MLSB), 10-year-old Border collie dog. Centrilobular, well-formed bone and/or cartilage are not evident and the lobular architecture is indistinct. The majority of the lesion is comprised of pleomorphic polygonal cells.

Table 9.1 Histologic grading scheme for multilobular sarcoma of bone (MLSB).

Criteria	Score	Grade
Borders		
pushing	1	
pushing and invasive	2	
invasive	3	
Size of lobules		
small and medium	1	
large	2	
Organization		
well-organized	1	
moderately well-organized	2	
poorly organized	3	
Mitotic figures/100 HPFs		
1 to 5	1	
6 to 10	2	
>10	3	
Pleomorphism of cells		
monomorphic	0	
mild	1	
moderate	2	
marked	3	
Necrosis		
none	0	
present	1	
	Total	
	7 or less	**Grade I**
	8 to 12	**Grade II**
	13 or greater	**Grade III**

Source: Derived from [9]

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References

9 Dernell, W.S., Straw, R.C., Cooper, M.F. et al. (1998). Multilobular osteochondrosarcoma in 39 dogs: 1979–1993. *J. Am. Anim. Hosp. Assoc.* 34: 11–18.

10 Meuten, D.J. (2017). *Tumors in Domestic Animals*, 5e. Ames, Iowa: John Wiley and Sons.

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9.4 Chondrosarcoma

Chondrosarcoma most often occurs in dogs, cats and sheep, and rarely in cattle and horses. In the dog, the most common anatomic sites are the ribs, nasal turbinates, scapulae, and pelvic bones, although it can arise from the endosteum (central/ medullary chondrosarcoma), or more rarely, periosteum (peripheral chondrosarcoma) of any bone. Primary chondrosarcomas arising from the maxilla, mandible, facial bones, larynx, or tongue are rare in all species, but do occasionally occur in dogs [11]. Chondrosarcoma arising from the nasal turbinates (one of the most common malignancies of the nasal cavity of dogs) can extend into the sinuses, hard palate, and oral cavity. In the authors' experience, the majority of oral chondrosarcomas originate as either (i) an extension from the nasal cavity, or (ii) progression of multilobular sarcoma of bone into chondrosarcoma. Benign chondromas are very rare in veterinary species, although they have been identified in the larynx of dogs. Most mesenchymal tumors producing recognizable hyaline cartilage are likely to be chondrosarcomas, not chondromas.

Chondrosarcoma in dogs is less aggressive than osteosarcoma (OSA). In different studies, metastasis of non-nasal chondrosarcomas has been reported as 17–20 or 40–60%. Grossly, chondrosarcomas often become large masses that are bone-invasive and destructive and may be associated with pathologic fractures. Chondrosarcomas arising in the nasal cavity obliterate the turbinates, obstruct the nasal passage and are often associated with nasal hemorrhage (Figure 9.16). Chondrosarcomas are often lobulated and may have a cerebriform gross appearance. On section, they may resemble hyaline cartilage, be semi-translucent, bluish white, ivory white, chalky white or gray. Some chondrosarcomas may have a gelatinous appearance and texture (myxoid matrix).

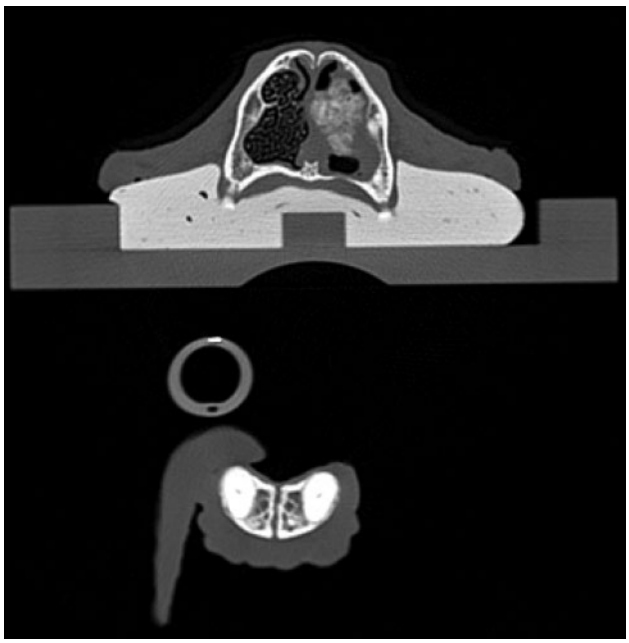


Figure 9.16 Computed tomography image of canine nasal chondrosarcoma. *Source:* J. Soukup, University of Wisconsin.

Many chondrosarcomas have microscopic features of *a malignant tumor of cartilage*. In these cases, the diagnosis of chondrosarcoma is relatively straightforward. However, it is also true that some chondrosarcomas can be a challenge to diagnose. The matrix produced by tumor cells is often the key to diagnosing many sarcomas. Chondrosarcoma is a *malignant mesenchymal tumor demonstrating some form of chondroid matrix production and lacking tumor-associated osteoidal matrix (*TAOM*)*. For chondrosarcomas, the nature of the matrix and the relationship of the matrix to the malignant mesenchymal cells are both critical to the diagnosis.

Box 9.5 Histological Differential Diagnoses for Chondrosarcoma

Osteosarcoma (chondroblastic subtype)
Chondroma
Myxosarcoma
Odontogenic mxyoma
Anaplastic sarcoma
Multilobular sarcoma of bone
Fracture callus
Chondroid metaplasia/dysplasia of the epiglottis

All chondrosarcomas, regardless of the degree of differentiation, need to be histologically distinguished from OSA. Many sarcomas arising from bone are derived from multipotent mesenchymal cells, capable of differentiating into chondroblasts, osteoblasts and/or fibroblasts. Malignant osteoblasts have a greater tendency for metastatic behavior relative to other mesenchymal cells like chondroblasts or fibroblasts. As a result, a convention has been established that if the tumor is a sarcoma and the malignant mesenchymal cells directly produce osteoidal matrix (TAOM), the lesion is defined as an OSA. From the presence of TAOM, we infer the presence of *malignant osteoblasts*. The bottom line is this – if TAOM is present within a sarcoma, it does not matter if the tumor produces abundant well-differentiated lobules of cartilage; such a tumor is still an OSA (of the chrondroblastic subtype).

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So, OSA is *always* a differential for any suspect chondrosarcoma; it is a matter of identifying the (potentially rare) intralesional expression of TAOM.

To complicate matters further, osteoid and/or bone *may still be present* within chondrosarcoma lesions. If TAOM defines an OSA, how is this possible? There are three ways that osteoid and/or bone can be present in chondrosarcoma lesions: (i) as *metaplastic bone* arising within the adjacent, non-neoplastic stroma, (ii) the cartilaginous matrix, produced by the malignant chondroblasts, can serve as the nidus for *endochondral ossification*, and finally (iii) islands of partially resorbed, *pre-existing (often lamellar) bone* may be marooned within the sarcoma. Remember that extracellular matrix is non-living and therefore cannot be neoplastic. The matrix can, however, serve as a substrate from which osteoid and bone can be formed by non-neoplastic osteoblasts that just happen to be within the tumor. Chondrosarcomas can be tricky lesions.

It can get trickier – not all chondroid matrices are created equal. Physiologically normal chondroid matrix stains blue (basophilic) with H&E stains as a result of the proteoglycan content, molecules like chondroitin sulfate that attract water and give cartilage its impressive resistance to compression. Malignant chondroblasts are biochemically not the same as normal chondroblasts. As a result, the matrix that some chondrosarcomas produce may be seriously deficient in proteoglycans, and may actually stain pink/ hyalinized (eosinophilic) and become fibrillar, in a manner similar to osteoid. Distinguishing between neoplasm-associated chondroid matrix lacking proteoglycans and osteoid may prove to be difficult. Identifying the presence of TAOM is discussed at greater length in Section 9.1.1.

Mineralization of the extracellular matrix does not necessarily imply osteoid, as cartilage can mineralize, too. Determining the nature of the mineralized, purple-staining matrix may require face decalcification of the paraffin block (see Appendix). Once the mineral is removed, the matrix often can more readily be interrogated. Tumor-associated chondroid matrix that lacks proteoglycan may stain pink, but it generally still maintains an architecture that implicates its chondroblastic creators – large, round lacunae that are unlike the smaller, lens-shaped lacunae of osteoid and bone (Figure 9.17). In less differentiated chondrosarcomas, the extracellular matrix may be less abundant, stain pale blue, lack identifiable lacunae, and be more myxoid-like (as would be found in a myxosarcoma).

Alcian blue stains may facilitate the identification of proteoglycan molecules within the matrix. Such poorly differentiated tumors begin to merge with myxosarcomas. Given sufficient time, multilobular sarcoma of bone can histologically and behaviorally merge with either

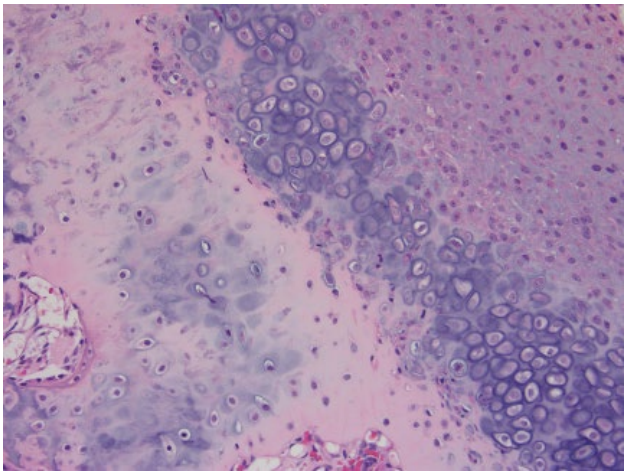


Figure 9.17 Primary mandibular chondrosarcoma, eight-year-old Labrador retriever dog.

OSA or chondrosarcoma. It is also possible that small core biopsies obtained from a proliferative fracture callus can histologically mimic chondrosarcoma. The authors have found that proliferative lesions on the epiglottis/ larynx of dogs may present as a nodular or irregular thickening, typically at the "leading edge" of the epiglottis, referred to as *nodular chondroid hyperplasia/ degeneration of the larynx and epiglottis* (see Section 10.1). Histologically, the abnormal tissue consists of hyaline cartilage that is variably mineralized and degenerate. Fibrosis and mild inflammation may be present. Obviously, history and imaging play a critical role in diagnosis of chondrosarcomas.

In differentiated chondrosarcomas, malignant chondroblasts produce and subsequently become embedded within the basophilic cartilaginous matrix. Neoplastic chondrocytes are often arranged as clustered aggregates of round cells with large, round nuclei, referred to as chondrones. In differentiated chondrosarcomas, the malignant cells are still recognizable as chondroblasts or chondrocytes. In some regions of the chondrosarcoma, the cells may fail to produce an extracellular matrix at all, forming extensive sheets of closely packed round, polygonal, or spindle-shaped cells. Less differentiated chondrosarcomas have less identifiable cartilage or chondroid matrix and a greater tendency to form extensive, often monotonous sheets. The neoplastic cells give fewer clues of their initial histogenesis and may begin to demonstrate anaplastic features. An easily implemented and useful chondrosarcoma grading scheme has been developed for non-nasal chondrosarcomas [12]. Bear in mind that this grading scheme was developed for non-nasal chondrosarcomas, while many "oral" chondrosarcomas arise as an extension from the nasal cavity (see Table 9.2).

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Table 9.2 Grading chondrosarcomas.

Grade	Histologic criteria
Low	Low cellularity
	Absence of mitoses
	Well differentiated with abundant matrix
	No obvious invasion
Intermediate	Moderate cellularity
	Low mitotic index (< 2/10 hpf)
	Well differentiated, but amount of matrix may be less than for low grade, at least in some areas
	Presence of invasion
High	Presence of mitoses with mitotic index (> 2/10 hpf)
	Areas of high cellularity
	Highly cellular areas lack matrix
	Invasiveness

Source: Table derived from: Waltman et al. [12].

References

11 Meuten, D. .J. (2017). *Tumors in Domestic Animals*, 5e. Ames, Iowa: John Wiley & Sons.

12 Waltman, S.S., Seguin, B., Cooper. B.J., & Kent, M. (2007). Clinical outcome of nonnasal chondrosarcoma in dogs: thirty-one cases (1986–2003). *Vet. Surg.* 36:266–271.

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10

Tumor-Like Proliferative Lesions of the Oral Mucosa and Jaws

10.1 Tumor-Like Proliferative Lesions of the Oral Mucosa

Benign, reactive mass lesions are commonly identified in the oral mucosa and gingiva of companion animals. Many of these lesions are the result of inflammation or local irritation. Lesions on the buccal and sublingual mucosa are frequently secondary to traumatic injury, and these masses represent exuberant growth of ulcerated granulation tissue. Clinical differential diagnoses include other forms of proliferative inflammation (e.g. eosinophilic granuloma) and neoplasia. Therefore, biopsy for microscopic examination is an important part of the diagnostic work-up. For discussion of inflammatory lesions and traumatic lesions, readers are referred to Sections 5.1 and 6.1. This section includes brief descriptions of other uncommon soft tissue mass lesions. Tumor-like lesions of the gingiva are presented in Section 10.2 on the tooth-bearing regions of the jaw.

Trauma-induced proliferation of granulation tissue is one of the most common non-neoplastic processes that results in a proliferative mucosal lesion in the oral cavity of companion animals. Synonyms for this type of lesion include "chewing granuloma" and "pyogenic granuloma." A thorough discussion of this entity is included in this textbook within the chapter on trauma and physical injury.

10.1.1 Calcinosis Circumscripta

Calcinosis circumscripta (formerly known as *tumoral calcinosis*) is a condition in which amorphous to crystalline, fluid to solid, mineral-rich material is focally or multifocally sequestered within connective tissues. In the oral cavity, these lesions are most often deep within the lingual muscle of the tongue (Figures 10.1 and 10.2), although superficial mucosal lesions of calcinosis circumscripta also occur. The pathogenesis has not been fully elucidated, but traumatic injury has traditionally been considered to be a contributing factor. Affected dogs do not have abnormal serum levels of calcium or phosphorus and young, large-breed dogs are over represented [1, 2]. In one study of the lesions in dogs, calcinosis circumscripta accounted for 4% of lingual lesions and another retrospective study of 77 cases in dogs showed that the tongue was the second most common site for calcinosis circumscripta (feet of the pelvic limbs was the most common site) [2].

Calcinosis circumscripta lesions may be discovered incidentally and cause no clinical signs or abnormalities unless the lesion is particularly large. As denoted by the name, lesions are circumscribed with a sharp edge, usually solitary, and most range from 0.5 to 3.0 cm diameter [2]. Clinically, calcinosis circumscripta may present as a subtle swelling of the tongue or as a polypoid mass. There may or may not be obvious yellow discoloration, depending on how closely the lesion approaches the mucosal surface. Surrounding and overlying tissue would be expected to demonstrate signs of inflammation and/or ulceration.

On section, the lesions are well-demarcated from the surrounding lingual muscle, and consist of encapsulated material that is homogeneous and pale yellow-tan with a soft to putty-like consistency (Figure 10.1). Calcinosis circumscripta lesions have a high concentration of mineral salts, and this material may be smooth or gritty when rubbed between one's fingers. Histologically, aggregates of amorphous to granular, lightly to darkly basophilic material is often, but not always, surrounded by a zone of macrophages and multinucleate giant cells and peripheral fibrosis. The histopathology is usually distinctive, although some lesions may be difficult to distinguish from a true granuloma with dystrophic mineralization. In such cases, special stains would be important to rule out an infectious cause.

Conservative surgical excision is the recommended treatment and there is no evidence to suggest that affected dogs are at increased risk for new or recurrent lesions. Calcinosis circumscripta should not be confused with diffuse patterns of soft tissue mineralization of the tongue that may occur secondary to systemic metabolic dyscrasia (e.g. uremia) or ischemia (see Inflammatory lesions of the oral mucosae).

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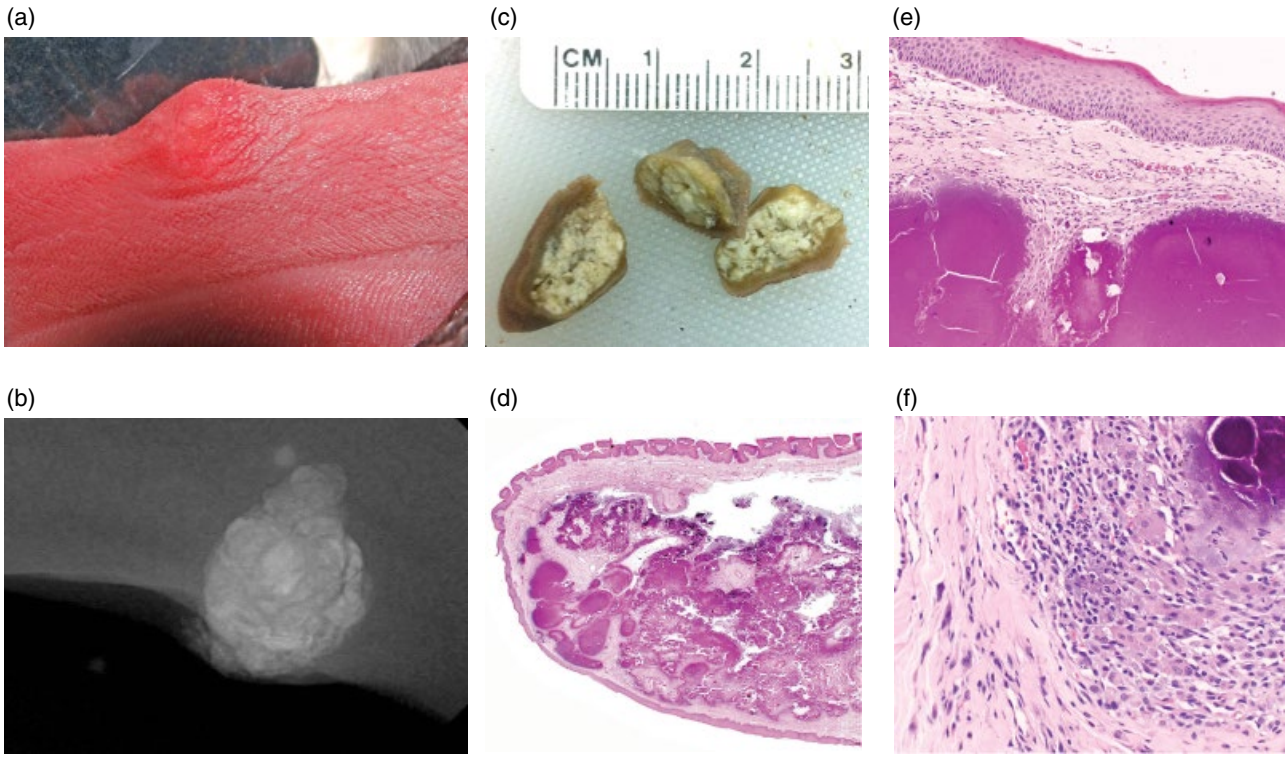


Figure 10.1 Gross and histologic images of calcinosis circumscripta of the tongue, seven-month-old, neutered male, Standard poodle dog. *Source:* B. Beckman.

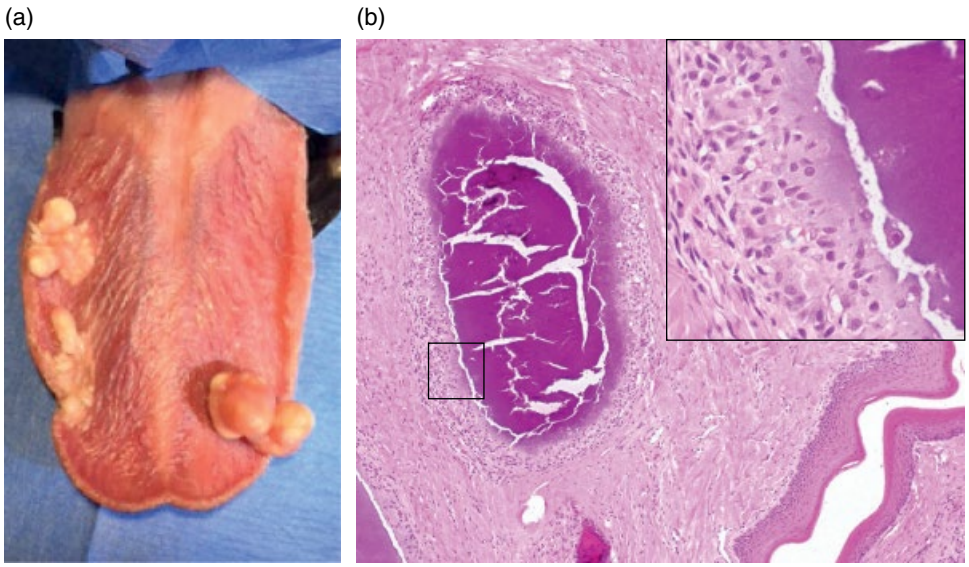


Figure 10.2 Gross and histologic images of calcinosis circumscripta of the tongue, neutered male Pomeranian of unspecified age. White fluid was reported to have drained from some of the masses. *Source:* C. Miles.

10.1.2 Ectopic Sebaceous Tissue

Dermal adnexal differentiation can occur either focally or multifocally within the oral mucosa. These lesions are a type of choristoma (i.e. appropriately organized benign tissue in an inappropriate location). They are usually small and discovered incidentally. Well-demarcated areas of sebaceous differentiation seem to be most common, although hair follicles also arise within the oral mucosa. Grossly, these ectopic foci appear as small glistening nodules on the vestibular, labial, or oropharynegeal

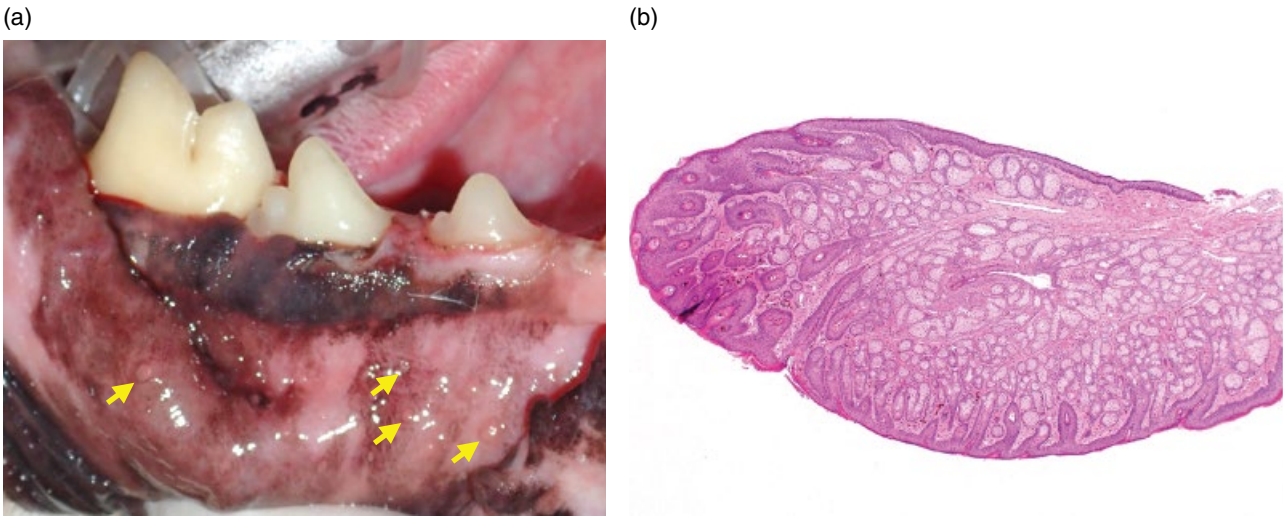


Figure 10.3 Gross and histologic images of ectopic sebaceous tissue, 12-year-old Beagle dog. (a) Ectopic sebaceous glands are round, smooth, pink nodules that are slightly elevated from the surrounding buccal mucosa (yellow arrows). (b) Histologically, the lesion is reminiscent of cutaneous sebaceous hyperplasia lesions. *Source:* D. Otten.

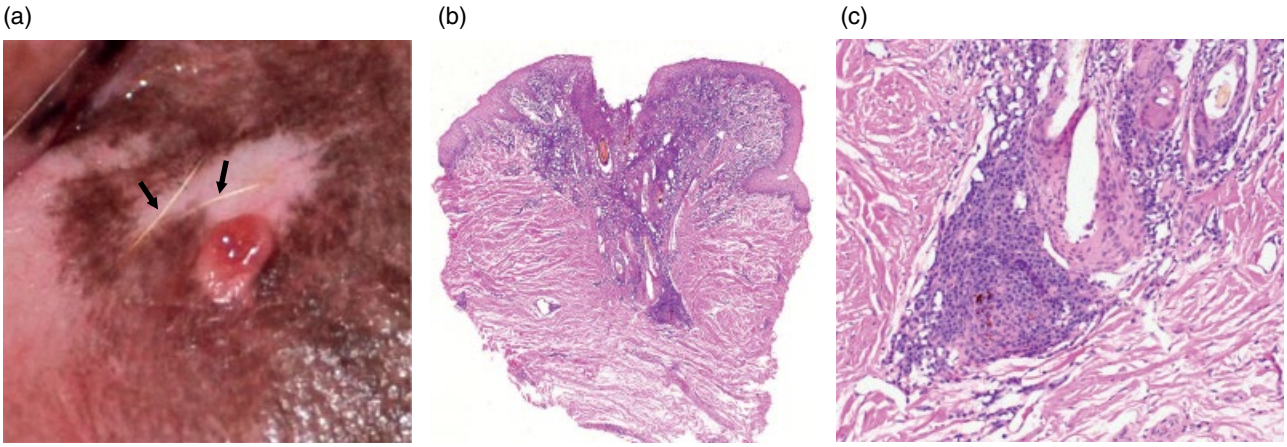


Figure 10.4 Gross and histologic images of ectopic adnexal tissue, three-year-old, Rhodesian ridgeback dog. (a) Ectopic hairs (arrows) associated with a focal, raised, and erythematous mucosal mass. (b) and (c) Inflammation is localized to an area of mucositis centered on a hair follicle. *Source:* D. Nossaman.

mucosa (Figures 10.3 and 10.4). In humans, the eponym "Fordyce spots" refers to focal or multifocal, well-differentiated sebaceous glands within the lamina propria [3].

10.1.3 Follicular Lymphoid Hyperplasia

Hyperplastic lymphoid tissue occasionally accounts for small lesions within the mucosa of the palate, caudal oral pharyngeal mucosa or mucosa of the larynx. These are usually discovered incidentally during an anesthetized oral exam, placement of an endotracheal tube, or upper airway endoscopy. The lesions are multifocal, flat, or slightly raised, non-ulcerated and variably erythematous (Figure 10.5). Histologically, there are small nodular aggregates of lymphocytes or larger organized lymphoid follicles within the lamina propria. Usually the lymphoid follicles have recognizable follicular microanatomy. However, some cases of reactive follicular lymphoid hyperplasia can present a diagnostic challenge when they are difficult to distinguish from follicular lymphoma. Although rare in animals, follicular lymphoma may be a concern when large follicles have indistinct germinal centers, ill-defined mantle zones, and/or lack tingible body macrophages [4].

In humans, follicular lymphoid hyperplasia most commonly occurs in the caudal hard palate of geriatric individuals [4]. Hyperplastic lymphoid tissue in the pharyngeal and laryngeal mucosa of racehorses is quite

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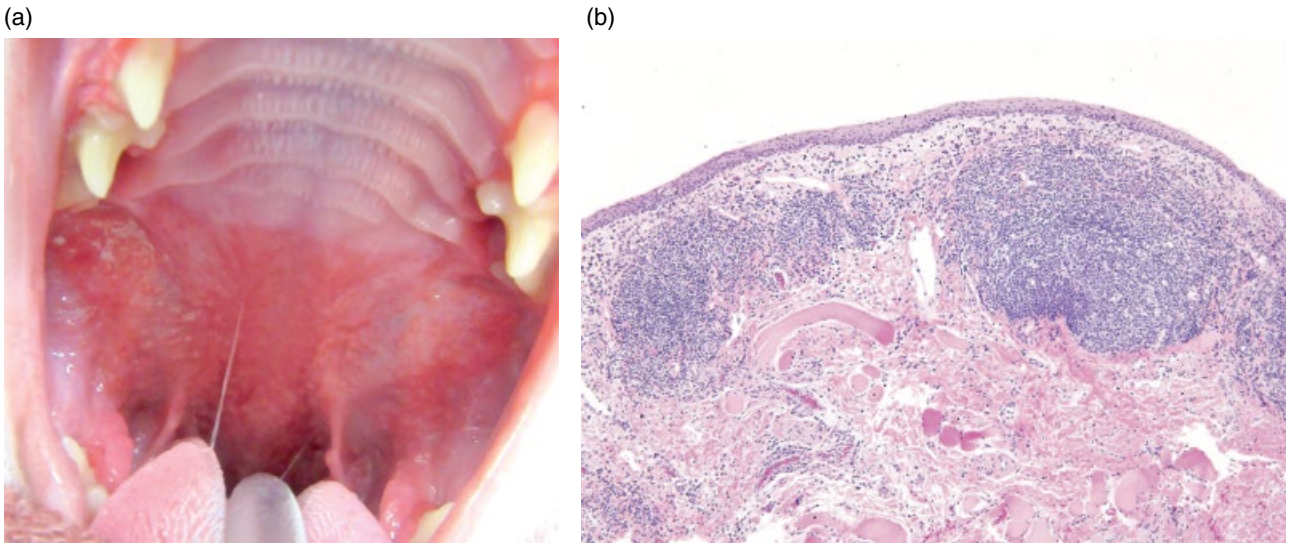


Figure 10.5 Gross and histologic images of diffuse follicular lymphoid hyperplasia of the palatal mucosa in a two-year-old, NM, Siamese cross cat. (a) The affected area is erythematous and has a roughened, granular appearance due to many slightly elevated, pink, glistening nodules. (b) Histologically, there are variably sized and organized lymphoid nodules within the mucosa propria. *Source:* C. Waterhouse.

common; prevalence was 34.2% in a study of upper respiratory tract endoscopy in thoroughbred racehorses [5].

10.1.4 Tonsillar Polyp

The shape of tonsilar polyps can vary, but in general they are flattened, elongated, and smooth on the mucosal surface. The polypoid mass may be the entire everted tonsil (Figure 10.6) or a projection from the tonsil (Figure 10.7). Histologically, the lesions have fibrovascular tissue cores, dilated lymphatics and veins, and include variable amounts of lymphoid tissue [6]. Occasionally, the fibrous connective tissue has a hyalinized or keloidal appearance. In humans, the fibrous connective tissue of tonsillar polyps may include adipose tissue or smooth muscle [7]. Polypoid lesions arising from the tonsil of dogs often are found incidentally during anesthesia in middle age to older dogs and, rarely, affected dogs have clinical signs such as gagging or retching [8]. One of the largest case series of tonsillar polyps in humans describes lesions as unilateral, polypoid, and often mistaken clinically as neoplasms [7].

One case report in a dog uses the term "lymphangiomatous polyp" for a smooth pedunculated mass with dilated lymphatic channels, and the authors discuss the apparently analogous entity in humans [8]. A larger case series in dogs did not use the term "lymphangiomatous" since some lesions had dilated veins rather than lymphatics and others had minimal vascular dilation [7]. Clinical history and gross appearance are similar despite the histological variation; therefore, the generic term "tonsillar polyp" is least confusing and most inclusive for referring to this entire group of lesions. Descriptive terms such as "fibroangiomatous" or "lymphangiomatous" may be used for lesions as appropriate for their specific histological appearance.

10.1.5 Sublingual Nodules and Polyps

Histologically benign, proliferative, reactive/ inflammatory sublingual lesions run the gamut from a focal to diffuse distribution featuring fibrous to angiomatous to histiocytc or lymphohistiocytic elements. There is seemingly unlimited variation of lesions having one or more of these characteristics. Many are benign but must be distinguished from malignancies such as histiocytic sarcoma, liposarcoma, and angiosarcoma. Clinical presentation and behavior are often helpful in elevating one's suspicion of a hyperplastic process or benign neoplasm. Benign proliferations under the tongue tend to be polypoid or nodular without thickening and invading the underlying lingual muscle. Rare sublingual nodules in dogs have histological features that are comparable to reactive histiocytosis (Figure 10.8), which has been reported in a dog [9]. Other benign entities reported include fibroma, vascular hamartoma, squamous papilloma, hemangioma, and sublingual mucinosis [1]. In our experience, fibroangiomatous lesions represent one of the more common forms of sublingual mucosal hyperplasia. These fibroangiomatous proliferations may range

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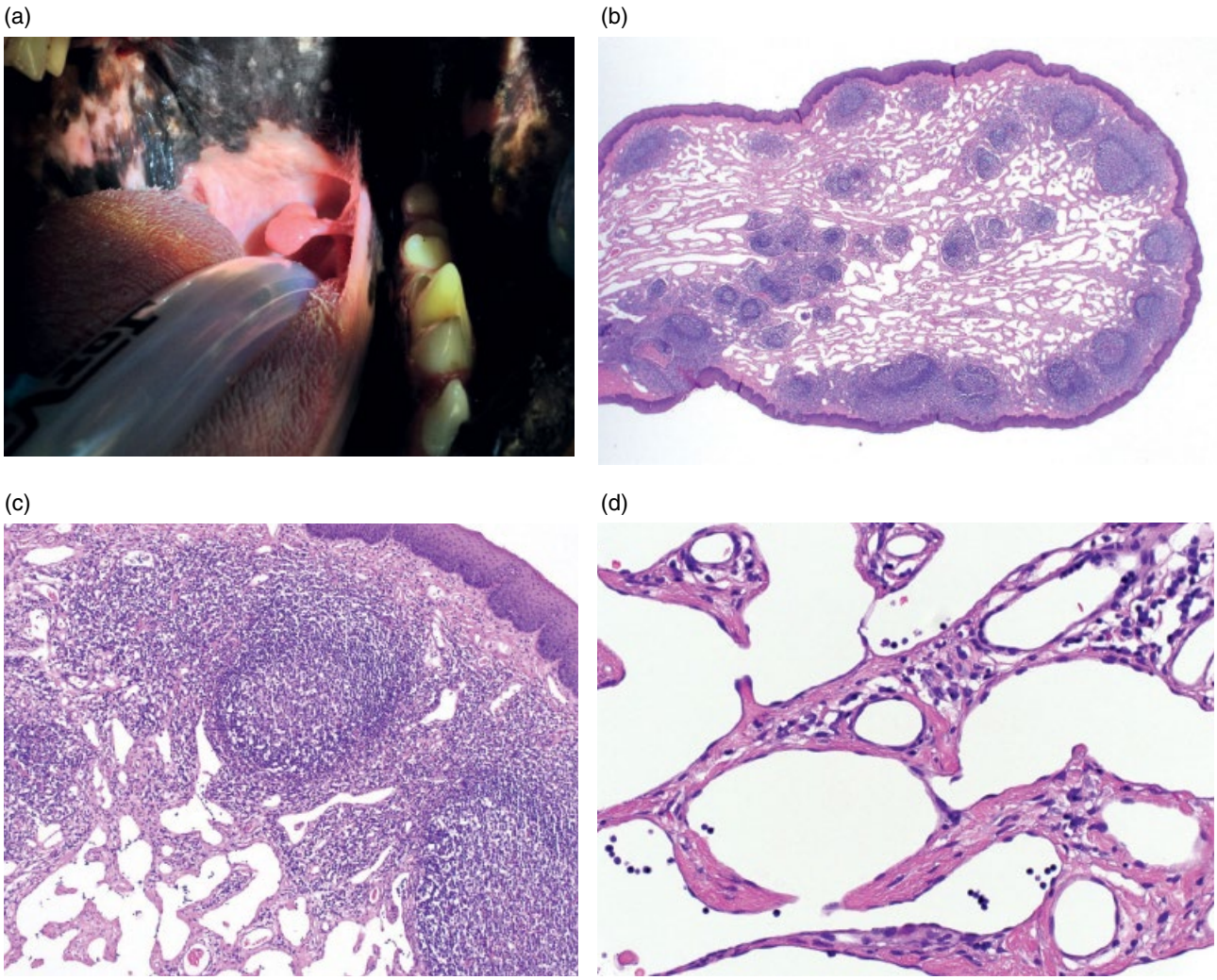


Figure 10.6 Gross and histologic images of a tonsillar polyp, seven-year-old, FS, golden retriever dog. (a) Everted and supported by a narrow stalk, the tonsil forms a polypoid mass that projects into the oropharynx. (b) Histologically, the mass has tonsillar architecture with organized lymphoid follicles although the fibrovascular stroma is expanded by many dilated vascular channels. (c) The lymphoid tissue is within normal histological limits, (d) while the vascular channels are lined by cytologically benign endothelial cells and have only occasional lymphocytes within the lumen. *Source:* E. Vicari.

from a focal polyp (Figure 10.9) to many coalescing nodules (Figure 10.10). Sublingual mucinosis is an uncommon condition of unknown etiology that presents as a regionally extensive swelling of the sublingual mucosa (Figure 10.11).

10.1.6 Histiocytic Foam Cell Nodules

Histiocytic foam cell nodules (HFCN), are a relatively newly described oral lesion initially identified in miniature Dachshund dogs [10]. They are thought to be inflammatory aggregates of histiocytic "foam" cells with vacuolated cytoplasm and occur multifocally on the ventral and lateral surfaces of the tongue. HFCN are perhaps analogous to the non-neoplastic *xanthoma* lesion. Xanthomas are common cutaneous lesions in birds and are composed of large foamy macrophages [11]. The pathogenesis of cutaneous xanthoma lesions can be associated with abnormal plasma levels of cholesterol or triglycerides, xanthomas can also have an idiopathic pathogenesis.

As a result of the vacuolated cytoplasm, HFCN shares some histological overlap with a number of other oral mass lesions (see below). HFCN are PAS negative and positive for the macrophage scavenger receptor CD204 [10]. At UC Davis and CCOMP, we have seen a total of four lingual lesions that are histologically reminiscent of HFCN. Interestingly, the lingual lesions we have identified have occurred in breeds other than miniature

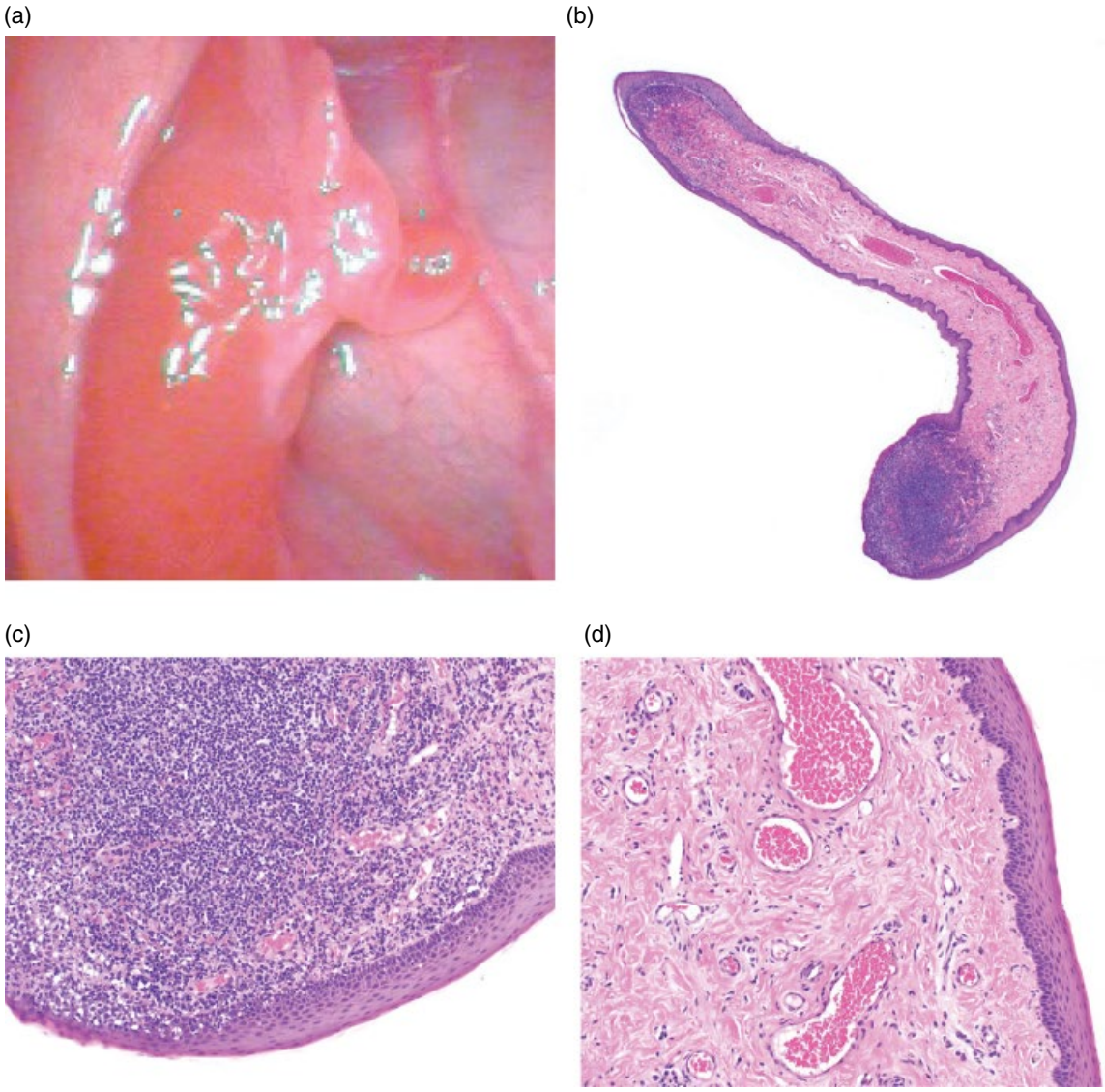


Figure 10.7 Gross and histologic images of a tonsillar polyp, seven-year-old, FS, American Staffordshire terrier dog. (a) A short, flattened polypoid mass projects off of the lateral mucosal edge of the tonsil. (b) Histologically, the appendage is primarily fibrovascular stromal tissue with multifocal tonsillar lymphoid tissue. (c) The lymphoid tissue is histologically unremarkable. (d) In this lesion, the vascular channels are less abundant than the lesion in Figure 10.6 and contain erythrocytes. *Source:* B. Shope.

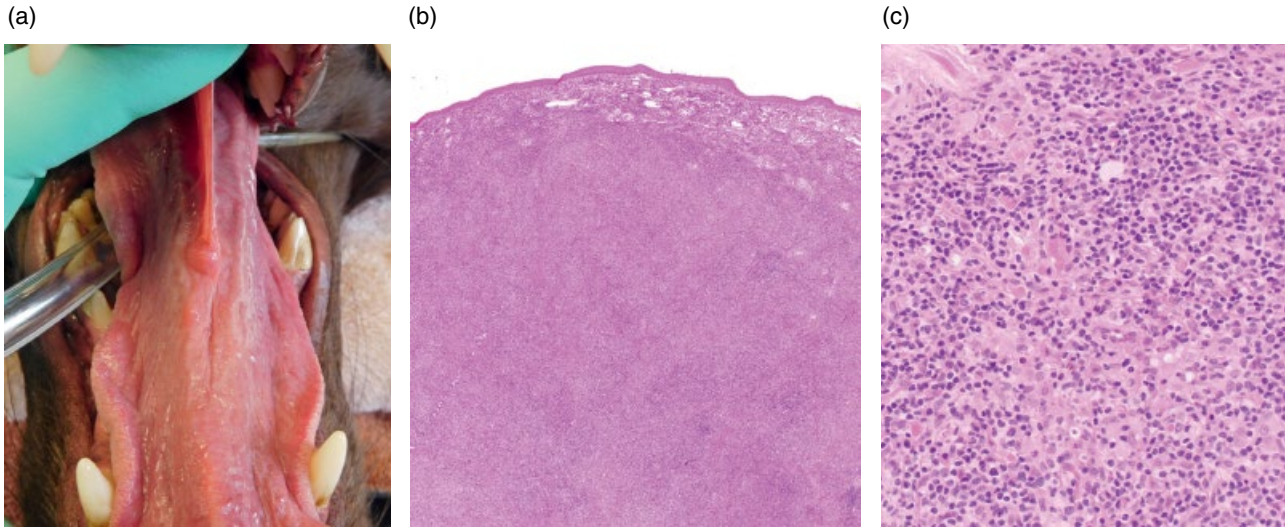


Figure 10.8 Gross and histologic images of a sublingual lymphohistiocytic nodule, nine-year-old, FS, flat coated retriever. *Source:* N Hoyer.

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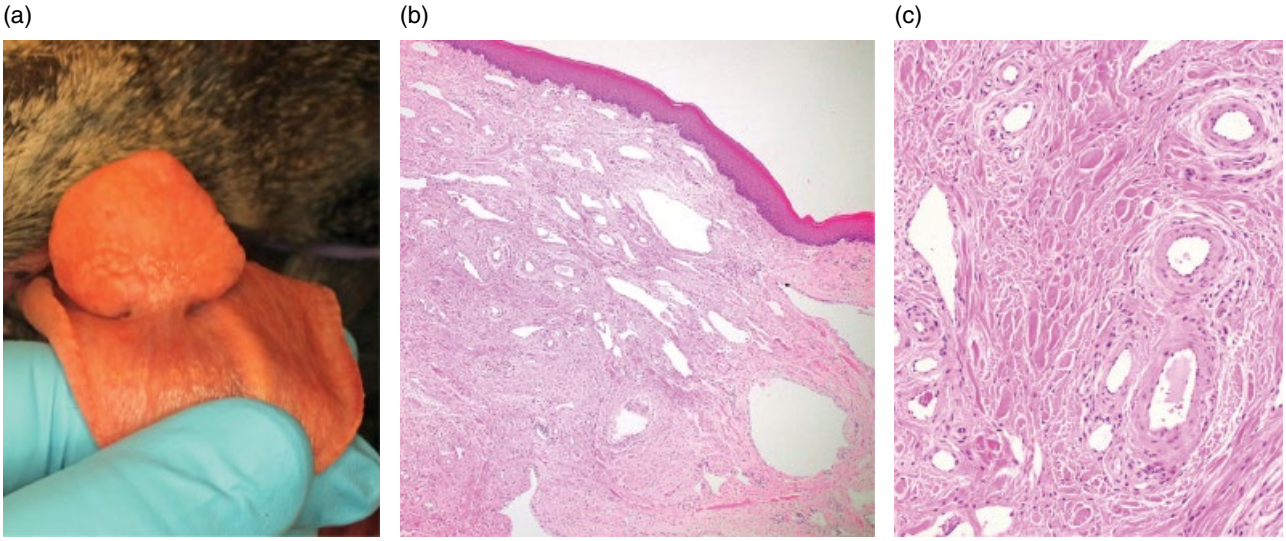


Figure 10.9 Gross and histologic images of a sublingual fibrovascular polyp, nine-year-old, FS, Labrador retriever. *Source:* J. Covino.

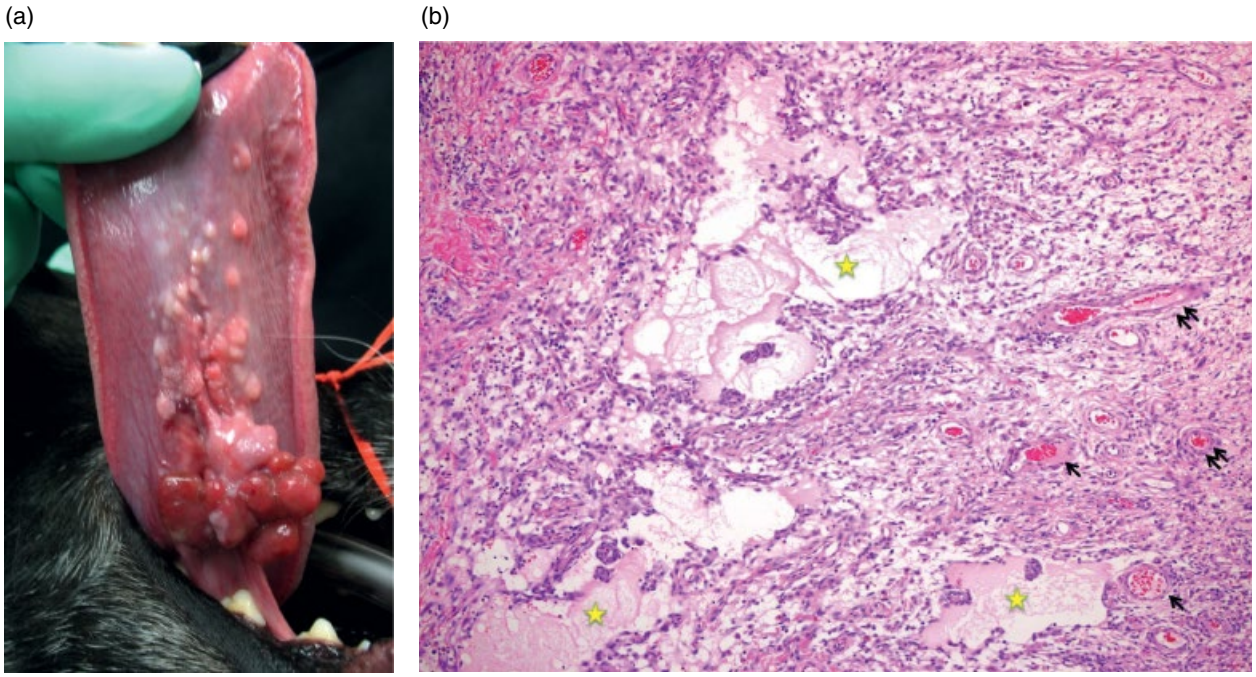


Figure 10.10 Gross and histologic images of diffuse sublingual swelling in a four-year-old, FS, Ragdoll cat diagnosed with sublingual mucinosis. Histologically, the submucosa was loosely arranged and proliferative fibrovascular tissue with lightly staining mucinous matrix. *Source:* J. Bellows.

Dachshunds – Labrador retriever, Mastiff, Shetland sheepdog and German shepherd cross dogs.

Lesions are comprised of variably sized, vacuolated histiocytes forming sheets and streams. Individualized skeletal myocytes and pre-existing collagenous stroma of the tongue may be surrounded by these vacuolated histiocytes (Figure 10.12). Small aggregates of lymphocytes may also be present. In our experience, HFCN are well-demarcated but not encapsulated, and may be mistaken histologically for a variety of neoplastic processes. The HFCN-type lesions in our databases were originally diagnosed as neoplasms: myxoma, low-grade liposarcoma, oncocytoma, rhabdomyoma, and granular cell tumor.

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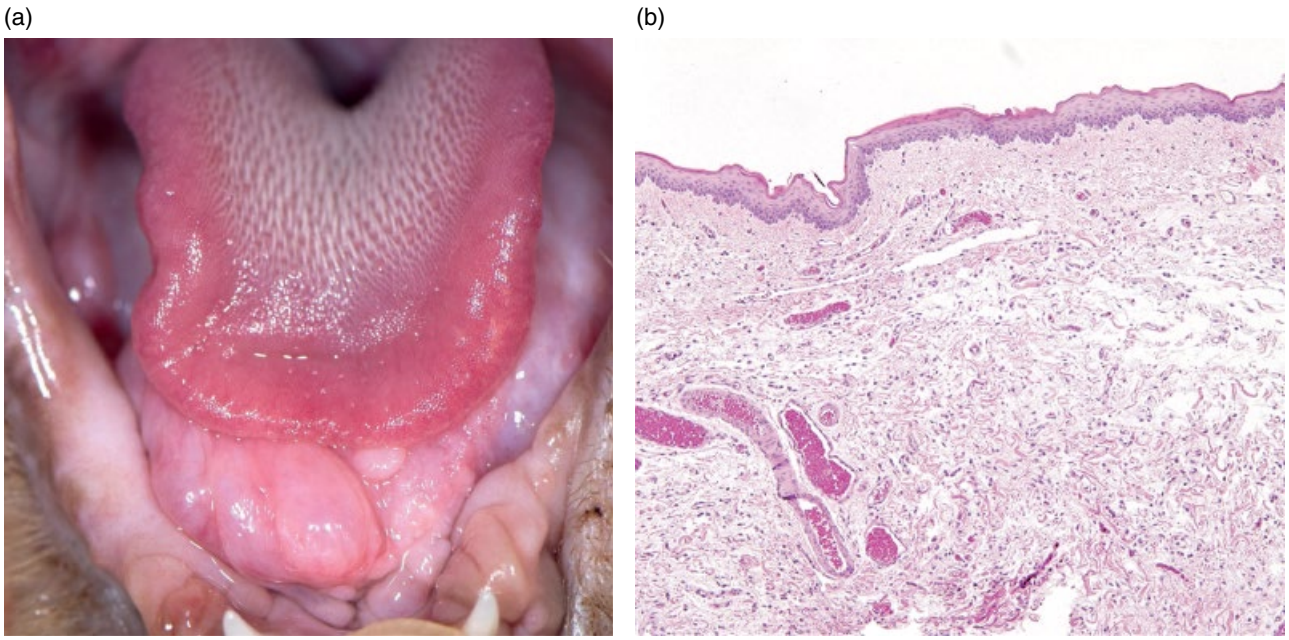


Figure 10.11 Gross and histologic images of sublingual lymphangiomatosis in a nine-year-old, NM, Labrador retriever cross with a history of dermatofibrosis. *Source:* N. Hoyer.

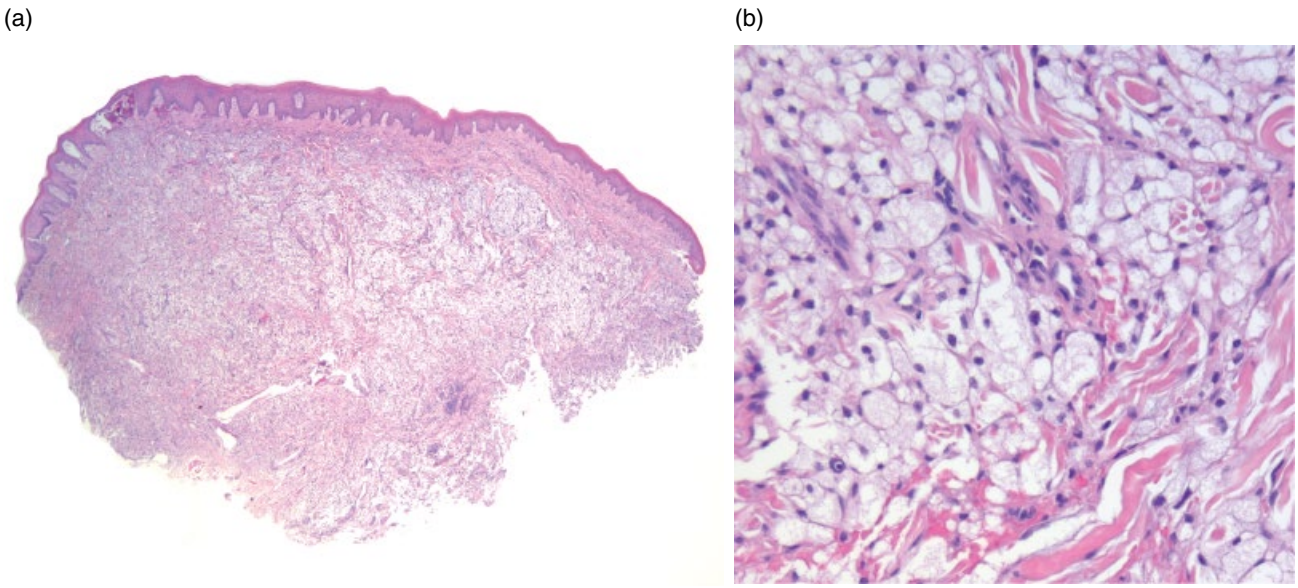


Figure 10.12 Histologic images of histiocytic foam cell nodule, 11-year-old Shetland sheepdog. (a) This sublingual nodule is moderately well-circumscribed but is not encapsulated. (b) The histiocytes ("foam cells") are closely packed, and have benign nuclear features and abundant vacuolated, slightly basophilic cytoplasm. These cells were positive for CD204 expression, consistent with a histiocytic lineage.

10.1.7 Nodular Chondroid Hyperplasia/ Degeneration of the Larynx and Epiglottis

These idiopathic, proliferative/degenerative lesions of the mucosa and underlying cartilage of the epiglottis/larynx manifest grossly as small elevated lesions within the mucosae of the epiglottis or larynx (arytenoid). These relatively common canine lesions may be initially identified on anesthetized oral exam or during placement of an endotracheal tube. The lesions are rarely biopsied, as surgical biopsies can be a challenge to obtain due to the

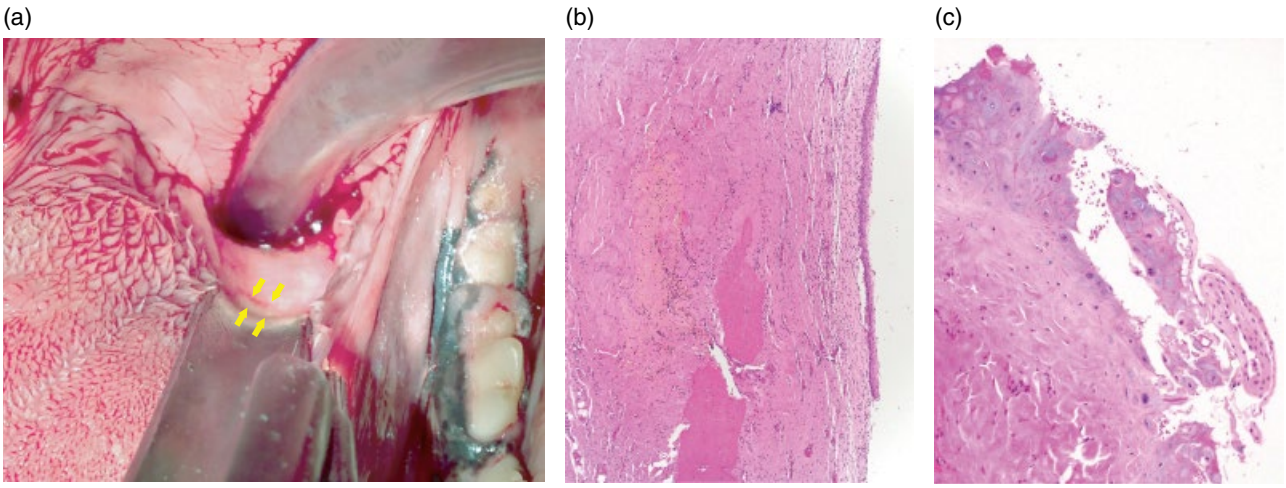


Figure 10.13 Gross and histologic images of an epiglottis with chondroid hyperplasia and degeneration, nine-year-old, NM, boxer dog. (a) Grossly, the lesion appears as a well demarcated area of pallor at the leading edge of the epiglottis (yellow arrows) due to metaplastic bone and proliferative/degenerative cartilage within the mucosa of the epiglottis. The lesion was an incidental finding. *Source:* D. Hansen.

risk of mucosal hemorrhage. As the submitted biopsy specimens are often small and distorted, clear communication between the pathologist and the submitting clinician is critical.

The nodules elevate or bulge from the overlying mucosa and are white, light pink or pale tan. Mineralization may cause the lesions to stand out from the surrounding mucosa. Histologically, the mucosa is expanded by nodular or amorphous cartilage, fibrous tissue and/or bone (Figure 10.13). The cartilaginous lesions may be most striking, and are composed of hyaline or fibrocartilage that is variably degenerate, necrotic, and calcified (dystrophic mineralization), and adjacent tissues may be ossified. Epiglottal mineralization has been reported in dogs with epiglottic retroversion [12]. These nodules may represent a form of tracheobronchopathia osteochondroplastica, which has been reported in the trachea of a dog [13].

References

1 Dennis, M.M., Ehrhart, N., Duncan, C.G. et al. (2006). Frequency of and risk factors associated with lingual lesions in dogs: 1,196 cases (1995–2004). *J. Am. Vet. Med. Assoc.* 228: 1533–1537.

2 Tafti, A.K., Hanna, P., and Bourque, A.C. (2005). Calcinosis circumscripta in the dog: a retrospective pathological study. *J. Vet. Med. A Physiol. Pathol. Clin. Med.* 52: 13–17.

3 Nanci, A. and Ten Cate, A.R. (2008). *Ten Cate's Oral Histology : Development, Structure, and Function*, 7e. St. Louis, Mo: Mosby Elsevier.

4 Menasce, L.P., Shanks, J.H., Banerjee, S.S., and Harris, M. (2001). Follicular lymphoid hyperplasia of the hard palate and oral mucosa: report of three cases and a review of the literature. *Histopathology* 39: 353–358.

5 Sweeney, C.R., Maxson, A.D., and Soma, L.R. (1991). Endoscopic findings in the upper respiratory tract of 678 thoroughbred racehorses. *J. Am. Vet. Med. Assoc.* 198: 1037–1038.

6 Lucke, V.M., Pearson, G.R., Gregory, S.P., and Whibread, T.J. (1988). Tonsillar polyps in the dog. *Small Anim. Pract.* 29: 373–379.

7 Kardon, D.E., Wenig, B.M., Heffner, D.K., and Thompson, L.D. (2000). Tonsillar lymphangiomatous polyps: a clinicopathologic series of 26 cases. *Mod. Pathol.* 13: 1128–1133.

8 Miller, A.D., Alcaraz, A., and McDonough, S.P. (2008). Tonsillar lymphangiomatous polyp in an adult dog. *J. Comp. Pathol.* 138: 215–217.

9 Cornegliani, L., Gracis, M., Ferro, S. et al. (2011). Sublingual reactive histiocytosis in a dog. *J. Vet. Dent.* 28: 164–170.

10 Katou-Ichikawa, C., Izawa., T., Sasai, H. et al. (2016). Multiple histiocytic foam cell nodules in the tongue of miniature Dachshund dogs. *Vet. Pathol.* 53: 625–628.

11 Meuten, D.J. (2002). *Tumors in Domestic Animals*, 4e. Ames, Iowa: Iowa State University Press.

12 Skerrett, S.C., McClaran, J.K., Fox, P.R., and Palma, D. (2015). Clinical features and outcome of dogs with epiglottic retroversion with or without surgical treatment: 24 cases. *J. Vet. Intern. Med.* 29: 1611–1618.

13 Sellon, R.K., Johnson, J.L., Leathers, C.W. et al. (2004). Tracheobronchopathia osteochondroplastica in a dog. *J. Vet. Intern. Med.* 18: 359–362.

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10.2 Tumor-Like Proliferative Lesions of the Tooth-Bearing Regions of the Jaw

10.2.1 Gingival Hyperplasia and Focal Fibrous Hyperplasia

Gingival hyperplasia is a common, non-neoplastic lesion in multiple animal species, but is most often identified in older dogs and cats. Gingival hyperplasia is a benign process that gives rise to a spectrum of lesions. These lesions vary with respect to cause, amount of inflammation, and proportions of proliferative gingival tissue (epithelial vs. fibrous tissue). Gingival hyperplasia in dogs is most often a nodular, idiopathic form of gingival overgrowth characterized by dense fibrous connective tissue with relatively little epithelial hyperplasia or inflammation. The term "focal fibrous hyperplasia" has been proposed for these lesions [14]. Focal fibrous hyperplasia (FFH) has been borrowed from human oral pathology and is defined as a reactive, *subepithelial fibrosis* resulting from chronic trauma [15]. However, the authors believe that *gingival hyperplasia* is a more versatile term that encompasses a range of reactive/inflammatory forms of gingival enlargement (e.g. subepithelial fibrosis, FFH).

Clinicians and pathologists are frequently tasked with distinguishing this common oral lesion from several more serious neoplastic lesions. Gingival hyperplasia can be the result of trauma, infection/inflammation (periodontitis, gingivitis), the administration of certain drugs (diltiazem, cyclosporine, phenytoin, amlodipine) or may be idiopathic (Figure 10.14). Gingival hyperplasia can be focal, multifocal to generalized and may involve the mandibular or maxillary gingiva.

Grossly, gingival hyperplasia manifests as a smooth to irregular nodular proliferation of the gingiva, usually affecting the free gingiva that cuffs the base of the tooth. The proliferative tissue is often asymmetrical and focal, but can be diffuse and circumferential around the entire tooth. In severe lesions, the tooth crown may become partially to completely entrapped in the proliferative tissue. Gingival hyperplasia should be differentiated from other nodular to diffuse proliferative processes of the gingiva such as fibromatous epulis of periodontal ligament origin (FEPLO)/ peripheral odontogenic fibroma (POF), canine acanthomatous ameloblastoma, and squamous cell carcinoma. Therefore, biopsy for histologic examination is strongly encouraged even when benign hyperplasia is suspected.

Histologically, the lesion exhibits, to varying degrees, hyperplasia of both the mucosal epithelium and the subepithelial lamina propria. The mucosal epithelium may be simply thickened (acanthotic) or may have a complicated sieve-like appearance with numerous long anastomosing epithelial rete pegs extending into the proliferative subepithelium (plexiform hyperplasia). The latter pattern of gingival epithelial hyperplasia can contribute significantly to mass effect and frequently occurs with inflammation. There is often asymmetry of the epithelium between the outer gingival epithelium and sulcular epithelium that faces the tooth. The outer gingival epithelium is more likely to demonstrate acanthosis with mild keratinization. The sulcular epithelium is more likely to demonstrate erosion, plexiform hyperplasia of rete pegs, and/or association with inflammation.

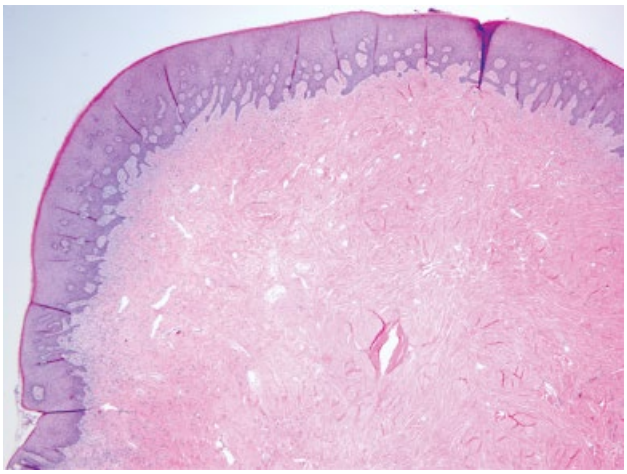


Figure 10.14 Diffuse gingival hyperplasia, eight-year-old German shepherd dog. Lesion associated with chronic cyclosporine administration. *Source:* S. Siso, U.C. Davis.

The fibrous subepithelium has numerous blood vessels and large bundles of extracellular collagen matrix. Subepithelial fibroblasts are individualized and sparse, reminiscent of histologically normal tissue ("just too much of it"). Often, a band of inflammatory cells (lymphocytes and plasma cells) is present at the epithelial/subepithelial interface. If the lesion is eroded or ulcerated, the inflammation will include neutrophils. The proliferative subepithelial component needs to be differentiated histologically from FEPLO/POF while the proliferative epithelium needs to be distinguished from oral squamous

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(a)



(b)

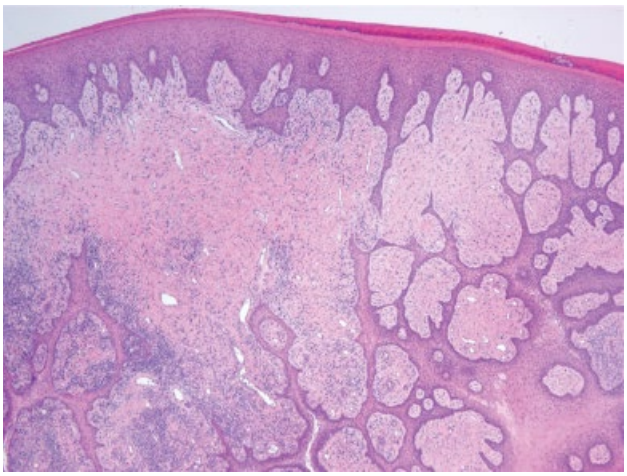


Figure 10.15 Histological images of gingival hyperplasia, seven-year-old English Bulldog. (a) Gingival hyperplasia is histologically characterized by the non-neoplastic proliferation of both the mucosal epithelium and submucosal mesenchyme. The proliferative epithelium demonstrates anastomosing rete pegs. (b) Gingival hyperplasia is often accompanied by subepithelial aggregates of infiltrating lymphocytes and plasma cells (gingivitis/stomatitis). Note the pronounced interanastomosing rete pegs.

cell carcinoma (OSCC) and canine acanthomatous ameloblastoma (CAA). Diffuse gingival hyperplasia in Boxer dogs often includes multiple foci of FEPLO/POF (see Figure 10.15).

10.2.2 Craniomandibular Osteopathy

Craniomandibular osteopathy (CMO), or *lion jaw*, is a self-limiting, idiopathic, non-neoplastic, hyperostotic lesion of dogs that concurrently affects multiple bones of the head including the mandible (body/ramus), temporal, occipital, and less often, the maxillary bones. The lesions can be unilateral or bilateral. The tympanic bullae

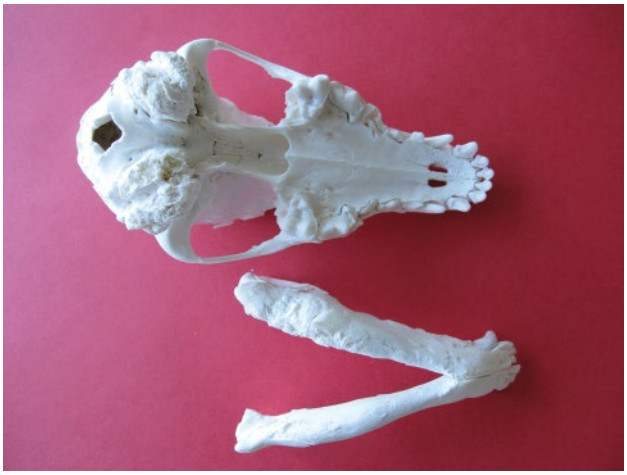


Figure 10.16 Skull and mandible demonstrating the proliferative bone of craniomandibular osteopathy, West Highland white terrier. *Source:* B.G. Murphy, U.C. Davis.

are often severely thickened (Figure 10.16). The lesion is most commonly diagnosed in West Highland White and Scottish terriers, but has been identified in other breeds. CMO is a young-dog disease, usually recognized at four to seven months of age and manifests as dysphagia or an inability/difficulty in opening the mouth [16]. Affected animals have intermittent to continuous enlargement of the affected bones until about 12 months of age [17]. A genetic cause is suspected.

Histologically, CMO is characterized by proliferative bone extending from both the periosteal and endosteal surfaces. The bone is comprised of interanastomosing sheets and is a combination of both woven and lamellar bone. Lesions may have evidence of fibrosis along with concurrent bone production and lysis (bone remodeling), and share some features with Paget's Disease of Bone in human patients. Oddly, some degree of mixed inflammation may also be present within the remodeling bone (lymphocytes, plasma cells and neutrophils).

CMO has characteristic radiographic features, which coupled with the signalment and clinical signs, may serve to adequately establish the diagnosis and preclude biopsy. As a result, this lesion tends to be rarely seen by pathologists. Although the disease is generally self-limiting, some dogs may be euthanized due to progressive anorexia or uncontrollable jaw pain. These animals may be submitted for necropsy examination, affording pathologists the opportunity to study this fascinating and idiopathic osteoproliferative disease (see Figure 10.17).

Dogs with metastatic thoracic neoplasia may also be affected by hypertrophic osteopathy (HO). Although HO typically affects the distal appendicular skeleton, one of the authors (BGM) has seen HO-affected animals with mandibular periosteal hyperplasia that radiographically and grossly mimics CMO to some degree (Figure 10.18).

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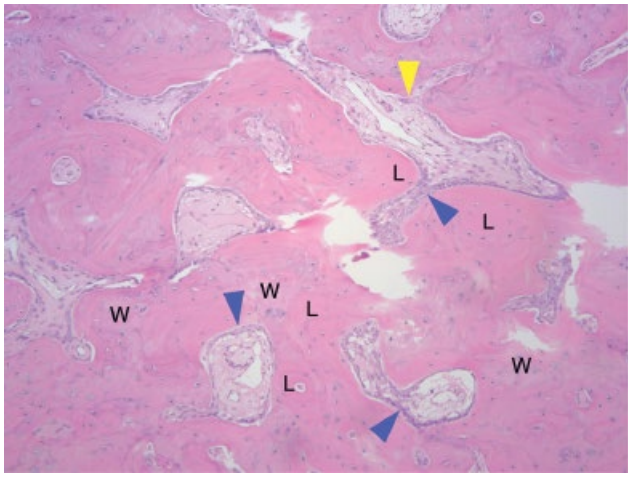


Figure 10.17 Histologic image of craniomandibular osteopathy, mandible, one-year-old West Highland White terrier dog. In this lesion, the mandible is focally replaced by contiguous sheets of woven (W) and lamellar (L) bone. Ongoing bone remodeling is evident and is characterized by palisades of hypertrophied osteoblasts (blue arrowheads) and rare osteoclasts (yellow arrowhead).

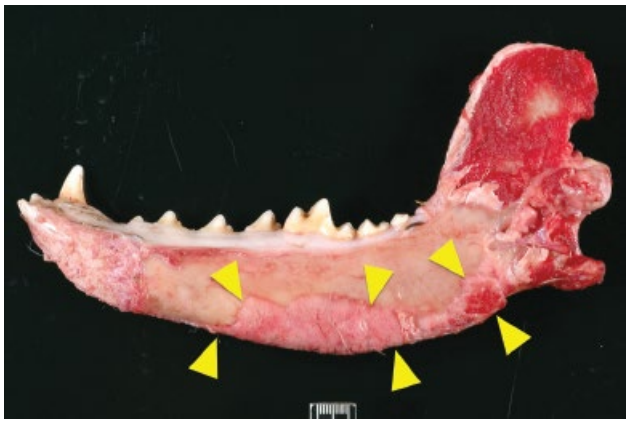


Figure 10.18 Gross image of mandibular hypertrophic osteopathy, nine-year-old Great Pyrenees dog. This dog had an appendicular osteosarcoma that had metastasized to the lungs. In this image, proliferative periosteal bone is evident along the ventral surface of the body of the mandible (yellow arrowheads). This proliferative and non-neoplastic lesion mimics some of the features of craniomandibular osteopathy. *Source:* M. Highland, U.C. Davis.

10.2.3 Peripheral Giant Cell Granuloma

Peripheral giant cell granuloma (PGCG), formerly called giant cell epulis, has been identified in the gingiva of dogs, cats, and cattle. Grossly, PGCG are a sessile to pedunculated soft-pink to purplish-blue mass with a smooth, ulcerated, or papillomatous surface [18]. PGCG is generally not thought to be connected to the underlying bone and is therefore distinct from giant cell tumor of bone [17]. However, the authors have seen cases of

(a)



(b)

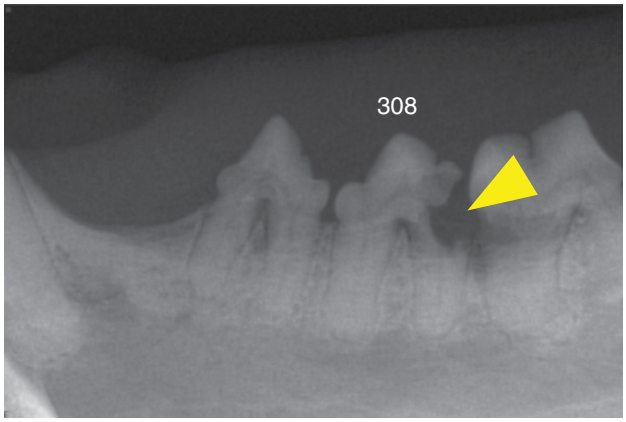


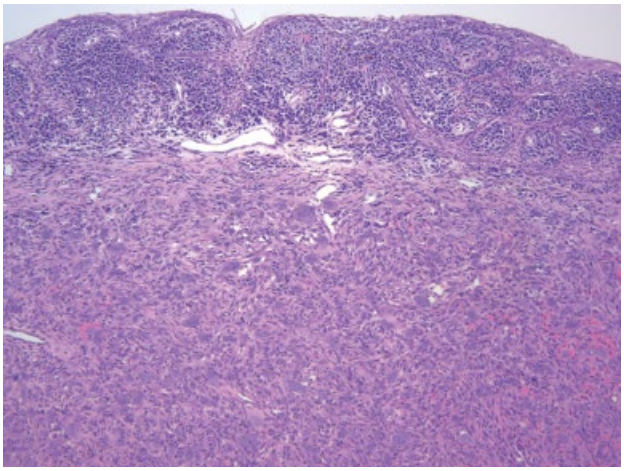
Figure 10.19 Clinical and radiographic images of peripheral giant cell granuloma (PGCG), 12-year-old Maine Coon cat. (a) Grossly, this PGCG is associated with mandibular premolar 308, exophytic and reddened. (b) The PGCG lesion is associated with focal tooth resorption (308) and loss of the alveolar bone (yellow arrowhead). This lesion had been present for approximately one year. *Source:* K. Feigin, Veterinary Dental Services.

PGCG in cats and dogs that have been associated with bone loss and/or tooth resorption (see Figure 10.19).

These interesting lesions are comprised of two cell populations, mononuclear spindle-shaped mesenchymal cells and intermixed multinucleate giant cells (MNGC). Although the relative proportion of these two cell types can vary, both are distributed amidst a collagenous matrix with variable osteoid deposition, hemorrhage, and hemosiderin [19]. The giant cells are scattered haphazardly and *are not* organized into true granulomas centered upon a causative agent (e.g. microbe/foreign material) (Figure 10.20). The MNGC have been demonstrated to be TRAP positive (tartrate-resistant acid phosphatase), consistent with an osteoclast origin [20].

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(a)



(b)

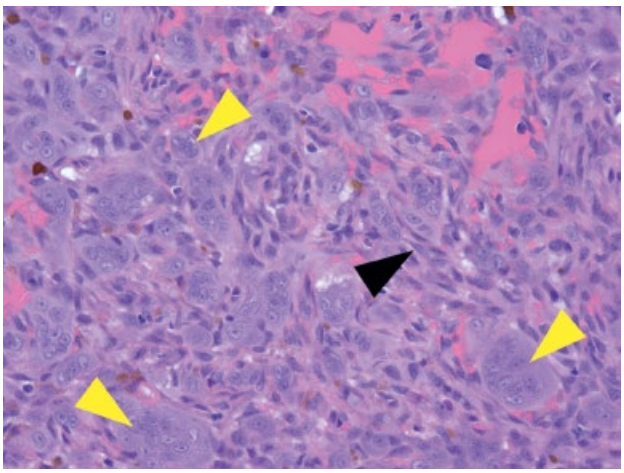


Figure 10.20 Histologic images of peripheral giant cell granuloma, oral mucosa, buccal to right maxillary premolar 108, two-year-old Labrador Retriever dog. (a) The PGCG is characterized by large numbers of multinucleate giant cells (MNGC) and intermixed mononuclear spindle cells within the subepithelium. The overlying mucosal epithelium has proliferative rete pegs and a band of infiltrating lymphocytes and plasma cells at the PGCG-epithelial interface. (b) MNGC (yellow arrowheads) have variable numbers of nuclei while the spindle cells form streams (black arrowhead). Brown hemosiderophages are scattered throughout the lesion.

In humans, giant cell granulomas are considered to be reactive and non-neoplastic localized proliferations of mononuclear cells and osteoclast-type giant cells that occur outside of bone in the alveolar and gingival mucosa [18]. In humans, PGCG is thought to occur as a result of local irritation by dental calculus or other chronic irritants. The authors of this textbook suspect that physical injury to the gingiva, often traumatic malocclusion, contributes to the development and recurrence of PGCG in animals. Any apparent source of gingival injury/trauma must be addressed to prevent recurrence. Traumatic injury also accounts for the presence of hemosiderin and frequent ulceration associated with these lesions.

In a group of 16 dogs with PGCG, only two of the lesions recurred after marginal excision [20]. In cats, PGCG are perhaps a bit more aggressive, with a faster growth and recurrence rate than the fibromatous epulides [21]. In a study examining 26 canine lesions, cellular pleomorphism or nuclear atypia were not identified, and while the mitotic index varied, it was not associated with biological behavior [20]. Some investigators have identified a *collision lesion* with features of both PGCG and FEPLO [20]. These collision lesions may simply represent PGCG developing within a traumatized area of a pre-existing FEPLO/POF.

Box 10.1 Differential Diagnoses for Peripheral Giant Cell Granuloma

Giant cell tumor of bone
Osteosarcoma (giant cell)
Giant cell sarcoma

Whether giant cell lesions of the gingiva/jaw represent a reactive or neoplastic process is controversial. Currently, both reactive and neoplastic lesions are recognized, although pathologists still must grapple with distinguishing a benign PGCG from one of the giant cell tumors. Although we have identified PGCG lesions associated with bone lysis, in most cases, PGCG is limited to the gingiva, whereas the various tumors with giant cells are expected to involve bone and exhibit aggressive clinical behavior.

10.2.4 Fibromatous Epulis of Periodontal Ligament Origin (FEPLO)/ Peripheral Odontogenic Fibroma (POF)

This common canine lesion was previously referred to by the non-specific term *epulis*, which is derived from Greek for "on the gum." A grossly similar, but histologically distinct neoplastic lesion, now known as canine acanthomatous ameloblastoma, was historically also referred to as an epulis. Use of the imprecise term epulis as a stand-alone name is now discouraged.

There is perhaps no single lesion in veterinary oral pathology that has been as controversial as FEPLO. This common, histologically interesting, clinically relevant, and problematic gingival lesion has had a contentious and convoluted history (Figure 10.21). For almost 40 years, investigators have struggled with both the *nature and the name* of this entity. Today, tension remains between those who favor the term FEPLO versus those who favor the

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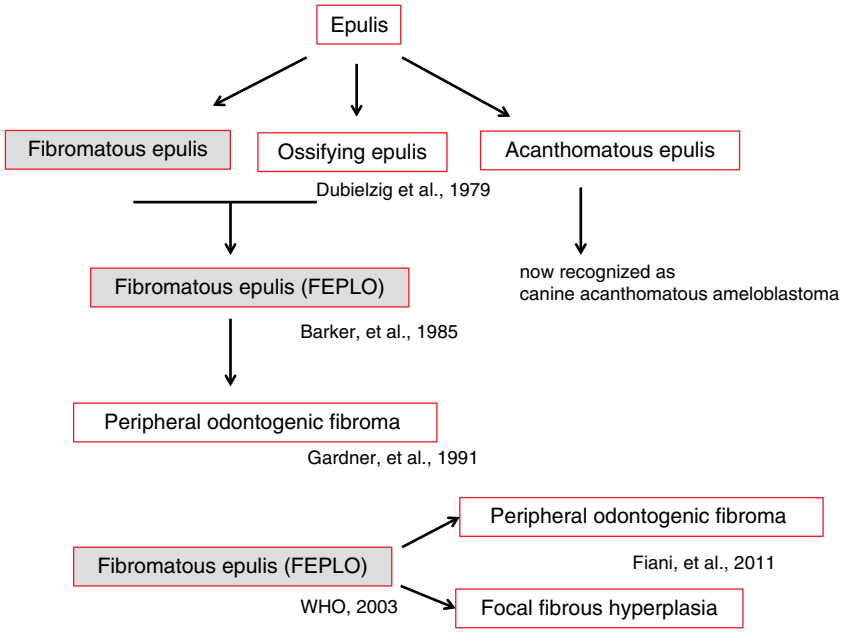


Figure 10.21 Evolution of FEPLO/POF terminology.

name POF. This controversy revolves around the lesion's proposed *histogenesis* and *pathogenesis*:

1) **Histogenesis** – is the lesion derived from the periodontal ligament (PDL), alveolar crest, or some other tooth-associated mesenchyme?
2) **Pathogenesis** – does the lesion represent a form of reactive hyperplasia or is it neoplastic?

Some might argue that in the end, it really does not matter what we call this lesion, after all, it's just a name. Others argue that it does matter – implicit within the name is the lesion pathogenesis, which dictates both prognosis and, indirectly, the treatment plan. To be clear, the authors of this textbook support the interpretation that this lesion (i) *derives from the PDL/gingival ligament at the site of gingival attachment to the tooth*, (ii) *the pathogenesis involves a form of reactive hyperplasia*, (iii) the canine lesion is not histologically analogous to the human lesion POF.

Some investigators have proposed that FEPLO represents two separable entities, and as a result, have proposed splitting FEPLO into two "distinct" lesions – the POF which was ascribed a neoplastic pathogenesis, and focal fibrous hyperplasia (FFH), thought to be a reactive/hyperplastic lesion [14, 22]. The diagnostic basis for the separation was purported to be the presence (or absence) of ribbons of odontogenic epithelium (OE) – if present the diagnosis was POF (neoplastic), if absent, FFH (reactive). The authors of this textbook contend that this taxonomy is inadequate to account for the histological variation of these lesions and does not appropriately weight the central diagnostic feature of this canine lesion – the proliferative mesenchyme itself.

Box 10.2 Problems With the Terms FEPLO and POF

Neither of the terms FEPLO or POF are entirely appropriate …

Peripheral odontogenic fibroma

- "Fibroma" implies a neoplastic pathogenesis
- "Odontogenic" implies that it makes or is derived of tooth elements, yet this lesion relates more to the periodontium than it does to the tooth
- POF in dogs is not directly histologically analogous to POF in humans

Fibromatous epulis of periodontal ligament origin

- FEPLO retains the term "epulis," which is antiquated and many consider moderately objectionable
- FEPLO implies that the lesion originates from the PDL, although *gingival ligament* origin is probably more accurate

As a result, the authors of this textbook (along with many others) are not satisfied with either of the terms FEPLO or POF. Although a change in the name of this common and problematic lesion is in order, we contend that enough gasoline has already been thrown on this fire. A working group of veterinary pathologists and clinicians interested in oral disease needs to meet and collectively establish a new name for this important lesion. Here, we will refer to this lesion as FEPLO/POF.

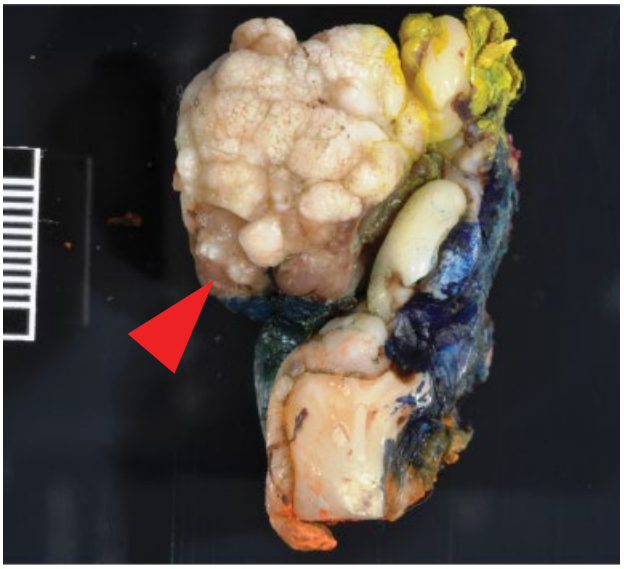
10.2.4.1 Clinical Presentation and Gross Pathology

FEPLO/POF is a common lesion in dogs of any age, although it is generally found in dogs older than three years

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of age. The authors have identified histologically similar lesions in cats and camelids. FEPLO/POF arises from the tooth-associated gingiva, with an anatomic predisposition for the rostral maxilla and caudal mandible. The lesion can vary markedly in size and gross appearance, often masquerading grossly as a locally aggressive neoplasm, particularly when the mass is broad-based and/or causes tooth displacement. FEPLO/POF typically manifests as an exophytic, white to pale-pink, smoothly rounded or roughened to cauliflower-like mass. The lesion is usually covered with intact gingival epithelium, but can be ulcerated if subjected to trauma (see Figure 10.22). Downward growth into the PDL space with destruction of the jawbone is not a feature of FEPLO/POF. While the lesion arises from tissue of the PDL, *it does not arise within or progress to involve the PDL space*. Importantly, FEPLO/POF can occur *either* as a solitary lesion or it can be multifocal. Boxer dogs with diffuse gingival hyperplasia often have concurrent, multifocal FEPLO/POF lesions scattered among the proliferative gingiva (Figure 10.23). This biology supports a reactive/ hyperplastic pathogenesis, not a neoplastic pathogenesis.

(a)



(b)

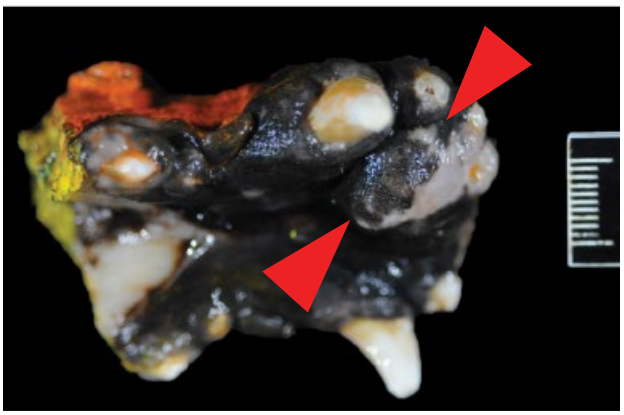


Figure 10.22 Gross images of FEPLO/POF lesions. (a) An exophytic, multinodular, pale lesion (red arrowhead) arises from the buccal gingiva adjacent to the maxillary P2–P4 teeth, 10 year old Doberman Pinscher dog. This lesion had been surgically excised twice prior to the partial maxillectomy surgery. *Source:* R. Translavina, U.C. Davis. (b) A smooth, partially pigmented sessile mass (red arrowheads) is lingual to the incisor teeth, 12 year old Labrador Retriever dog. *Source:* K. Watson.



Figure 10.23 Gross image of mandibular gingival hyperplasia with interspersed multifocal FEPLO/POF lesions, seven-year-old Boxer dog. This non-neoplastic proliferative lesion partially entraps the incisor and canine teeth. Generalized gingival hyperplasia, common in certain dog breeds, often has histological evidence of FEPLO/POF. *Source:* J. Winer, Dentistry Oral Surgery Service, U.C. Davis.

10.2.4.2 Histological Features

The FEPLO/POF lesion has three concurrent histological features: (i) variably dense and proliferative mesenchymal cells embedded in a collagenous stroma reminiscent of PDL/gingival ligament, (ii) variable amounts of odontogenic epithelium (OE), arranged as scattered follicles or anastomosing plexiform ribbons, and (iii) islands, lakes, or interlinking trabeculae of variably mineralized cemento-osseous matrix. Although it is most often a tripartite lesion, FEPLO/POF is foremost *a lesion of proliferative mesenchymal cells with features of PDL-derived fibroblasts*. The bulk of the lesion is fibrous mesenchyme (at least initially, before extensive deposition of mineralized matrix).

The presence of extensive fibrous mesenchyme is the minimal criterion and must be present in the FEPLO/POF lesion. It is the opinion of the authors of this textbook that it is possible to have a FEPLO/POF lesion which does not demonstrate OE or cemento-osseous matrix. Stated another way, it is possible to have *sections* of a candidate FEPLO/POF lesion which demonstrate only the characteristic mesenchyme, but not the epithelium

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or matrix. This interpretation is in alignment with the 2003 veterinary WHO fascicles [17] but is in conflict with the definition put forth by Fiani et al. [14]. The authors of this textbook believe that the diagnosis of FEPLO/POF is dependent upon the identification of PDL-like mesenchymal stroma, while the human POF lesion "pivots" on the presence or absence of OE. This is a critical diagnostic difference.

The *fibrous mesenchyme* is comprised of regular and densely arranged, small, angular, kite-shaped to stellate fibroblast-like cells that are embedded within a collagenous stroma reminiscent of the PDL/gingival ligament. The matrix is abundant, *finely fibrillar* collagen with regularly positioned, dilated, empty blood vessels. The collagen fibers are distinct from the large, coarse collagen fibers of the normal subepithelium of the gingiva (Figures 10.24 and 10.25). These histologic features are unique and generally unlike other fibrous mesenchymal tissues: subepithelial mucosal connective tissue, reparative fibrous tissue (scar), immature granulation tissue, fibroma, or fibrosarcoma. However, the pathologist should be wary, as inflammation and other pathologic processes can mask or distort the appearance of the proliferative mesenchyme.

Islands of cementum/bone (aka cemento-osseous matrix or COM) within a FEPLO/POF lesion arise focally or multifocally from areas of fibrillar matrix deposition within the exophytic gingival mass. Some of the more chronic lesions have relatively large areas of organized intralesional COM that can connect to the underlying jawbone. We believe that this process accounts for

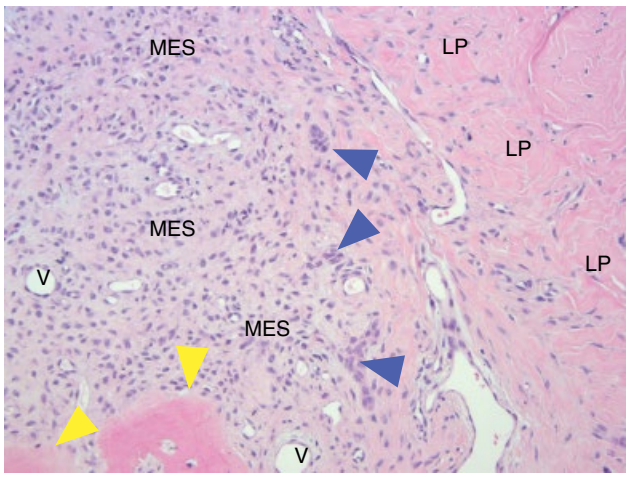


Figure 10.25 Histologic image of FEPLO/POF lesion, 14-year-old Border terrier dog. In this image, the proliferative mesenchyme with angular cytological features (MES), unmineralized cemento-osseous matrix (yellow arrowhead), islands of odontogenic epithelium (OE) (blue arrowheads), open vessels (V), and adjacent histologically normal lamina propria (LP) are evident. Note the histologic difference between the collagen bundles in the lesional mesenchyme (MES) and the adjacent normal LP.

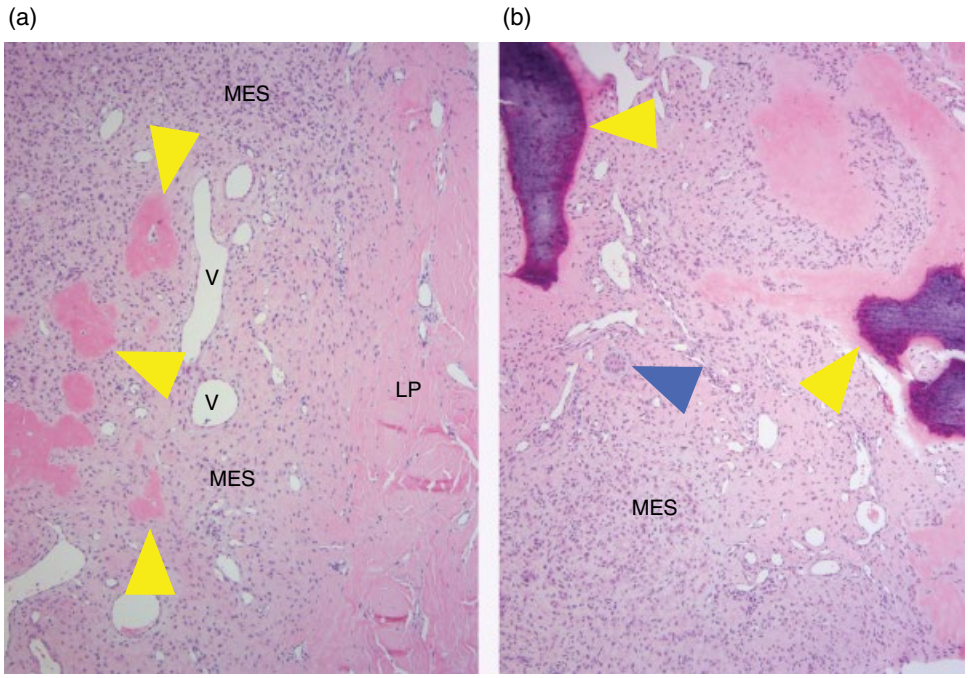


Figure 10.24 Histologic images of FEPLO/POF lesions. (a) In this image, the proliferative mesenchyme (MES), unmineralized cemento-osseous matrix (yellow arrowhead), open vessels (V) and normal adjacent lamina propria (LP) are evident. (b) In this image, partially mineralized cemento-osseous matrix (yellow arrowheads), a follicle of odontogenic epithelium (OE) (blue arrowhead), and proliferative mesenchyme (MES) are evident.

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lesions that have continuity with underlying jawbone and should not be mistaken for invasive behavior.

The OE embedded within the FEPLO/POF is most often arranged as round follicles or plexiform ribbons only a few cells thick. Although not usual, the basal cell layer may have cardinal features of ameloblasts. Many pathologists have puzzled over the fact that the OE within the FEPLO lesion often directly connects to the overlying hyperplastic gingival epithelium. This is consistent with the concept that the proliferative tissue arises from the fibrous tissue that attaches the gingiva at the neck of the tooth. It is worth remembering that epithelium lining the sulcular surface of the gingiva is odontogenic in origin – it is derived from reduced enamel epithelium prior to eruption of that tooth.

10.2.4.3 Clinical Features

Prognostically, neither ossification nor amount of OE within the lesion seems to have any effect on outcome (likelihood of recurrence, rate of growth). In the experience of the authors, local excision alone (with minimal alveolar margin removal) is generally curative. This suggests that the location of origin of FEPLO/POF initiates at the site of gingival attachment. Whether we consider these fibers and associated mesenchymal cells as PDL or as gingival fibers is a matter of viewpoint. Because the fibers of FEPLO/POF anchor at the neck of the tooth, extraction of the associated tooth or *en bloc* excision of the mass with surrounding structures may be necessary for complete excision, particularly the fibrous gingival attachment.

10.2.5 Proliferative Fibro-Osseous Lesions of the Oral Cavity and Jaws

Proliferative fibro-osseous lesions (PFOL) are a group of somewhat poorly defined, benign entities with overlapping clinical, gross, and histological features. PFOL of the jaws are characterized by replacement of normal bone by fibrous tissue containing a newly formed mineralized product [23]. This group includes intraosseous lesions like *ossifying fibroma (*OF*)* and *fibrous dysplasia (*FD*)*. Some investigators include *osteoma* in this taxonomic group as there is some suspicion that FD, OF and osteoma form a pathologic continuum. We have purposefully excluded oral fibrous lesions that generally lack aggregates of mineralized bone-like tissue (e.g. fibrosis, fibroma, and fibrosarcoma) from this group.

As the term *proliferative fibro-osseous lesion* implies, these various entities are comprised of fibrous mesenchyme (which may be dense and highly cellular) with varying amounts of interspersed bone-like tissue (note the intentional equivocation in the term "bone-like tissue"). The histogenesis of the fibrous mesenchyme, that is, the actual tissue of origin, is much debated and will continue to be debated until future ancillary tests unequivocally implicate a specific tissue type. The precise histogenesis of PFOL is not known but is suspected to be bone-associated. Whether PFOL represent a form of neoplasia, reactive hyperplasia, dysplasia, or other pathology also remains an open question. However, it is important to remember that these lesions *are not aggressive sarcomas*.

In some cases, differentiating histologically between the various PFOL can be challenging. Small, suboptimal biopsy specimens (fragmented, inadequate decalcification, crush/procurement artifact) can further complicate matters. In such situations, misclassification is all but inevitable. Ancillary clinical information such as the signalment, history, gross appearance and imaging features should be considered before rendering a morphologic diagnosis [24]. At present, this dark corner of oral pathology remains a work in progress.

10.2.5.1 Ossifying Fibroma

OF is a rare solitary, benign, slowly progressive, intraosseous neoplasm of the jawbone that has been described in the maxilla and mandible of horses, dogs, cats, a rabbit, llama, and sheep. OF has been most often recognized in young horses, occurring in the rostral mandible in animals less than a year of age [16], referred to as *equine juvenile mandibular OF* [25] (Figure 10.26). OF may be associated with loose teeth and may interfere with mastication.

OF is a firm, non-painful, expansile, well-demarcated lesion that expands and distorts the jawbone. In affected human patients, OF arises from the tooth-bearing regions of the jaw and forms a painless expansion of the buccal or lingual plates of the affected jaw bone [18]. In the maxilla, OF can be associated with nasal obstruction and epistaxis, while in the orbit OF can result in proptosis of the eye. Radiographically, "immature" OF lesions may be radiolucent, becoming progressively denser in time. OF have a w*ell-circumscribed, sharply defined border*. As a result of the circumscribed margin, these lesions in human patients can often be "shelled out" from the surrounding jaw tissue [18] and conservative, marginal excision often results in cure.

Histologically, OF has been simply described as "fibrous tissue with bone in it." The lesion has a well-delineated margin, may be encapsulated, and is comprised of highly cellular "fibroma-like" mesenchyme with interspersed islands and spicules of bone at varying stages of maturity (woven to lamellar bone). Cellularity of the spindle cell population can vary from lesion to lesion and small to moderate numbers of osteoclasts may be distributed throughout. The spindle-shaped mesenchymal cells generally have bland cytological features,

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(a)



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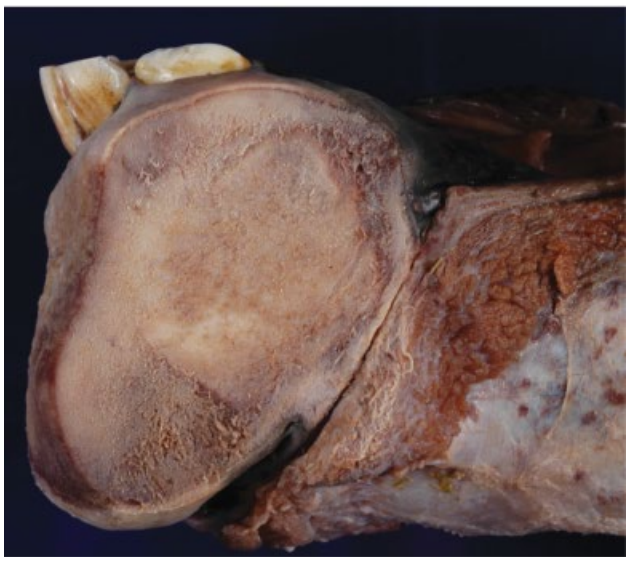
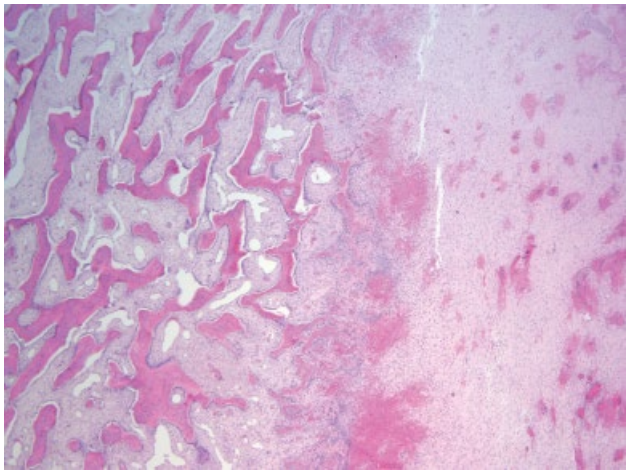


Figure 10.26 Gross images of mandibular ossifying fibroma (OF), seven-month-old Quarter horse colt (*equine juvenile mandibular OF*). A 6×4×4 cm, well-demarcated, ulcerated, bony mass expands the rostral mandible and partially entraps the incisor teeth. Sectioned (a) rostral and (b) lateral views. *Source:* S. Kubiski, U.C. Davis.

(a)



(b)

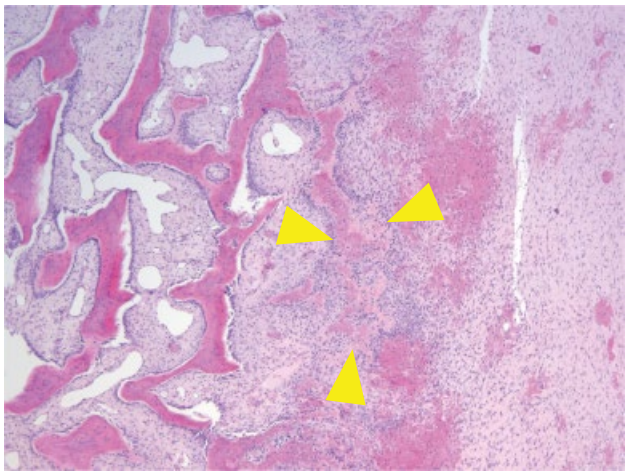


Figure 10.27 Histologic images of ossifying fibroma (OF), seven-month-old Quarter horse colt (same lesion as Figure 10.26). (a) The right aspect of this image is comprised of proliferative mesenchymal (fibrous) tissue with numerous congested vessels and interspersed hemorrhage. The left aspect has islands and interlinking trabeculae of well-differentiated woven bone suspended in fibrous mesenchyme. The more well-differentiated portion of this OF lesion is reminiscent of an osteoma. (b) At the interface of these two regions, new intramembranous bone formation is evident (yellow arrowheads) surrounded by palisading osteoblasts.

very few (if any) mitotic figures, and lack cytological evidence of malignancy [24]. Some investigators have argued that OF may arise from the PDL [25], however at present, the histogenesis of OF remains an unsettled topic.

Interspersed throughout the fibrous stroma are numerous mineralized bony structures and/or rounded, isolated islands of cementum, referred to as *cemental spheroids*. Islands of bone are primarily woven (at least initially) and form spicules and variably thick, interlinking trabeculae. The bone in OF appears to form intramembranously through osseous metaplasia. The amount of bone that is suspended amidst the fibrous tissue can markedly vary from region to region and with lesion maturity (Figure 10.27). Bony trabeculae may be oriented perpendicular to the lesional surface, forming a radiating array. Intralesional cementum is generally more basophilic than osteoid and may have multiple

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basophilic cementing lines or swirling pink/blue-staining regions. The presence of cemental spheroids suggests the diagnosis of *cemento-ossifying fibroma* (COF: aka cementifying fibroma). It is not unusual for both bone and cementum to be concurrently present in a lesion. In human patients, the terms OF and cementifying fibroma are considered to be essentially synonymous [15] (see Figures 10.28 and 10.29).

Differentiating histologically between FD and OF can be a diagnostic challenge [15, 24]. The presence of palisading osteoblasts rimming the embedded spicules of bone was previously used as a diagnostic criterion separating FD and OF. However, this feature is no longer recognized as diagnostically useful [24], as the bone in OF may or may not demonstrate this feature. Some pathologists believe that while OF lesions contain actual differentiated bone or cemental tissue, in FD, the lesional bone is "in a less differentiated state" (so-called proto-bone). Spicules of proto-bone are thin and have a feathery, poorly-defined edge. If the pathologist asks the question "I think this is bone, but I am not certain," it may be proto-bone. However, the differentiated state of bone in these two PFOLs is not universally accepted as a diagnostic feature. Gross features of these lesions (invasiveness) and imaging can be useful, as OF should have a sharply delineated/circumscribed lesional margin, while FD does not [15.24]. Radiographs play a key role in the diagnosis of OF (and FD) and should not be ignored.

Box 10.3 Differential Diagnoses for OF/FD

Ossifying fibroma/cemento-ossifying fibroma
Fibrous dysplasia
Osteoma
Osteosarcoma (low grade)
Fibrous osteodystrophy
Multilobular sarcoma of bone
Osteomyelitis
FEPLO/POF

10.2.5.2 Fibrous Dysplasia

FD is an odd PFOL that is histologically similar to OF. As the name implies, FD is currently classified as a *dysplastic* rather than *neoplastic* process and although it can be locally destructive, FD is generally self-limiting. FD is rarely identified in the jawbones of animals, but has been reported as a focal to multifocal lesion in the jawbones of young horses, dogs, and domestic cats. One of the authors (BGM) has identified several cases in the canine zygomatic bone.

The hereditary pathogenesis of FD is relatively well-established in humans, occurring as a result of an activating mutation in a G-protein leading to abnormalities of osteoblast differentiation [23]. FD is a component of the hereditary, polyostotic McCune Albright Syndrome [23]. In humans, FD lesions (also known as craniofacial FD)

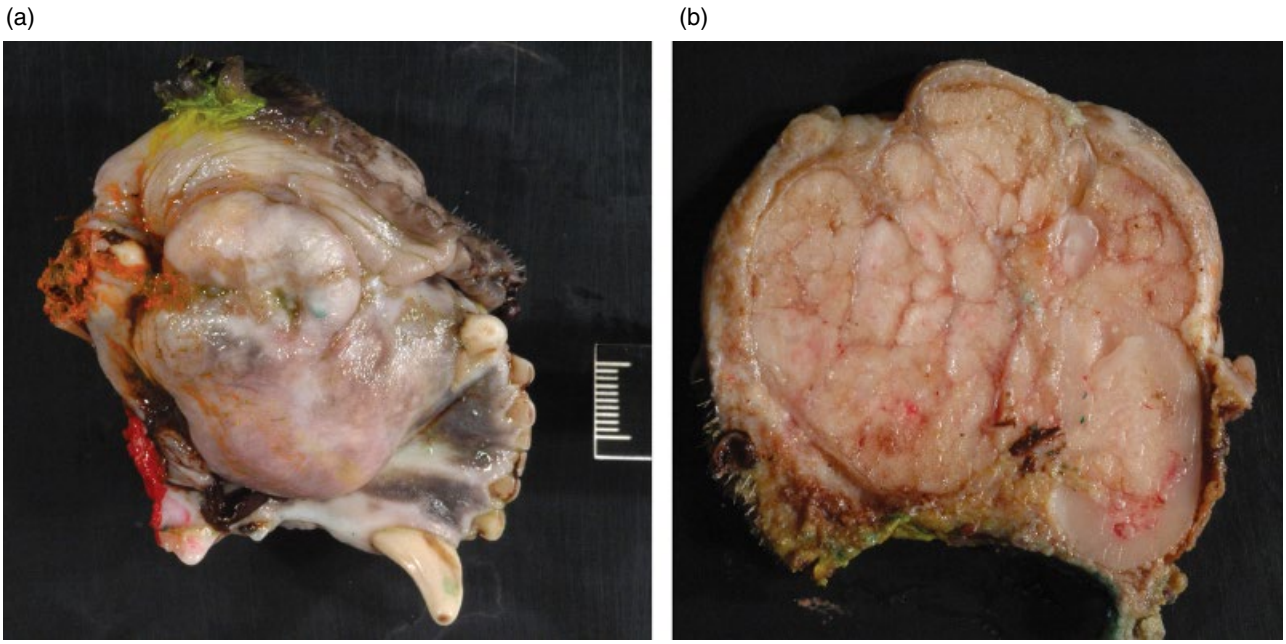


Figure 10.28 Gross images of cemento-ossifying fibroma (COF), eight-year-old Great Dane dog. (a) Surgical specimen (bilateral mandibulectomy) of a slowly progressive, expansile, bony, rostral mandibular mass. (b) Cross section demonstrates the obliteration of the left mandibular bone. Surgical excision of this lesion was curative. *Source:* C.N. Alarcon, U.C. Davis.

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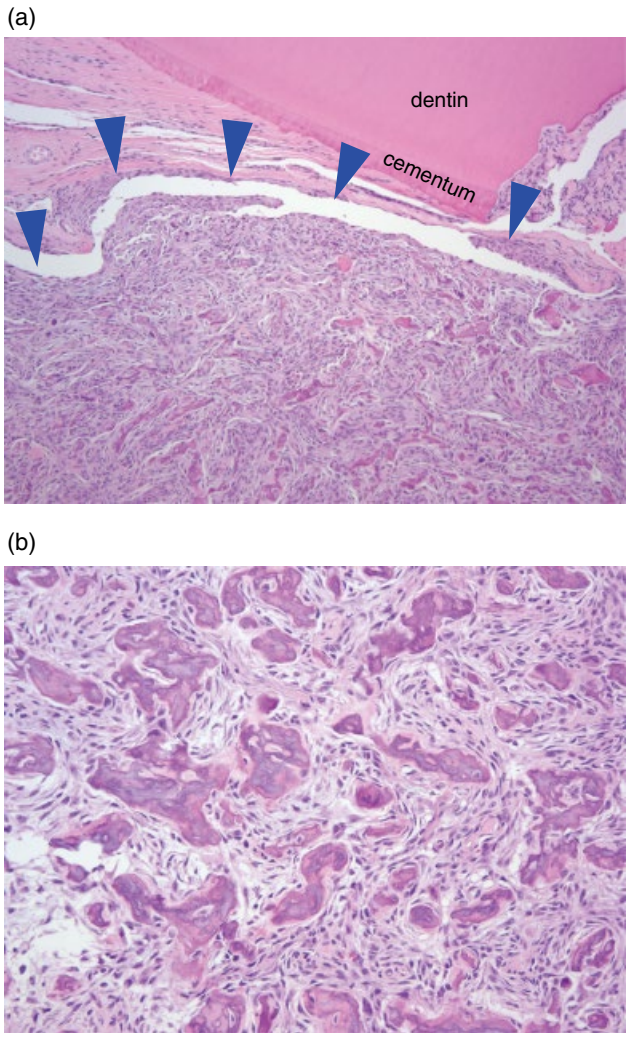


Figure 10.29 Histologic images of cemento-ossifying fibroma (COF), eight-year-old Great Dane dog (same lesion as Figure 10.28). (a) A portion of an incisor tooth (dentin/cementum) with tooth resorption is evident in the upper portion of the image; blue arrowheads delineate the margin of the COF (the clear cleft is an artifact of slide preparation). (b) The COF is characterized by unlinked irregular to rounded aggregates of basophilic cemento-osseous matrix suspended in proliferative mesenchyme lacking cytological atypia. *En bloc* surgical excision of this lesion was curative.

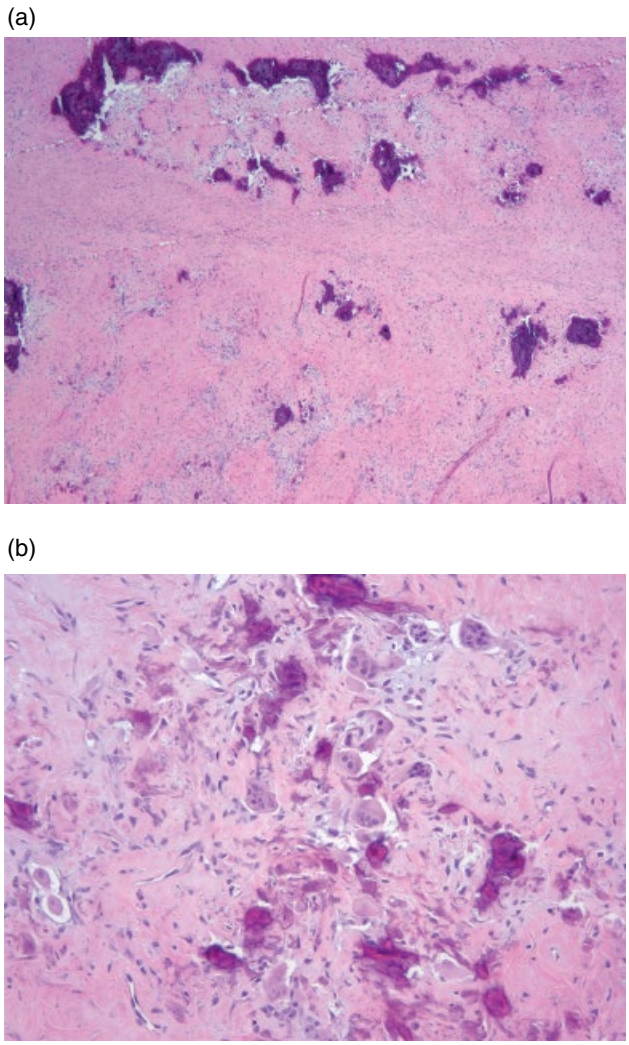


Figure 10.30 Histologic images of fibrous dysplasia (FD), nine-year-old Boston terrier dog, zygomatic bone. (a) Poorly delineated and variably mineralized spicules of "bone-like tissue" (proto-bone) are scattered amidst proliferative fibrous tissue (non-demineralized section). The lesion obliterates and replaces the zygomatic bone. (b) Large numbers of multinucleate osteoclasts are associated with the spicules of proto-bone. Proliferative mesenchymal cells have bland cytological features.

seem to stabilize with skeletal maturation, therefore, surgical intervention in younger patients is advised against [18]. There is no cure for FD in humans [23]. The pathogenesis of FD in veterinary species remains enigmatic.

Similar to OF, in FD, normal bone tissue is replaced with proliferative fibro-osseous stroma. Histologically, FD features sheets and streams of proliferating spindle cells with bland cytologic features. Mitotic figures are rare to absent. Individual or clusters of multinucleate giant cells (MNGC) (resembling osteoclasts) are a common finding [25]. It is the status of the intralesional osseous elements that remains persistently controversial. Some references describe these bone-like elements as interspersed, poorly organized, disoriented trabeculae of woven bone without obvious transition of cells to osteoblasts [16]. That is, it is the absence of a palisading rim of osteoblasts that differentiates FD from OF [26]. The 2017 edition of the WHO Classification of Head and Neck Tumors (human) states that "the osseous tissue is composed of irregularly shaped trabeculae of immature woven bone without osteoblastic rimming" [18]. However, the presence or absence of palisading osteoblasts is not universally accepted as a diagnostic feature distinguishing these two lesions (see Figure 10.30, and discussion for OF in Section 10.2.5.1 above) [24].

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The osseous component of FD has been likened to "Chinese characters" [18] lacking a functional (load-bearing) orientation [15]. The poorly differentiated bone in FD has also been referred to as "proto-bone" and may have a feathery, poorly delineated edge (see discussion for OF, above). The bony spicules of FD are often poorly mineralized; it may be possible to obtain non-decalcified histological sections demonstrating the degree of mineralization. Such non-decalcified sections should be compared to sections that have been face decalcified (see Appendix). Radiographically, FD lacks the circumscribed margin of OF and tends to blend imperceptibly into the surrounding uninvolved bone [18]. One of the authors (CB) has noted a strong association between tooth resorption and FD. Is it possible that both FD and tooth resorption share a common pathogenic mechanism involving activation of osteoclasts? The pathologist should consider clinical features of the lesion in addition to histopathology in arriving at the final diagnosis.

The triad of lesions, OF, FD and osteoma, share certain histological features. All three of these proliferative lesions arise from the membranous bones of the skull, and some pathologists consider these lesions to represent different stages of the same entity, osteoma representing the most differentiated extreme, FD the least differentiated, and OF somewhere between. OF most often occurs as an expansile lesion of the jaws, as opposed to osteoma, which typically arises from a sessile base on the surface of bone (periosteum) [26].

References

14 Fiani, N., Verstraete, F.J., Kass, P.H., and Cox, D.P. (2011). Clinicopathologic characterization of odontogenic tumors and focal fibrous hyperplasia in dogs: 152 cases (1995–2005). *J. Am. Vet. Med. Assoc.* 238: 495–500.

15 Regezi, J.A., Sciubba, J.J., and Jordan, R.C.K. (2012). *Oral Pathology: Clinical Pathologic Correlations*, 6e. St. Louis, Mo: Elsevier/Saunders.

16 Maxie, M.G. (2016). *Jubb, Kennedy, and Palmer's Pathology of Domestic Animals*, 6e. St. Louis, Missouri: Elsevier.

17 Head, K. W., Armed Forces Institute of Pathology (U.S.), American Registry of Pathology., & WHO Collaborating Center for Worldwide Reference on Comparative Oncology. 2003. Histological classification of tumors of the alimentary system of domestic animals. Published by the Armed Forces Institute of Pathology in cooperation with the American Registry of Pathology and the World Health Organization Collaborating Center for Worldwide Reference on Comparative Oncology, Washington, DC.

18 El-Naggar, A. K., Chan, J. K. C., Rubin Grandis, J., Takata, T., & Slootweg, P. J., International Agency for Research on Cancer. 2017. WHO classification of head and neck tumours. International Agency for Research on Cancer, Lyon.

19 Gardner, D.G. (1996). Epulides in the dog: a review. *J. Oral Pathol. Med.* 25: 32–37.

20 Desoutter, A.V., Goldschmidt, M.H., and Sanchez, M.D. (2012). Clinical and histologic features of 26 canine peripheral giant cell granulomas (formerly giant cell epulis). *Vet. Pathol.* 49: 1018–1023.

21 de Bruijn, N.D., Kirpensteijn, J., Neyens, I.J. et al. (2007). A clinicopathological study of 52 feline epulides. *Vet. Pathol.* 44: 161–169.

22 Gardner, D.G. and Baker, D.C. (1991). Fibromatous epulis in dogs and peripheral odontogenic fibroma in human beings: two equivalent lesions. *Oral Surg. Oral Med. Oral Pathol.* 71: 317–321.

23 Neville, B.W., Damm, D.D., Allen, C.M., and Chi, A.C. (2016). *Oral and Maxillofacial Pathology*, 4e. St. Louis, Missouri: Elsevier.

24 Soltero-Rivera, M., Engiles, J.B., Reiter, A.M. et al. (2015). Benign and malignant proliferative fibro-osseous and osseous lesions of the oral cavity of dogs. *Vet. Pathol.* 52: 894–902.

25 Meuten, D.J. (2017). *Tumors in Domestic Animals*, 5e. Ames, Iowa: John Wiley & Sons.

26 Perez-Garcia, S., Berini-Aytes, L., and Gay-Escoda, C. (2004). Ossifying fibroma of the upper jaw: report of a case and review of the literature. *Med. Oral* 9: 333–339.

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11

Odontogenic Cysts

A cyst is defined as a pathologic cavity that is lined by epithelium. Other cavitated spaces, sometimes called "pseudocysts," occur within the interstitial tissues but lack an epithelial lining, for instance seroma or hematoma. The true cyst is generally lined by epithelium that is normally located at the particular anatomic site (e.g. hair follicle epithelium in dermal follicular cysts, tubular epithelium in renal cysts, respiratory epithelium in nasopalatine duct cysts, etc.). As such, odontogenic cysts occur in tooth-bearing regions of the jaw and are lined by odontogenic epithelium, including residual dental lamina (rests of Serres), reduced enamel epithelium, and remnants of the epithelial root sheath (rests of Malassez) (see Figure 11.1).

Odontogenic cysts are traditionally classified as either developmental or inflammatory. Dentigerous cysts are classic developmental cysts and are the most common type of odontogenic cyst in dogs and cats. Dentigerous cysts arise from a developmental structure – the follicular sac that envelops the crown of an unerupted tooth. Radicular (periapical) cysts are classic inflammatory cysts that arise in the context of endodontic disease (e.g. pulpitis or pulp necrosis). In this chapter, we will not emphasize the distinction of developmental vs. inflammatory cysts, because some odontogenic cysts do not fit nicely into one category or another. The specific types of odontogenic cysts are discussed in detail below. We refer the reader to non-veterinary oral pathology texts for information about other types of odontogenic and maxillofacial cysts that have not been recognized or described in animals.

11.1 Radiologic Features of Odontogenic Cysts

Odontogenic cysts share many of the same general radiographic features, all having a well-defined, corticated border that results from the interface of the cyst wall (usually fibrous tissue and bone) and the lumen (usually fluid). Odontogenic cysts are generally spheroid to ovoid (balloon-like) and may occasionally be scalloped with internal septa (multi-loculated). The center is usually completely radiolucent. Because they generally enlarge slowly, cysts have a tendency to displace (but may also resorb) teeth, and expand/distort rather than destroy cortical bone plates. Specific radiologic features are discussed below as they pertain to a particular type of odontogenic cyst.

11.2 Histological Features of Odontogenic Cysts

Histopathologic examination plays a critical role in the diagnosis of odontogenic cysts. The pathologist must confirm that a lesion is a true cyst by identifying an epithelial lining and the absence of neoplastic epithelium (cystic odontogenic tumors will be discussed in more detail below). The majority of odontogenic cysts, regardless of type, are lined by benign non-proliferative epithelium with few distinctive features. It is important to note that most odontogenic cysts are lined by epithelium lacking odontogenic features! The epithelial basement membrane is typically flat, having little to no rete peg formation, and the cells show a low level of proliferation except where epithelial hyperplasia may be induced by inflammation. The supporting stroma of fibrous connective tissue varies in density and cellularity, which is most likely influenced by the extent of local inflammation and tissue remodeling. The outer layer of the cyst wall merges with the surrounding mandibular or maxillary bone. When sampled with the cyst lining as part of a biopsy sample, bone within the cyst wall is usually mildly proliferative, organized woven bone.

The following are common histological features of an odontogenic cyst, but are not specific for any particular type:

- Non-keratinized stratified squamous epithelial lining
- Cyst wall comprised of fibrous connective tissue +/– embedded bone
- Hemorrhage degradation products (hemosiderin and/or cholesterol crystals)

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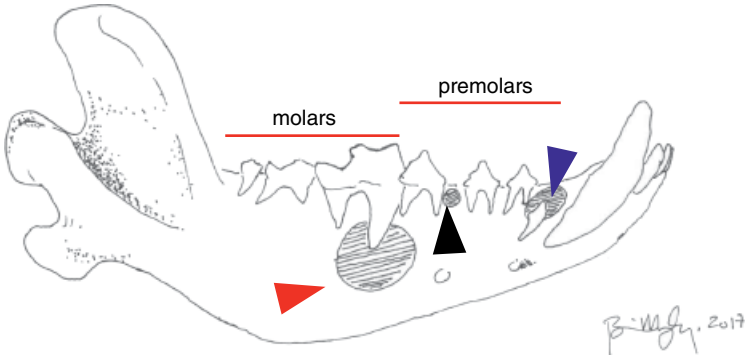


Figure 11.1 Diagram depicting the association between teeth and common anatomic locations of different odontogenic cysts. These cysts include: a dentigerous cyst associated with the crown of the 1st premolar tooth (blue arrowhead), a lateral periodontal cyst between the premolar teeth (black arrowhead) and a radicular cyst associated with the root of the 1st molar tooth (red arrowhead).

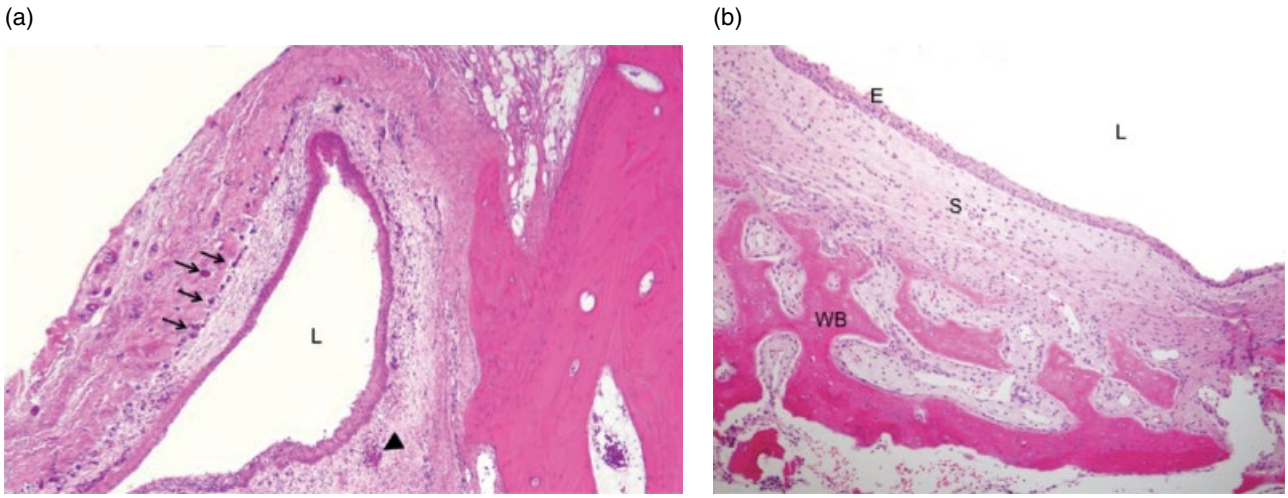


Figure 11.2 Histologic images showing generic and typical histological features of odontogenic cysts. (a) The empty lumen (L) of an odontogenic cyst lies adjacent to dense osteonal (lamellar) bone. The cyst lining is non-keratinized, stratified squamous epithelium with mild variation in thickness. The subepithelial fibrovascular tissue has congested small blood vessels (arrows) and minute hemorrhage (arrowhead). (b) A section from another odontogenic cyst shows similar epithelium (E) and fibrovascular stroma (S) with fine and loosely separated collagen fibers. The presence of woven bone (WB) is evidence of proliferative remodeling of the adjacent/surrounding jawbone.

Although some guidelines cite the number of epithelial layers in the cyst lining as a diagnostic criterion, the authors believe that this has no meaningful significance. Similarly, parakeratosis of the upper (luminal) epithelial cell layers may occur in various types of odontogenic cysts. Secondary inflammation is common, so the presence of inflammatory cells within the cyst wall cannot reliably differentiate between a developmental cyst (e.g. dentigerous cyst) and an inflammatory cyst (e.g. radicular cyst). While small epithelial rests may be embedded within the supporting fibrous connective tissue, differentiated ameloblasts should not be present in any of the various types of odontogenic cysts. The presence of ameloblasts would be more consistent with a cystic ameloblastoma or other odontogenic tumor.

The cyst lumen may contain serous fluid, hemorrhagic fluid, low numbers of leukocytes, degraded cellular debris, and hemorrhage-degradation products. It is uncommon for odontogenic cysts to contain keratin (see discussion of keratinized cysts below). The human literature on odontogenic cysts includes description of hyaline bodies (Rushton bodies), which are rarely identified in canine odontogenic cysts and are defined as extracellular, calcified, or amyloid-like deposits within the cyst epithelium. The nature of these deposits is uncertain, but studies suggest that they are comprised of erythrocyte degradation products and enamel proteins secreted by the epithelium [1]. The cyst epithelium has the potential for various metaplastic changes including ciliated, mucous, or sebaceous cells. While these are reported in humans, our experience is that metaplastic epithelial changes are rarely identified in the odontogenic cysts of domestic animals. Immunohistochemical (IHC) panels have been proposed for cysts in humans [2]; however, there is currently no evidence that IHC is useful for the diagnosis and classification of odontogenic cysts in animals. Also in humans, the proliferation marker Ki67 has

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been used to identify the proliferative cell fraction in certain odontogenic cysts (e.g. odontogenic keratocyst (OKC)/keratocystic odontogenic tumor).

11.3 Types of Odontogenic Cysts

Accurate classification of odontogenic cysts requires an active collaboration between the pathologist and clinician in order to integrate the histologic, radiologic, and clinical features of a case. The anatomic relationship of the cystic structure to the adjacent tooth or teeth is one of the most important diagnostic clues. For many reasons, radiographs are essential for diagnosis and classification of cysts. Some cases must be diagnosed as an unclassified odontogenic cyst when the histological features are consistent, but adequate history or radiographs are not available to support further classification (see Table 11.1).

11.3.1 Dentigerous Cyst

Dentigerous cysts are the most common type of odontogenic cyst in dogs, cats, and horses. By definition, a dentigerous cyst is an odontogenic cyst that forms around the crown of an impacted tooth. Therefore, the epicenter of the cyst will surround the crown of the tooth, and this feature should be radiographically apparent. The cyst is an expanded tooth follicle space lined by reduced enamel epithelium, which attaches to the unerupted tooth at the cementoenamel junction. In dogs, impacted 1st premolars are the most common site for development of a dentigerous cyst, followed by canine teeth [3].

Dentigerous cysts are most likely to occur in boxer dogs and other brachycephalic dog breeds, primarily because these breeds, secondary to dental crowding, are the most likely breeds to have impacted teeth. Dentigerous cysts are occasionally multiple, this is particularly true of bilateral dentigerous cysts of the mandibular or maxillary 1st premolars. Dentigerous cysts have the potential to become very large and involve several teeth; such lesions have been reported up to 7 cm^3 [4]. In these cases, the integrity of the jaw can be compromised, and it is common to see bone loss and resorption of adjacent teeth. Dentigerous cysts may occur in association with a supernumerary tooth, in which case a missing (impacted) tooth may not be apparent during the clinical oral examination, but might be identified with dental radiographs.

When trauma at a young age interferes with proper tooth development and/or eruption, a dentigerous cyst can form around the impacted tooth. These trauma-induced dentigerous cysts can be complex lesions since the odontogenic cyst may coexist with one or more dysplastic teeth, hamartomatous proliferations, and/or craniofacial malformations. The pathologist can minimize confusion and time spent attempting to reconcile bizarre histological features by inquiring about the pet's history of early life trauma (see Figures 11.3 and 11.4).

Table 11.1 Distinguishing features of the most common types of odontogenic cysts in dogs.

Type of cyst	Characteristic feature	Most likely location in dogs
Dentigerous cyst	Occurs at the site of an impacted tooth	1st premolar, canine, incisors
Radicular (periapical) cyst	Centered on the root apex of a tooth with endodontic disease	maxillary 4th premolar, mandibular 1st molar, incisors
Lateral periodontal cyst	Occurs along the lateral surface of a vital tooth	—
Gingival cyst	Confined to the gingiva with minimal or no bone involvement	—

11.3.2 Lateral Periodontal Cyst and Gingival Cyst

Lateral periodontal cysts (LPC) are developmental cysts that arise from various sources of residual odontogenic epithelium, as discussed previously. These lesions are uncommon in animals and, as in humans, they may cause no visible swelling or clinical signs. It is not unusual for a lateral periodontal cyst to be discovered incidentally on survey dental radiographs. The cyst forms along the lateral root surface of a vital tooth and usually does not cause tooth displacement. In humans, a diagnostic feature of LPC is the presence of plaque-like thickenings of the lining due to multifocal epithelial hyperplasia – this feature may or may not be consistently present in dogs (see Figures 11.5 and 11.6).

Gingival cysts are peripheral versions (i.e. no bone involvement) of the lateral periodontal cyst. Gingival cysts are lined by sulcal epithelium, which appears as non-keratinized stratified squamous epithelium as in most other odontogenic cysts. Gingival cysts have been reported to occur in young dogs with cyclosporine-induced gingival overgrowth [5]. One of the authors (CB) has seen small gingival cysts (rarely more than 1 cm diameter) occur spontaneously within hyperplastic gingival lesions of boxer dogs.

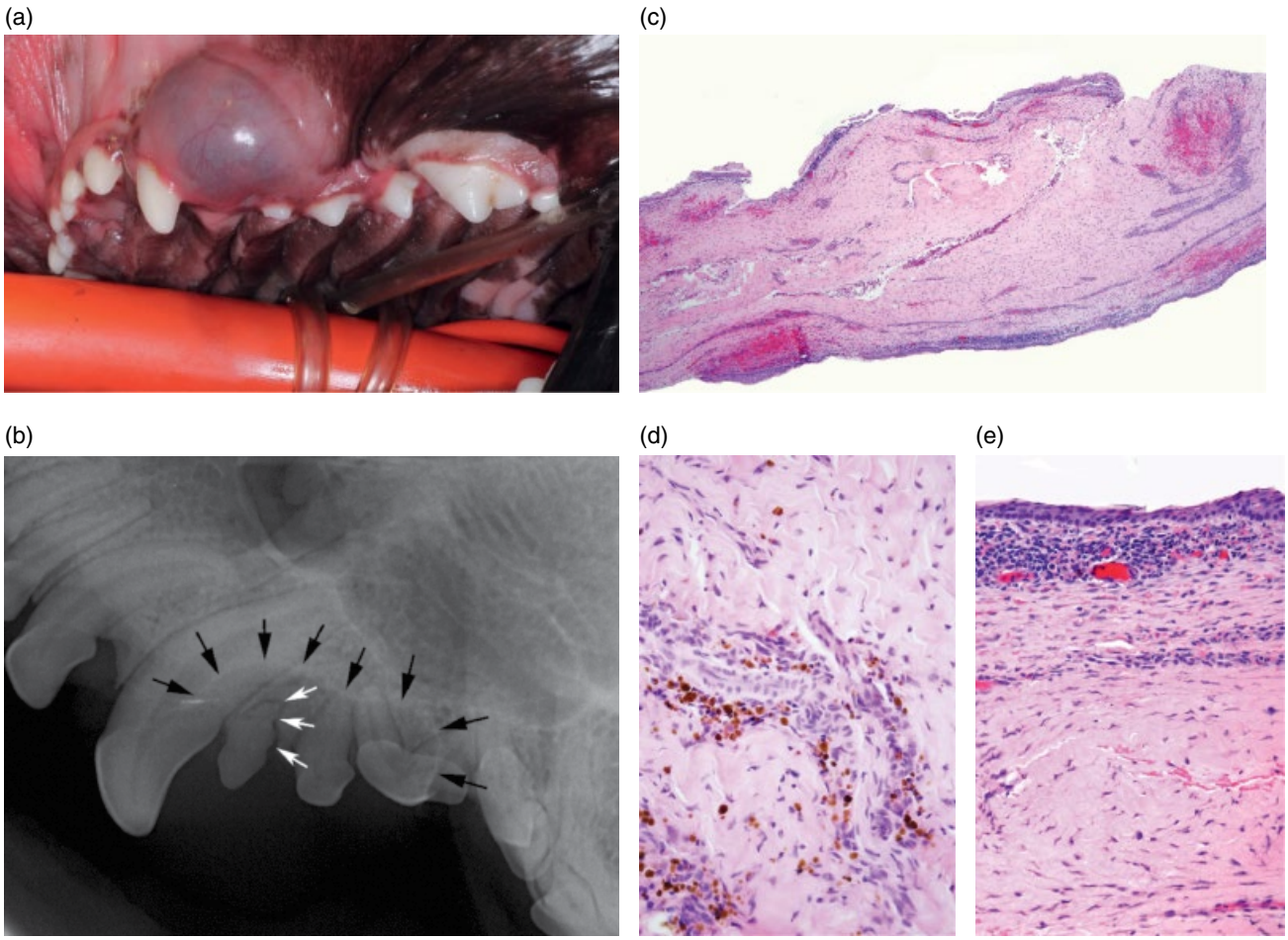


Figure 11.3 Gross, radiographic, and histologic images of a dentigerous cyst associated with a supernumerary impacted 205 in a one-year-old, spayed female, boxer dog. (a) A smooth gingival swelling is apical to 204 and all teeth of the left maxillary arcade are erupted and visible. (b) The intraoral oblique radiograph of the left maxilla shows an impacted supernumerary 1st premolar that has a shortened root due to tooth resorption (white arrows) and lies immediately distal to the canine. The dorsal corticated border of the cyst is apparent (black arrows). (c) The enucleated cyst lining has moderately dense fibrovascular connective tissue of the cyst wall and variably attenuated epithelium covering the luminal surface. The stroma has fine vasculature and acute hemorrhages. (d) Perivascular aggregates of hemosiderin-laden macrophages are present in some areas. (e) Mild, superficially oriented lymphoplasmacytic inflammation is located near the epithelial basement membrane. *Source:* C. Schor.

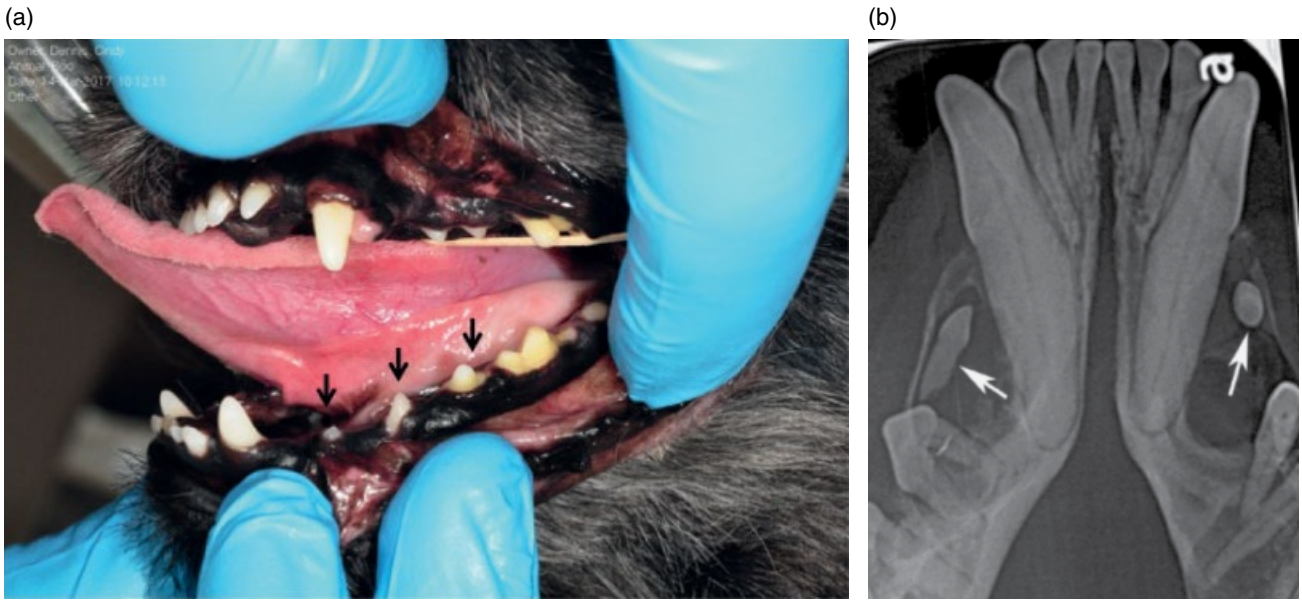


Figure 11.4 Gross and radiographic images of an eight-year-old, neutered male, Shih tzu dog with bilateral dentigerous cysts that are centered on the impacted mandibular 1st premolars (teeth 305 and 405). (a) On the left mandibular arcade, crowns of the 2nd, 3rd, and 4th premolars are visible (teeth 306–308, arrows) and swelling of the mandibles is difficult to appreciate. (b) Radiographs reveal much more obvious lesions with marked bilateral expansion of the mandibles in the premolar regions with central radiolucency and impacted 305 and 405 (white arrows) at the epicenters. *Source:* W. Gingerich.

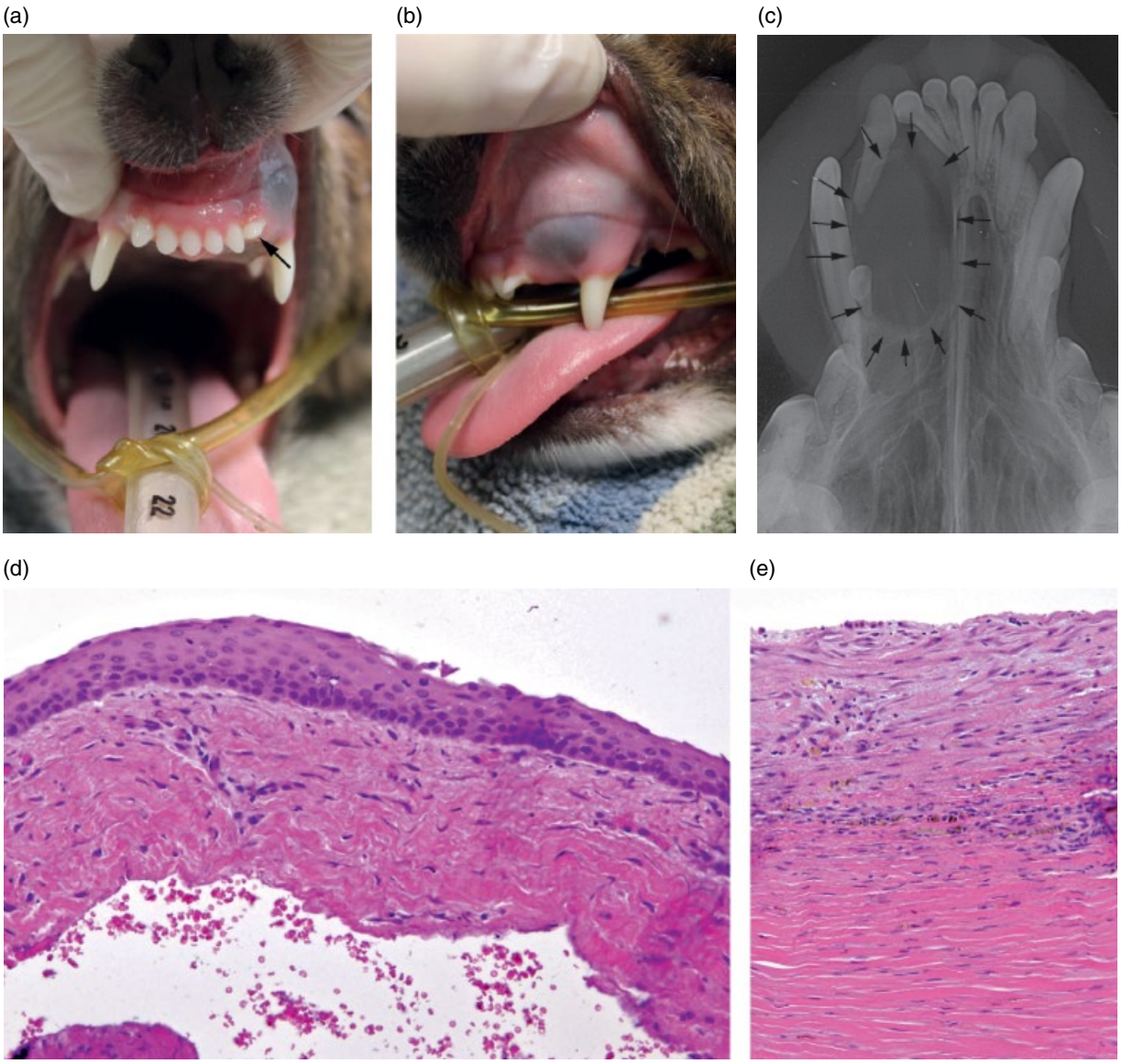


Figure 11.5 Gross, radiographic, and histologic images of a lateral periodontal cyst in a 1.5-year old, neutered male, Chihuahua cross dog. (a) and (b) A dark purple swelling is apical and mesial to the left maxillary canine tooth and the adjacent 3rd incisor is displaced. (c) A radiolucent structure with a corticated border (black arrows) is centered between the maxillary left 2nd incisor and 3rd incisor, the roots of which are displaced. The pulp chambers are radiographically unremarkable. (d) A fibrous cyst wall is lined by a flat, uniform layer of non-keratinized, stratified squamous epithelium. (e) Some areas of the cyst lumen may lack epithelial lining. Golden brown hemosiderin is commonly deposited within the fibrous wall of most types of odontogenic cysts. *Source:* D. Hoover.

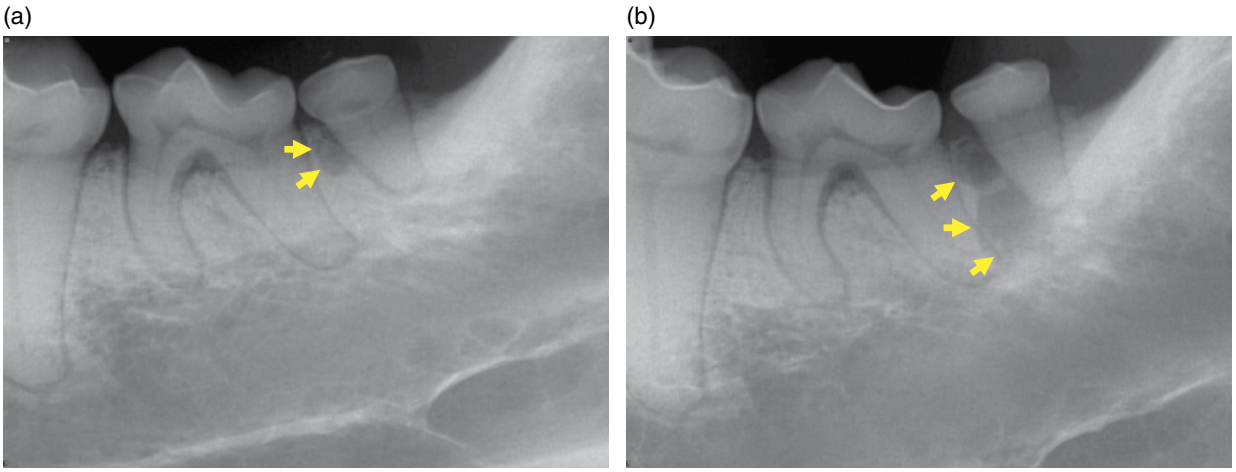


Figure 11.6 Radiographic images of a lateral periodontal cyst in an 11-year-old, neutered male, golden retriever dog. (a) A cyst-like radiolucency (arrows) along the mesial surface of the 2nd mandibular molar was discovered incidentally on survey dental radiographs. (b) A radiograph taken one year later shows enlargement of the same lesion, which was enucleated at that time and diagnosed as lateral periodontal cyst. *Source:* B. Shope.

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11.3.3 Periapical (Radicular) Cyst

When a cyst forms near the tooth apex secondary to endodontic disease/apical inflammation it is called a periapical (radicular) cyst. Periapical cysts are the most common type of odontogenic cysts in humans, but are less common than dentigerous cysts in domestic animals [3]. Periapical cysts are more associated with inflammation-induced bone resorption than with bone expansion from cyst growth; therefore, they are generally smaller than dentigerous cysts and may only be detected with dental radiographs. The pathogenesis is initiated by endodontic disease (pulpitis/pulp necrosis), which is followed by inflammation at the root apex, bone loss, proliferation of residual epithelium (e.g. rests of Malassez), and fluid transport into the lumen of an epithelium-lined cavity (i.e. cyst) (see Figure 11.7).

Clinically, the primary differential diagnosis for a periapical cyst is apical periodontitis (i.e. periapical granuloma or tooth root "abscess"). Periapical granuloma is more common in domestic animals than periapical cyst, and presents as a poorly demarcated radiolucency without a corticated border at the apex of an infected, non-vital tooth. Since periapical cysts arise in association with non-vital teeth, other radiographic changes

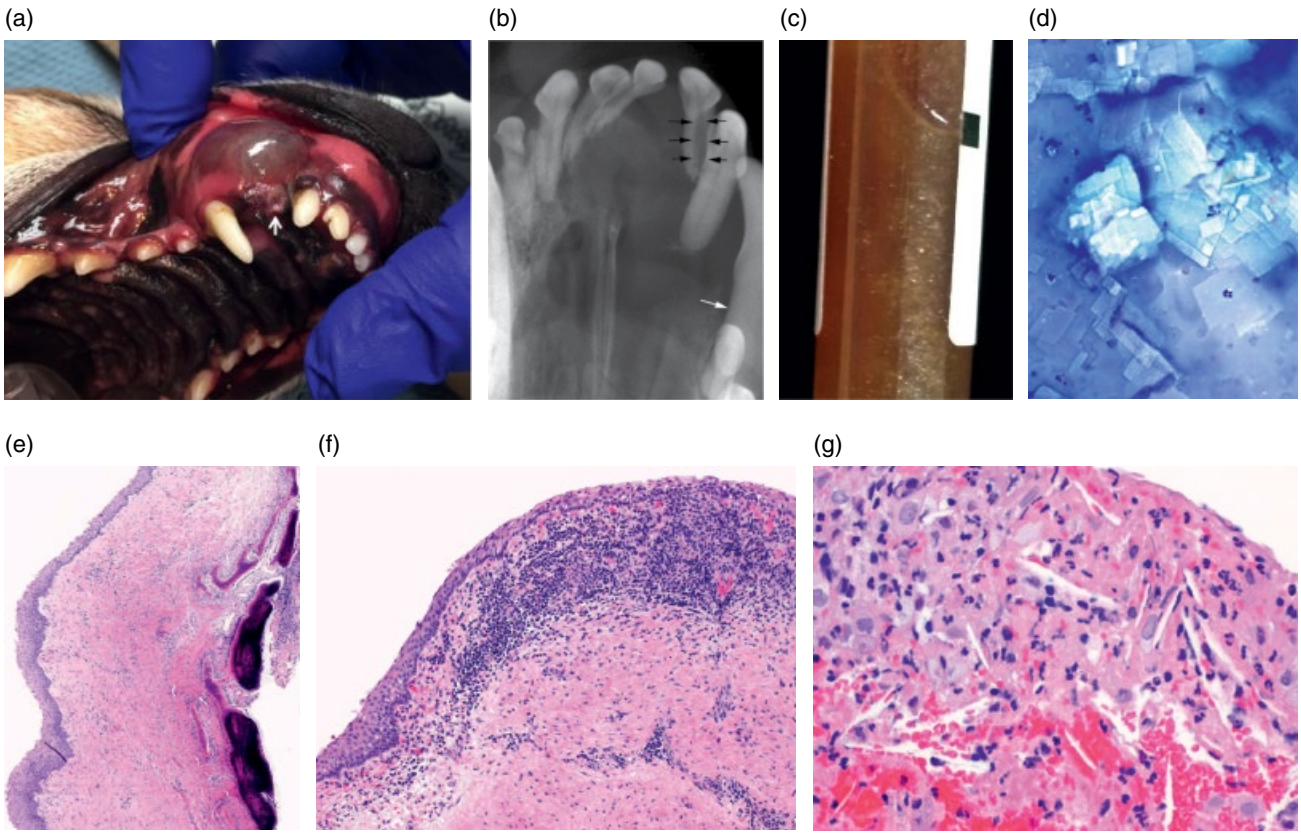


Figure 11.7 Gross, radiographic, and histologic images of a radicular cyst in a seven-year-old, spayed female, Chihuahua cross dog. (a) A smooth, fluctuant swelling bulges from the labial aspect of 103–104. There is rotation and distal displacement of the canine tooth, creating a pathologic diastema. In the diastema distal to 103 is a focal depression with a rim of tan discoloration (arrow) which is most likely due to traumatic occlusion of the opposing mandibular canine tooth. (b) Ventral–dorsal (VD) intraoral radiograph of the rostral maxilla shows a large radiolucency extending from the mesial aspect of the left 2nd incisor to the right premolar region. The root of the right canine tooth (white arrow) is displaced labially and distally. A comparatively wide root canal space (outlined by black arrows) is visible in the right 2nd incisor, consistent with pulpal necrosis. Additionally, the apex of this tooth appears to be at the epicenter of the cyst. These findings are supportive of the diagnosis of a radicular cyst secondary to pulpal necrosis of the right maxillary 2nd incisor. Additionally, displacement and apical root resorption is seen in several adjacent incisors. (c) Fluid aspirated from the lesion was brown, non-viscous, and described as having "sparkly" sediment. (d) Cytological evaluation of the fluid revealed numerous cholesterol crystals, which account for the reflective properties of the fluid. Neutrophils and macrophages were also identified in the sample of cyst fluid. (e) A fibrous cyst wall is supported by bone along the peripheral/outer surface (right side of image) where the cyst sac was surgically curetted from the surrounding maxillary bone. The luminal surface (left side of image) is lined by non-keratinizing stratified squamous epithelium. (f) A different segment of the same cyst has chronic inflammation as lymphocytes and plasma cells infiltrate the subepithelial stroma. (g) A cellular, hemorrhagic clot from the lumen of the cyst included epithelioid macrophages, neutrophils, erythrocytes, and clear spaces (left by cholesterol crystals that dissolved during processing). *Source:* S. Bonner.

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may include evidence of premature termination of dentinogenesis or internal tooth resorption evidenced as comparatively wide root canals.

11.3.4 Keratin-Filled Cysts

While not considered to be a separate class of odontogenic cysts, keratin-filled cysts are perhaps the most confusing and least well-characterized cysts in animals. The odontogenic keratocyst (OKC; now referred to as keratocystic odontogenic tumor in humans) is the only distinct type of odontogenic cyst that is defined by keratinization. However, OKC is quite rare in animals, is not the only type of cyst that may contain keratin, and should not be a default diagnosis when keratin is present. Other oral cysts that may contain keratin include inclusion cysts and keratinizing variants of other types of odontogenic cysts. Despite the name, the canine parakeratinized odontogenic cyst (CPOC) proposed by Verstraete et al. [3] does not contain significant amounts of luminal keratin, so does not fit into this discussion on keratin-filled cysts.

The OKC is reported to have a multilocular structure and is lined by a thin, refractile and parakeratinized epithelium with palisading basal cells. Several features support the argument that the OKC is a tumor, including a high rate of epithelial proliferation (Ki67 IHC), budding of the basal cell layers, formation of daughter cysts, and a high recurrence rate. One case report in a cat describes convincing features of an OKC, analogous to the same entity in human [6]. However, published reports of keratinized odontogenic cysts in dogs, which were called OKC, were later determined to not match the entity as described in humans [3].

Keratin-filled cysts can develop from disruption of the normal gingival anatomy and subsequent migration of the surface gingival epithelium into subgingiva and/or bone. A keratinized inclusion cyst was reported to arise at a site of previous tooth extraction [3]. An exposed cavity within the jaw can occur for various reasons including: trauma, an inadequately treated odontogenic cyst, tooth loss or extraction, and rupture of an inflammatory cavity (abscess). Each of these situations could permit the surface gingival epithelium to migrate from the surface into the tissue void. Inverted or entrapped gingival epithelium is likely to over-produce keratin as a physiological response to obliterate the lumen. In contrast, epithelium of odontogenic origin is unlikely to keratinize except in the case of some tumors. Keratinized cysts are rare and, in the authors' experience, tend to be open to the surface such that a hard, often mineralized mass of keratin within the cyst is exposed and visible (see Figure 11.8).

Finally, some cysts remain unclassified due to practical limitations in establishing a diagnosis and/or a lack of relevant case information. Some cysts simply do not fit into any currently recognized class even in the light of a complete history, radiographs, and histopathology. If a cystic jaw mass appears to possess properties consistent with an odontogenic cyst, but defies a more precise designation, *odontogenic cyst* is perhaps an appropriate diagnosis.

Canine parakeratinized odontogenic cyst (CPOC) was recently described [3] as a distinctive cyst in dogs that occurs in the maxilla at sites of normally erupted teeth that lack evidence of endodontic disease. These cysts are reported to be lined by non-keratinizing stratified squamous epithelium (as are nearly all other types of odontogenic cysts) and have a parakeratinized luminal surface (as may many other types of cysts including dentigerous cysts, LPC and radicular cysts). At present, CPOC is a descriptive diagnosis made after a thorough effort to exclude all other types of odontogenic cysts.

Box 11.1 Differential Diagnoses for Odontogenic Cyst

Cystic odontogenic tumor

- Ameloblastoma
- Canine acanthomatous ameloblastoma
- Ameloblastic fibroma/fibro-odontoma

Non-odontogenic cysts

- Salivary duct ectasia/cyst
- Nasopalatine cyst

11.4 Treatment and Considerations for Biopsy of Oral Cystic Lesions

Generally speaking, odontogenic cysts can be enucleated while the affected tooth is maintained. In order to prevent recurrence, the entire cyst lining must be removed. However, because the tooth associated with a radicular cyst is, by definition non-vital, it will require root canal therapy or extraction. It is generally recommended that an impacted tooth be extracted when associated with a dentigerous cyst. Larger cysts often require additional considerations, such as when root resorption of the associated or nearby teeth is present or when the degree of bone resorption compromises the periodontal integrity of adjacent teeth. The clinical and radiographic information must be used to determine whether the associated tooth and/or nearby teeth require extraction. Larger odontogenic cysts may be surgically marsupialized for a period of time in order to reduce the size of the cyst prior to definitive enucleation. Cystic odontogenic tumors, keratinized cysts, and OKC may require *en bloc* excision of the cyst rather than cyst enucleation.

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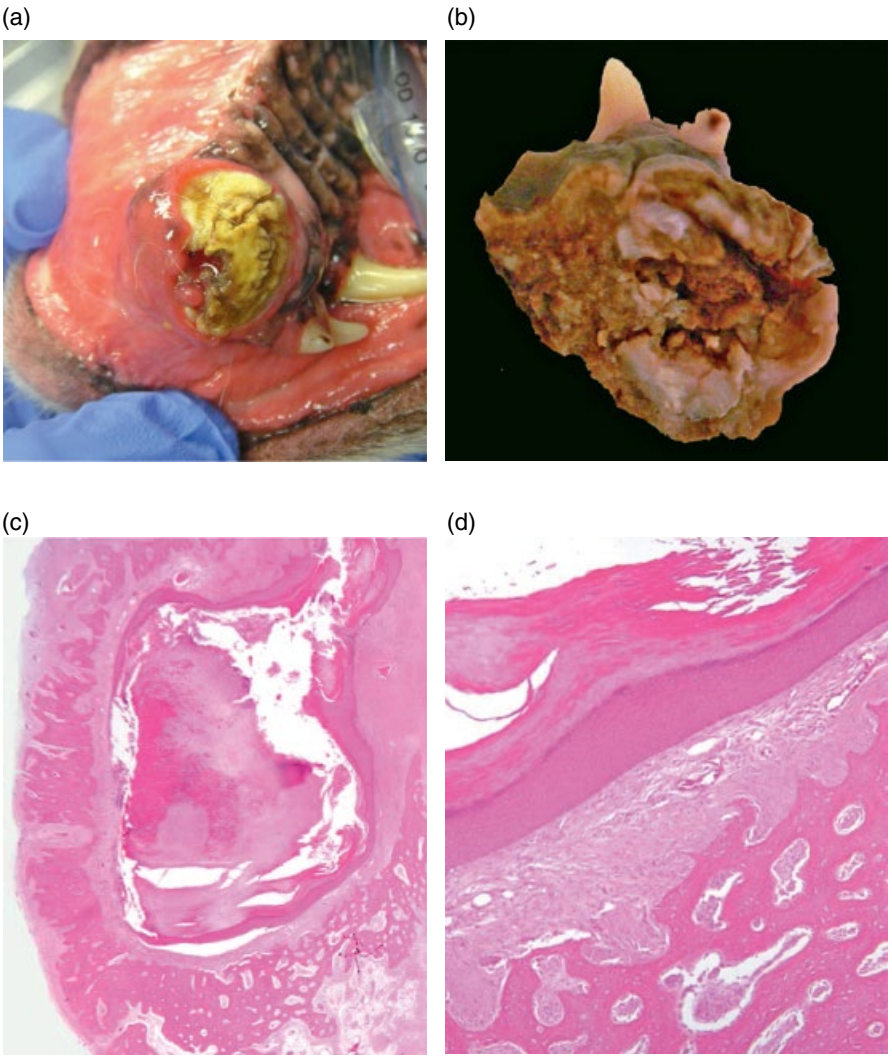


Figure 11.8 Gross, radiographic, and histologic images of a keratinized cyst in an 11-year-old, spayed female, Beagle dog. (a) A mass expands the left rostral maxilla and lobular yellow tissue is exposed at the broadly ulcerated surface. One month prior, a cavitated lesion had been excised and left open to drain. (b) The formalin-fixed maxillectomy specimen was bisected to expose an irregular, cavitated center. (c) A section of a similar keratinized cyst has a unilocular, epithelium-lined cavity within bone that contains keratin. (d) The stratified squamous epithelium produces dense, laminated, compact keratin and resembles an ungual inclusion cyst. *Source:* K. Stepaniuk.

Although difficult, an effort should be made to preserve the architecture of the lesion during enucleation. This requires an attempt to maintain any attachment of the cyst to the associated tooth/teeth during the enucleation procedure. Maintaining this architecture can improve the pathologist's ability to provide an accurate diagnosis and gain insight to potential etiologic factors. Perhaps most importantly, the surgical pathologist must be privy to the clinical and radiographic features of the biopsied lesion. Active and detailed correspondence between pathologist and clinician is strongly encouraged.

11.5 Pathogenesis of Odontogenic Cysts

The mechanism of cyst development and expansion is likely to include proliferation of the lining epithelium, hydrostatic enlargement, and bone resorption. An early event in cyst formation is stimulation and proliferation of otherwise quiescent odontogenic epithelium, which can be induced by inflammatory mediators or other triggers. Since the rate of epithelial proliferation is generally low in cysts, fluid transport and bone loss are more likely to contribute to cyst enlargement [7]. The histology of the typical odontogenic cyst lining does not support the

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concept that the epithelial cells have an active secretory role. Instead, fluid is more likely to be plasma filtrate, and fluid transport into the cyst lumen is most likely driven by osmosis. The osmotic gradient may be established by luminal accumulation of necrotic epithelial cells, inflammatory debris, and/or hemorrhagic debris [8].

There appears to be no satisfactory explanation for why blood degradation products are so common within the lumen and wall of odontogenic cysts. Is hemorrhage into a pathologic void, either before or after it has been epithelialized, a possible mechanism for cyst initiation and/or expansion? We do not know the answer to this question, but suspect that trauma may be more important in the development of cysts than has been appreciated. A cemental tear or other type of avulsion could create a void within the otherwise firmly adhered tissues of the tooth alveolus. This type of trauma would likely also cause some degree of hemorrhage into the void. A cyst might form if nearby odontogenic epithelial rests were stimulated to proliferate and eventually migrate over the inner (luminal) surface of the void.

11.6 Do Odontogenic Tumors Arise from Odontogenic Cysts?

This is a proverbial "chicken and egg" dilemma. The veterinary literature includes reports of tumors arising within odontogenic cysts [9, 10], and this risk is regularly referenced in recently published articles and in the comments of biopsy reports. But is it true? It is tempting to assume that the answer is "yes" when a long-standing cystic lesion eventually begins to grow more quickly and is diagnosed as a neoplasm. But is it not possible that such a lesion may have been a cystic tumor all along? The authors of this text remain skeptical that malignant transformation occurs within simple odontogenic cysts. Nevertheless, the risk of tumor development within odontogenic cysts is regularly referenced in both the human and veterinary literature on odontogenic cysts. Pathologists and clinicians are encouraged to determine the most logical answer based on findings specific to each case and with consideration of the following:

- Some odontogenic tumors are frequently cystic, particularly ameloblastoma.
- Odontogenic tumors tend to be slow-growing.
- The rate of enlargement ("growth") of a cystic mass may depend more on luminal accumulation of fluid than on proliferation of neoplastic tissue.
- The cystic portion of an odontogenic tumor may have a compressed lining of neoplastic epithelium that no longer resembles the solid areas of neoplastic epithelium.
- Cystic tumors tend to be asymmetrical (often bulging from the vestibular aspect), which can be perceived as a tumor arising from one portion of the cyst wall.

References

1 Sarode, G.S., Sarode, S.C., Tupkari, J.V. et al. (2016). Pathogenesis of Rushton bodies: a novel hypothesis. *Med. Hypotheses* 93: 166–169.

2 Tsuneki, M., Yamazaki, M., Cheng, J. et al. (2010). Combined immunohistochemistry for the differential diagnosis of cystic jaw lesions: its practical use in surgical pathology. *Histopathology* 57: 806–813.

3 Verstraete, F.J., Zin, B.P., Kass, P.H. et al. (2011). Clinical signs and histologic findings in dogs with odontogenic cysts: 41 cases (1995–2010). *J. Am. Vet. Med. Assoc.* 239: 1470–1476.

4 Doran, I., Pearson, G., Barr, F., and Hotston-Moore, A. (2008). Extensive bilateral odontogenic cysts in the mandible of a dog. *Vet. Pathol.* 45: 58–60.

5 O'Hara, A.J., Collins, T., and Howell, J.M. (2002). Gingival eruption cysts induced by cyclosporine administration to neonatal dogs. *J. Clin. Periodontol.* 29: 507–513.

6 LaDouceur, E.E., Walker, K.S., Mohr, F.C., and Murphy, B. (2014). Odontogenic keratocyst in a cat. *J. Comp. Pathol.* 151: 212–216.

7 Browne, R.M. (1991). *Investigative Pathology of the Odontogenic Cysts*. Boca Raton: CRC Press.

8 Bilodeau, E.A. and Collins, B.M. (2017). Odontogenic cysts and neoplasms. *Surg. Pathol. Clin.* 10: 177–222.

9 Poulet, F.M., Valentine, B.A., and Summers, B.A. (1992). A survey of epithelial odontogenic tumors and cysts in dogs and cats. *Vet. Pathol.* 29: 369–380.

10 Dubielzig, R.R. and Thrall, D.E. (1982). Ameloblastoma and keratinizing ameloblastoma in dogs. *Vet. Pathol.* 19: 596–607.

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12

Lesions of the Salivary Gland

Salivary glands play critical roles in oral health and the initiation of digestion. Mammalian salivary gland tissue includes the six major glands (right and left *parotid, mandibular,* and *sublingual*) along with hundreds of diffuse or minor salivary glands, which are distributed throughout the oral mucosa (including the tongue). Carnivores have an additional major gland, the *zygomatic salivary gland*, located beneath the rostral aspect of the zygomatic bone. Cats have a *lingual molar gland* that is linguocaudal to the mandibular first molar tooth. Those not familiar with the feline lingual molar gland may inappropriately identify it as a lesion.

Saliva has a lubricative function that facilitates mastication, tasting, and the transportation of the food bolus into the esophagus and stomach. In many species, saliva contains the enzyme *amylase*, which initiates the breakdown of complex carbohydrates into simpler structures like maltose and glucose. Further digestion and absorption of these simple carbohydrates occur in the small intestine. The venom glands of some poisonous snakes and lizards are actually modified salivary glands.

The mechanisms of salivary gland injury are numerous and include toxic, inflammatory, obstructive, ischemic, and neoplastic processes. A survey of salivary gland disease in dogs and cats identified four major pathologic categories: malignant neoplasia, sialoadenitis, silocele, and salivary gland infarction [1]. Toxic injury can result in excessive salivation (ptyalism). Inflammation and obstruction of salivary glands are relatively common and can lead to dilation and/or rupture of the glandular duct system. Even without a functional duct system, saliva is still produced, at least initially. Depending upon the anatomic location of the gland and the obstruction, the errant saliva accumulates in the adjacent mucosa or connective tissues, resulting in the formation of a sialocele, ranula, or mucocele. Infarction of salivary glands, which occurs most often in dogs, may produce a characteristic scar-like lesion (necrotizing sialometaplasia) that can histologically mimic squamous cell carcinoma. Primary neoplasms of the salivary gland are very rare in veterinary species, but most often arise from the glandular or ductular epithelium, resulting in the formation of adenomas or carcinomas. Overall, salivary gland disease is uncommon in dogs and cats, with a reported incidence of 0.17 % [2].

12.1 Microanatomy and Physiology

Salivary glands are complex exocrine glands and have anatomic and physiologic similarities to other exocrine glands like the mammary gland and exocrine pancreas. Salivary glands also have a number of unique structural and functional aspects that differentiate them from these other glandular tissues. The major salivary glands are *compound tubuloacinar glands*, comprised of tubules/ducts that constitute the glandular plumbing system along with the terminal acinar component, which produces the saliva itself (Figure 12.1). Minor salivary glands are 1–2 mm in diameter and are *simple tubuloacinar glands*. The oral cavity has up to one thousand minor salivary glands. The minor salivary glands are distributed throughout the oral, pharyngeal, and laryngeal mucosae.

Salivary glands are subdivided into numerous lobules. Each lobule is invested in a connective tissue stroma, which also supports the glandular blood supply and innervation. Lobules have numerous terminal acini, small saclike structures that produce mucous secretions (mucous acinus), serous secretions (serous acinus), or both (mixed or mucoserous acinus). In a mixed acinus, the serous component of the gland forms a crescent-shaped cup surrounding the mucous component of the gland. These cup-like structures have a special name, *serous demilunes*, from "half moon."

Different glands secrete saliva with varying characteristics: primarily serous (parotid) or a mixture of serous and mucous (mandibular, zygomatic and sublingual). The glandular acini are partially surrounded by a plexus of myoepithelial cells; nerve-mediated contraction of these cells results in the expulsion of saliva through the duct system and eventually into the oral cavity.

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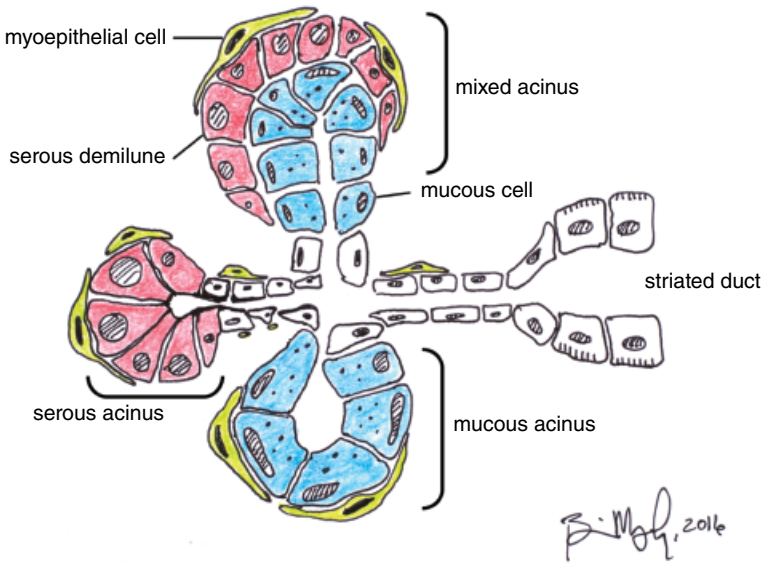


Figure 12.1 Diagram of salivary gland microanatomy.

Small intralobular salivary ducts (i.e. intercalated and striated) lead to larger interlobular ducts (secretory), eventually emptying into the oral cavity though terminal excretory ducts at a small orifice (oral papillae). Intercalated ducts receive secretory material directly from the acinus; they are short and lined by low cuboidal epithelial cells. The intralobular striated ducts are easiest to find in histological sections since they are larger than intercalated ducts and lined by plump cuboidal to columnar cells. The interlobular excretory ducts are lined by one to two layers of cuboidal to columnar epithelium and the terminal excretory ducts are lined by non-keratinized stratified epithelium. Formation and secretion of saliva is under control of the autonomic nervous system (see Figure 12.2).

Acinar serous cells contain granular material; their secretions are a thin, watery fluid containing electrolytes (sodium, potassium, bicarbonate) and the enzyme amylase, which initiates the enzymatic digestion of food (carbohydrates). In carnivores and cattle, amylase is either absent or present in only very small quantities. Salivary bicarbonate is an important buffer, especially in ruminant species that lack secretory forestomachs. Mucus-secreting cells are filled with numerous pale-staining vacuoles of mucin, displacing a flattened nucleus to the basal pole. Salivary mucus serves to lubricate the food bolus for efficient mastication and transport. When the cytoplasmic contents of the glandular epithelial cells have been secreted into the duct, the cells may be difficult to differentiate. Each of these cell types and salivary gland subcomponents can play a role in various types of pathology.

12.2 Salivary Duct Obstruction, Cysts, and Pseudocysts

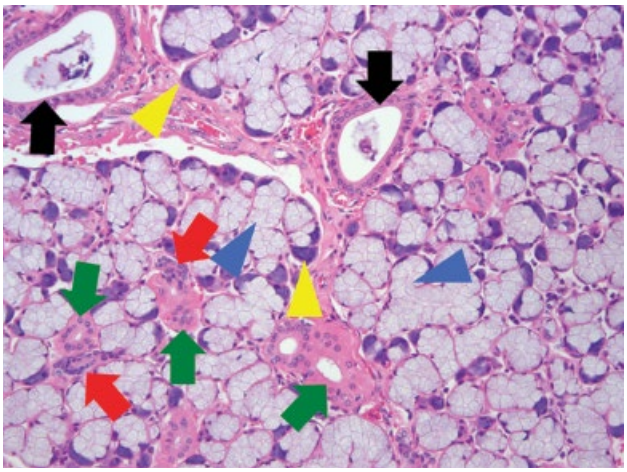
Obstruction of the salivary gland duct can be the result of luminal calculi (sialoliths), foreign bodies (plant material), trauma, inflammation, and fibrosis (sialoadenitis), vitamin A deficiency (ductular squamous metaplasia), and neoplasia. Duct obstruction can occur in either the major or minor salivary glands. Although duct obstruction eventually results in glandular atrophy and fibrosis, glandular secretions continue to be produced for some time, resulting in cystic dilation (mucus retention cyst) or ductal rupture and subsequent pseudocyst formation (mucocele/sialocele, also referred to as *mucus extravasation phenomenon*).

Sialoliths, or luminal salivary calculi, relatively common in humans, are uncommonly diagnosed in cats, dogs, and horses. Sialoliths are white, cone-like structures composed of laminated concretions of precipitated calcium salts (calcium carbonate, calcium phosphate, calcium oxalate; see Figure 12.3). Mineralized salts aggregate around a central nidus of desquamated cellular debris, inspissated mucin, and/or bacteria. In humans, predisposing factors include salivary glandular stasis, chronic sialoadenitis, and gout (uric acid calculi).

Sialoliths can form and lodge anywhere between the glandular parenchyma and the excretory duct orifice. Sialolith formation has been reported after a parotid duct transposition procedure for the treatment of dry eye in a dog. Occasionally, foreign bodies, such as plant awns or fibers, can lodge inside the orifice of the salivary gland excretory duct, resulting in partial to complete outflow

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(a)



(b)

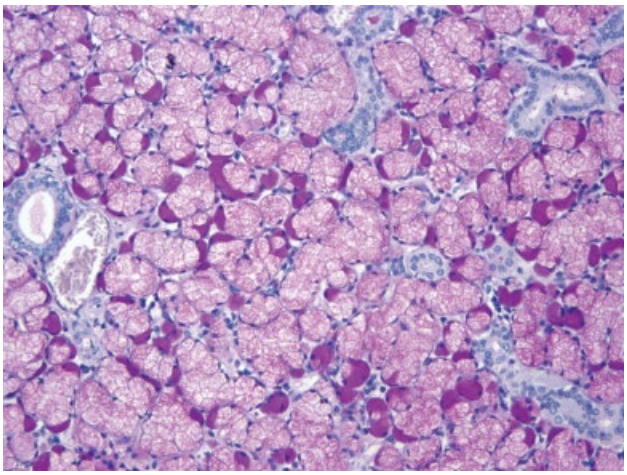


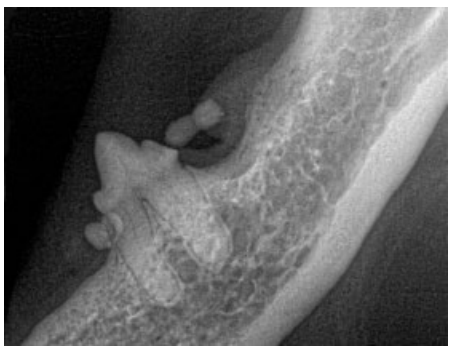
Figure 12.2 Histologic images of normal canine mandibular salivary gland. (a) In this mixed salivary gland, mucous cells (blue arrowheads), serous demilunes (yellow arrowheads), intercalated ducts (red arrows), striated ducts (green arrows), and excretory ducts (interlobular, black arrows) are indicted (H&E stained section). (b) Canine mandibular salivary gland stained with PAS.

obstruction. The presence of sialoliths or foreign bodies like plant material within the glandular outflow tract may subsequently initiate an inflammatory process focused on the duct (sialodochitis or ductal sialoadenitis). Sialodochitis and subsequent fibrosis may further exacerbate outflow obstruction. Outflow obstruction, initiated by either sialoliths or luminal foreign bodies (plant material), results in either mucus retention cysts (if the ductular epithelium remains intact) or pseudocysts (if the duct ruptures). Mucus retention cysts tend to be small and are less common than pseudocysts. Trauma of sufficient severity (induced by choke collars, bite wounds, acute impact, or chewing on hard materials like sticks or bones) can actually sever or focally destroy the ductular system, resulting in extravasation of saliva into the adjacent connective tissues and pseudocyst formation.

There is some controversy concerning the terms *sialocele, mucocele,* and *ranula*. Many authorities agree that the terms sialocele and mucocele are synonyms, although some use mucocele or sialocele to refer to small or large lesions, respectively. Some investigators specifically define sialocele as a *subcutaneous* saliva-filled cavity (as in cervical sialocele), reserving the use the terms mucocele and ranula for oral lesions. Most people agree that a ranula is a type of mucocele that occurs sublingually in the floor of the mouth. Grossly, ranulas are smooth, rounded, fluctuant distensions that are semi-translucent. The name ranula (derived from the Latin for frog, *rana*) apparently evokes the image of a frog's belly or throat (see Figure 12.4).

The real controversy revolves around whether these ductal lesions are *cysts or pseudocysts*. In human oral pathology, mucoceles, and ranulas can represent *either* a mucus retention cyst, a dilated but intact duct lined by attenuated epithelium, or a pseudocyst, with free salivary mucus [3]. However, veterinarians tend to define mucocele and ranula as pseudocysts, that is, saliva-filled cavitations lacking an epithelial lining. It may be that true mucus retention cysts, which are relatively common in human patients, are quite rare in veterinary patients.

(a)



(b)



Figure 12.3 (a) Radiograph and (b) gross specimens of sialoliths, feline molar salivary gland. *Source:* University of Wisconsin-Madison.

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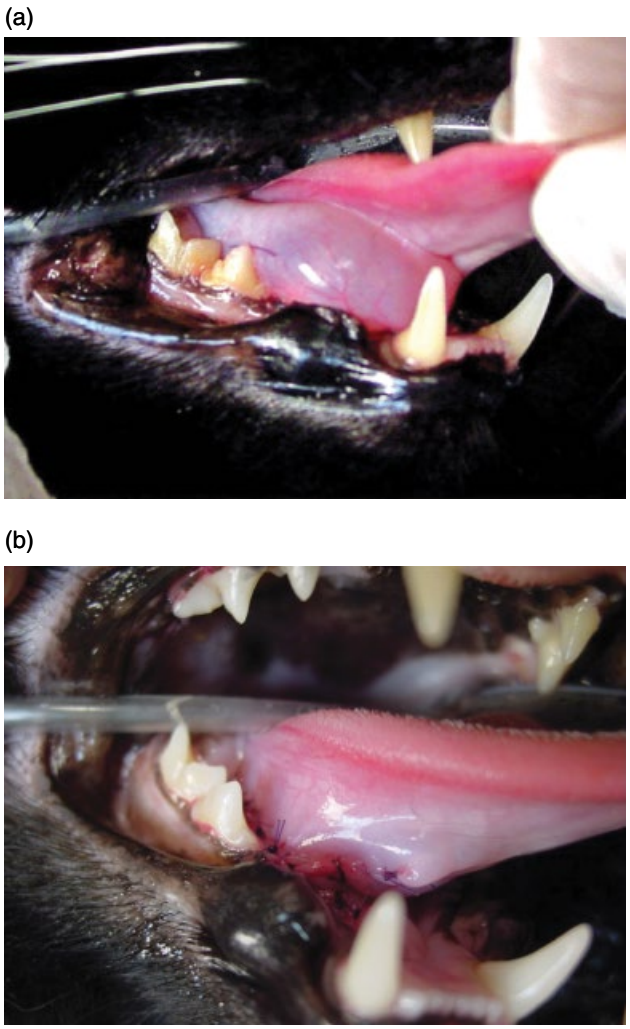


Figure 12.4 Gross images of a feline sublingual ranula, (a) prior to surgical removal, and (b) after surgical removal. *Source:* K. Stanley.

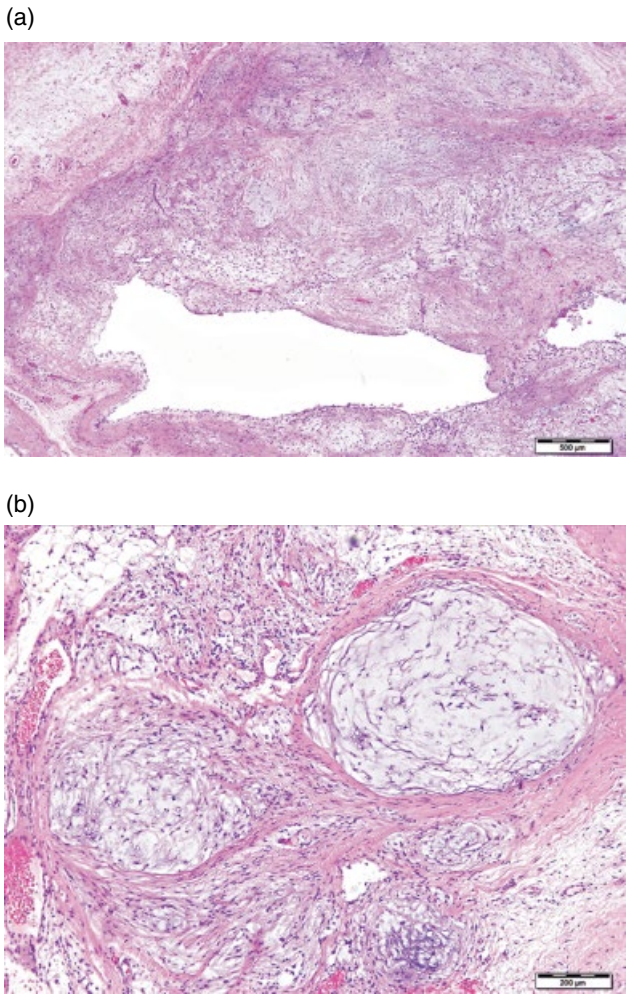


Figure 12.5 Histologic images of a canine mucocele at (a) low- and (b) high-power magnification. Extravasated mucus has basophilic-staining properties and is associated with histiocytic inflammation and fibrosis (H&E-stained section). (b) Extravasated mucus mimics chondroid tissue.

Or it may be that by the time of diagnosis, these lesions in veterinary species have progressed to rupture. Regardless, the gross features and pathogenesis of these lesions are similar.

Oral and cervical salivary duct-associated pseudocysts are common in dogs, and have also been reported in cats and cattle. In these lesions, saliva leaks out from the duct (extravasates), forming a saliva-filled cavitation within the subepithelial connective tissue (Figure 12.5). The inappropriate presence of extraductal mucus induces a histiocytic inflammatory response (cellulitis) with subsequent granulation tissue formation followed by fibrosis. Variable numbers of neutrophils may also be present in the lesion. Extraductal mucus generally gives the lesion a basophilic appearance, and in some cases can mimic chondroid tissue or pulp-like mesenchyme (see Figure 12.6). Such lesions may be grossly mistaken for tumors, and some pathologists (including at least one of the authors) have misinterpreted small biopsy specimens of mucus extravasation to be a neoplastic process. In biopsy specimens, the cavitation is often bordered by palisading histiocytes embedded within granulation or fibrous tissue (depending upon lesion chronicity). Pseudocysts can become quite large (up to 10 cm in diameter), especially in the submandibular/cervical region.

12.3 Salivary Gland Infarction (Necrotizing Sialometaplasia)

Necrotizing sialometaplasia is a rare condition that has been described in humans, dogs, and cats. Recognition of this entity is important because it mimics malignancy

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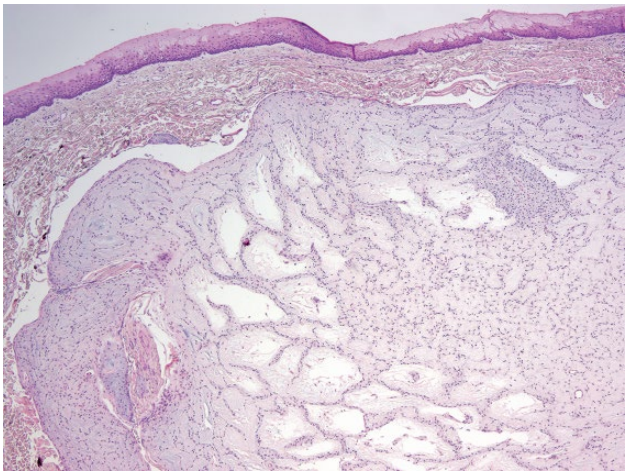


Figure 12.6 Histologic image of a mucocele, seven-year-old Great Dane dog. This lesion features extravasated basophilic mucus surrounding arborizing cords of fibroblasts and macrophages. This relatively common, benign lesion can be histologically misinterpreted as an odontogenic myxoma or chondroid neoplasm.

both clinically and histologically [3]. In affected humans, the minor salivary glands of the palate are most often affected. The mandibular salivary gland of small breed dogs, terriers in particular, is most often affected, and is enlarged and firm. The pathogenesis of this lesion is not completely understood, but is thought to be either the result of trauma (surgery, local anesthesia) or due to an immune-mediated vasculitis. Affected animals may present with acute and extreme pain and may also have centrally mediated recurrent vomition.

Vessels within the lesion may have luminal thrombi and fibrinoid necrosis of the vascular wall (infarction). Vascular infarction is associated with a well-delineated area of coagulative necrosis, hemorrhage, fibrin, edema, and inflammation. Squamous metaplasia of the ductular epithelium is a characteristic feature of this lesion, and the lesion may be encapsulated. Necrotizing sialometaplasia can mimic squamous cell carcinoma or other neoplasms of the salivary gland (e.g. mucoepidermoid carcinoma). Importantly, the necrotic portion of the sialometaplasia lesion should not include squamous metaplasia. This is unlike squamous cell carcinoma, in which the tumor itself (squamous epithelium) often demonstrates coagulative necrosis. Neutrophils may infiltrate into the metaplastic epithelium, which may contain increased numbers of mitotic figures. Preservation of the lobular architecture of salivary glands serves to distinguish this process from neoplasia [3]. Irregular lobules of epithelium may be separated by proliferative and inflamed fibrous tissue (see Figure 12.7).

The pathologist should recognize that primary salivary gland tumors are very rare and squamous cell carcinoma of the salivary gland particularly so. The patient signalment, concurrent presence of vascular infarction, coagulative necrosis, and squamous metaplasia organized into a lobular pattern should steer the pathologist to the correct diagnosis.

12.4 Salivary Gland Inflammation (Sialoadenitis)

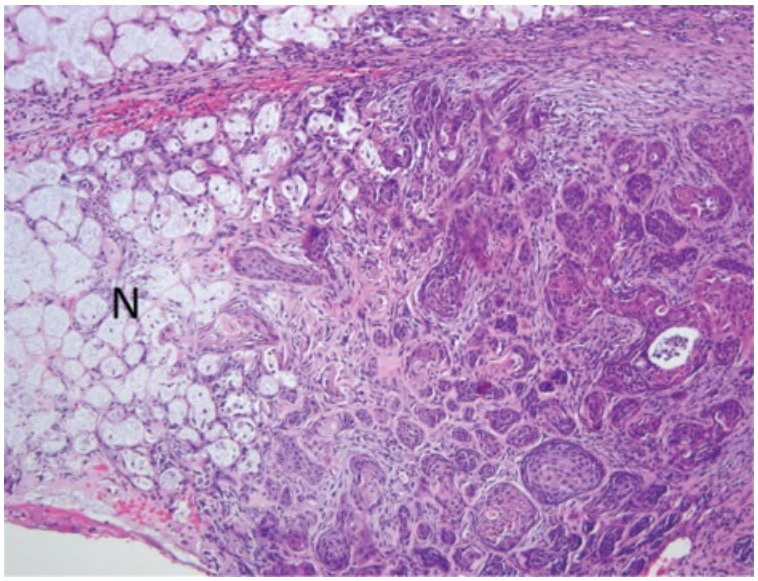
Sialoadenitis likely occurs in most veterinary species but is most often diagnosed in the dog, cat, and horse. Inflammation can be the result of an ascending or hematogenous infection, or alternatively may be the result of a penetrating wound. Clinically, sialoadenitis can cause pain, inappetence, and dysphagia. It is important to realize that a diagnosis of sialoadenitis may be based upon a combination of clinical examination, microbial cultures and imaging (ultrasonography), and *may not involve* clinical or anatomic pathology (see Figure 12.8).

Bacterial infections lead to suppurative inflammation and glandular edema (*septic sialoadenitis*). With chronicity, the lesion may demonstrate glandular atrophy and fibrosis. Inflammatory and necrotic exudates within the salivary gland lumina can result in duct obstruction (see: Salivary duct obstruction). Sialoadenitis (if the pathologist takes the time to look for it), can often be found concurrently present with salivary duct obstruction, sialoceles, mucoceles, etc. (Figure 12.9). Sialoadenitis can also be found in association with chronic stomatitis or salivary gland neoplasia. In horses, dental disease and sialolith formation may play important roles in the pathogenesis of septic sialoadenitis [4]. *Fusobacterium* spp. are frequently isolated from equine septic sialoadenitis lesions, and *Streptococcus equi* (strangles) has also been associated with sialoadenitis. Inflammation of the canine zygomatic gland can result in periocular abscess formation.

Viral sialoadenitis is generally characterized by mononuclear infiltrates (lymphocytes) and, depending upon the virus, inclusions. Viral agents that may induce sialoadenitis include rabies virus, sialodacryoadenitis virus of rats (rat coronavirus) and encephalomyocarditis virus of small rodents. A suspected autoimmune inflammatory process, or Sjögren-like syndrome, has been described in the salivary glands of dogs and cats, and is characterized by plasma cell infiltrates. Infectious or immune-mediated destruction of multiple salivary glands can lead to xerostomia (dry mouth). Xerostomia does not result from the surgical removal of the major salivary glands due to the presence of numerous minor salivary glands.

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(a)



(b)

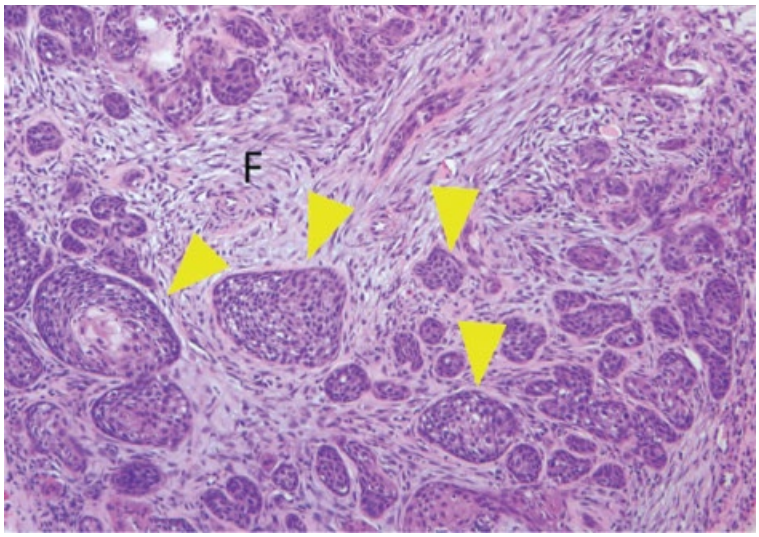


Figure 12.7 Histologic images of necrotizing sialometaplasia (eight-year-old poodle mix, mandibular salivary gland). (a) Infarcted glandular tissue (necrosis, N) is evident on the left margin, while squamous metaplasia is evident on the right. Note that the regions of squamous metaplasia of the salivary gland ducts are not necrotic. (b) Numerous glands and tubules are replaced by islands of metaplastic squamous epithelium mimicking squamous cell carcinoma (yellow arrowheads). These metaplastic islands are surrounded by a fibro-myxoid stroma (F).

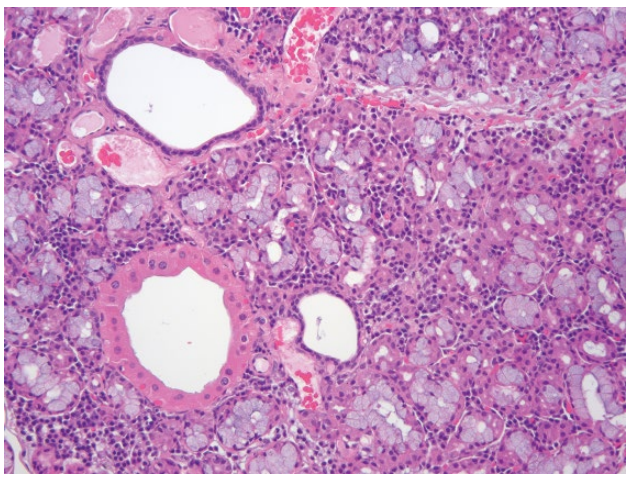


Figure 12.8 Nonsuppurative sialoadenitis, mandibular salivary gland, dog. Note the multiple aggregates of lymphocytes and plasma cells infiltrating throughout the interstitium of this mixed salivary gland. Several ducts lacking evidence of inflammation are present in this image.

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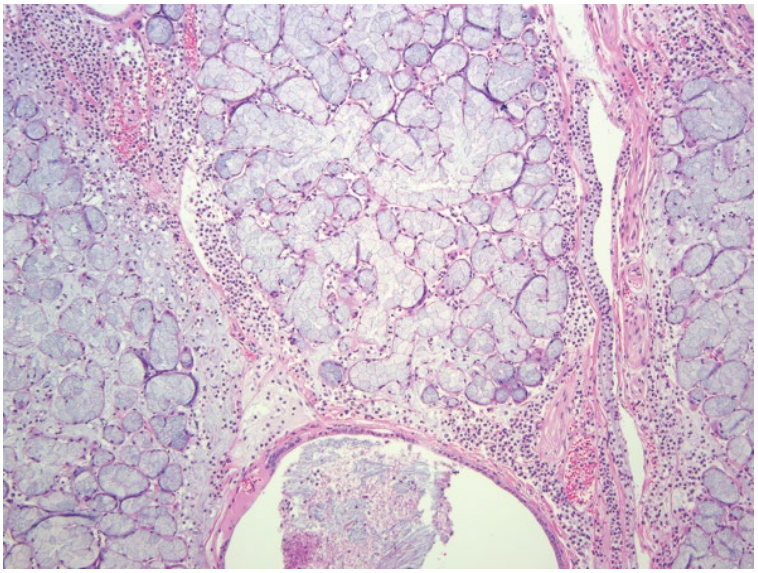


Figure 12.9 Suppurative sialoadenitis, zygomatic salivary gland, 11-year-old German shepherd dog. This inflamed salivary gland was associated with a sialocele, periglandular cellulitis, and ductular distension. Inflammation extends into the ductular lumina.

References

1 Spangler, W.L. and Culbertson, M.R. (1991). Salivary gland disease in dogs and cats: 245 cases (1985–1988). *J. Am. Vet. Med. Assoc.* 198: 465–469.

2 Hammer, A., Getzy, D., Ogilvie, G. et al. (2001). Salivary gland neoplasia in the dog and cat: survival times and prognostic factors. *J. Am. Anim. Hosp. Assoc.* 37: 478–482.

3 Regezi, J.A., Sciubba, J.J., and Jordan, R.C.K. (2012). *Oral Pathology: Clinical Pathologic Correlations*, 6e. St. Louis, Mo: Elsevier/Saunders.

4 Kilcoyne, I., Watson, J.L., Spier, S.J. et al. (2015). Septic sialoadenitis in equids: a retrospective study of 18 cases (1998–2010). *Equine Vet. J.* 47: 54–59.

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12.5 Salivary Gland Neoplasia

Salivary gland neoplasms are rarely identified in veterinary species, having been most often reported in dogs, cats, and horses. Although the majority of salivary gland tumors are epithelial, the histologic diversity and taxonomy of salivary gland tumors are notoriously complex. In dogs and cats, the parotid and mandibular salivary glands are most often affected by salivary gland neoplasia, although lesions have been reported in the zygomatic, sublingual, and minor (diffuse) salivary glands as well [5]. The 2017 edition of the WHO classification of head and neck tumors in humans [6] lists 21 malignant and 11 benign salivary gland tumors (Box 12.2). Whether this human classification system provides an appropriate template for veterinary species remains controversial.

In the 2003 edition of the WHO Classification of Tumors of the Alimentary System of Domestic Species, the authors make an argument for splitting diagnoses into separate categories [7]:

> The first step in devising a histological classification of tumors is to identity those tumors with a more or less similar pattern. The second step is to divide the broad groups into subsections. The third step is to test whether theses subgroups have sufficiently different patterns of behaviors, responses to treatment, and etiology to justify the subdivision.

Although steps one and two appear to have been achieved, the apparent rarity of these lesions has prevented Step 3 from being adequately accomplished. In this World Health Organization reference, the authors base their classifications on the human system, defining six benign and eight malignant salivary gland tumors in veterinary species (Box 12.1). More recently, the Fifth Edition of *Tumors of Domestic Animals* briefly describes six benign and nine malignant salivary gland tumors in domestic species [8]. Most of these diagnoses are derived from small case reports published in the peer-reviewed literature. Reports based on large (or at least moderate) numbers of cases with treatments and outcomes are needed.

Whether variations in biological behavior justify a "splitting approach" to salivary gland neoplasia in veterinary species has not been definitively proven either way. As a result of the extreme rarity of these tumors in domestic species, even busy university teaching hospitals may have very few salivary gland tumors in their collections. Even within a particular subtype of salivary gland tumor, histologic variation can be pronounced, as tumors (i) may be composed of multiple *cell types*, (ii) have cells arranged in *different architectural patterns* (e.g. solid, tubular, cribriform, trabecular, etc.), and (iii) the tumor-associated stroma can markedly vary from lesion to lesion (and within a particular lesion). Rarity and histologic complexity have conspired to thwart forward progress on pinning a particular diagnosis to a particular outcome.

The authors of this textbook believe that the pathologist's primary goal in regard to salivary gland tumor diagnosis should be to attempt to correctly assign the lesion into an appropriate "broad category of neoplasia" – is the lesion benign or malignant? Is the tumor derived from the salivary gland itself (a primary tumor) or alternatively, is it the result of direct extension or metastasis from another glandular tissue? For primary tumors, is the lesion comprised of neoplastic epithelium, myoepithelium, or both? Most malignant salivary gland lesions are variations on the theme of adenocarcinoma. At present, correctly identifying a lesion as a "malignant epithelial neoplasm of presumed salivary origin" is arguably more accurate and useful than giving a tenuous but specific diagnosis such as "myoepithelial carcinoma." This attitude follows the philosophy that it is better to be broadly correct than to be precisely wrong.

Along these lines, the authors advocate the following streamlined diagnostic approach to salivary gland neoplasms. The pathologist should attempt to determine (i) Is the neoplasm within the salivary gland benign or malignant? (ii) If malignant, is the neoplasm primary? If epithelial, a morphologic diagnosis of *salivary gland carcinoma* is warranted. (iii) If epithelial and the pathologist considers the lesion to be benign, a morphologic diagnosis of *salivary gland adenoma* is warranted. Beyond this, the pathologist should attempt to categorize the neoplasm according to the various entities that have been recognized in veterinary species [7] and/or humans [6] (Boxes 12.1 and 12.2). This process might lead to a diagnosis such as *salivary gland carcinoma (favor basal cell carcinoma)* or *salivary gland carcinoma (adenocarcinoma* vs. *mucoepidermoid carcinoma)*.

Box 12.1 Benign and Malignant Salivary Gland Tumors Recognized in Domestic Animals [7]

Benign	Malignant
pleomorphic adenoma	mucoepidermoid carcinoma
oncocytoma	adenocarcinoma
canalicular adenoma	cystadenocarcinoma
sebaceous adenoma	acinic cell carcinoma
ductal papilloma	myoepithelial carcinoma
cystadenoma	malignant mixed tumor
	squamous cell carcinoma
	undifferentiated carcinoma

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Box 12.2 Benign and Malignant Salivary Gland Tumors Recognized in Humans [6]

Benign	Malignant
pleomorphic adenoma	mucoepidermoid carcinoma
myoepithelioma	adenoid cystic carcinoma
basal cell adenoma	acinic cell carcinoma
warthin tumor	polymorphous adenocarcinoma
oncocytoma	clear cell carcinoma
lymphadenoma	basal cell carcinoma
cystadenoma	intraductal carcinoma
sialadenoma papilliferum	adenocarcinoma, NOS
ductal papillomas	salivary duct carcinoma
sebaceous adenoma	myoepithelial carcinoma
canalicular adenoma	epithelial-myoepithelial carcinoma
	carcinoma ex pleomorphic adenoma
	secretory carcinoma
	sebacous adenocarcinoma
	carcinosarcoma
	poorly differentiated carcinoma
	lymphoepithelial carcinoma
	squamous cell carcinoma
	oncocytic carcinoma
	sialoblastoma

Once this (admittedly modest) diagnostic goal is achieved, pathologists, clinicians, and oncologists can assemble sets of lesions which are, hopefully, correctly categorized at a broad level of classification (malignant vs. benign). With this aggregated data, investigators may be able to tie various diagnoses to biological behavior, with an eventual goal of justifying either a lumping or splitting approach to this complex group of lesions.

In this light, we intend to describe the diagnostic features of the most common neoplasms that convincingly arise from salivary tissue.

12.5.1 Benign Salivary Gland Tumors

Adenomas of the salivary gland are very rarely diagnosed in dogs and cats, representing only 5 % of all salivary tumors [5]. Salivary gland adenomas have rarely been identified in horses. Here we describe only the most commonly diagnosed benign tumor of the salivary gland, *the pleomorphic adenoma*. More extensive details on the diagnostic features of the less commonly identified benign tumors of the salivary gland are available elsewhere [6, 7, 9].

12.5.2 Pleomorphic Adenoma (Salivary Gland Mixed Tumor)

Pleomorphic adenoma is analogous to a benign mixed tumor of the mammary gland and as such, is a biphasic tumor demonstrating both epithelial and myoepithelial (mesenchymal) features along with the associated stromal components. Current molecular evidence suggests that the neoplasm initiates as a single transformed cell, capable of concurrently differentiating down both the epithelial and myoepithelial pathways. These biphasic histological features separate it from most of the other salivary gland neoplasms.

Pleomorphic adenoma is the most common tumor of the salivary glands in humans [9]. This tumor is an expansile lesion and the presenting clinical signs relate to lesion size and anatomic location. In humans, pleomorphic adenoma of the salivary gland can become quite large and may be surrounded by a pseudocapsule. Although mixed tumors of the mammary gland are relatively commonly identified in the bitch, the analogous salivary gland tumor is not. In the dog, pleomorphic adenoma has been described in both the major and minor salivary glands.

The term *pleomorphic* indicates the wide architectural variety this tumor can demonstrate. The ratios of the epithelial to myoepithelial components vary from lesion to lesion, as does the architectural arrangement of the epithelium. These tumors can be predominantly composed of epithelium, primarily myoepithelium, or a more or less equal ratio of both. The neoplastic epithelium can form ducts, tubules, plexiform ribbons, sheets, or trabeculae. Mitotic figures are rare. The epithelium is entrapped within the myoepithelial stroma, which is comprised of spindloid cells associated with a myxoid or even cartilaginous ground substance (extracellular matrix) (see Figure 12.10). As is true for mixed tumors of the mammary gland, metaplastic bone can also develop within these lesions. The treatment of choice is surgical excision; incomplete excision leads to recurrence. In humans, untreated lesions have been known to undergo malignant transformation (*carcinoma ex-pleomorphic adenoma*).

12.5.3 Malignant Salivary Gland Tumors

As is true for veterinary species, malignant salivary gland tumors in humans are rarely encountered and few pathologists have experienced the full range of salivary cancers [10]. The wide range of morphologic diversity both between and within tumor types means that a diagnosis may not be achievable based upon small incisional biopsy submissions [10]. In humans, large salivary gland malignancies tend to have poor prognosis [10]. Malignant salivary gland tumors in humans can be graded as low or high-grade based upon mitotic rate, cellular pleomorphism, and glandular differentiation [11]. A battery of immunohistochemistry (IHC) assays provide useful tools for pathologists who work with human tissues; in

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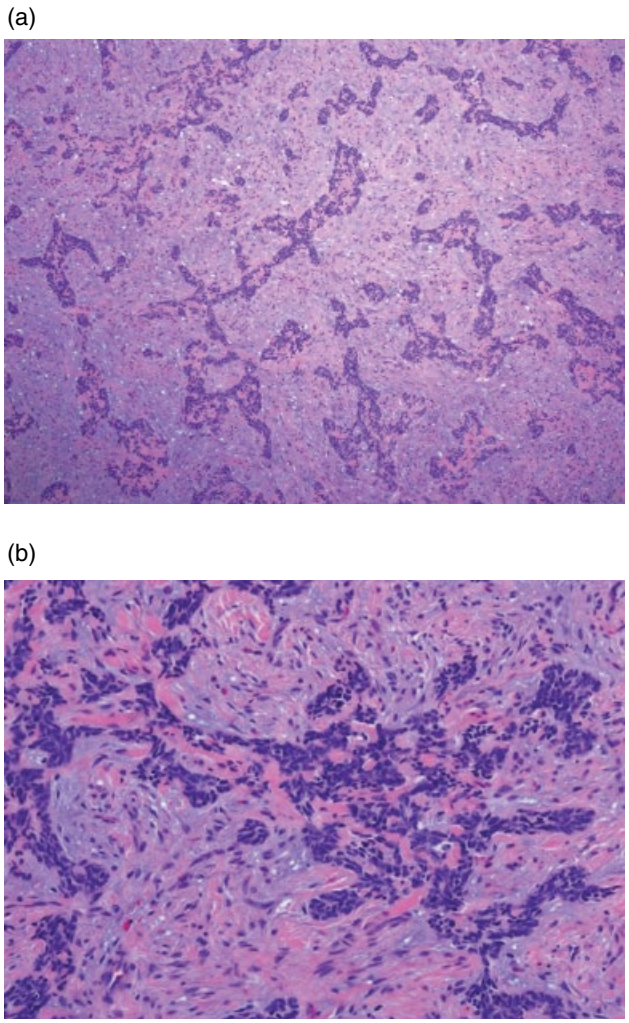


Figure 12.10 Histological images of pleomorphic adenoma, submandibular salivary gland, 28-year-old horse. This biphasic tumor is composed of branching plexiform ribbons of epithelium with bland cytological features embedded within a myxomatous mesenchymal stroma (myoepithelial stroma). (a) Low magnification and (b) high magnification images. *Source:* S. Diab, California Animal Health & Food Safety (CAHSFS), San Bernardino, CA.

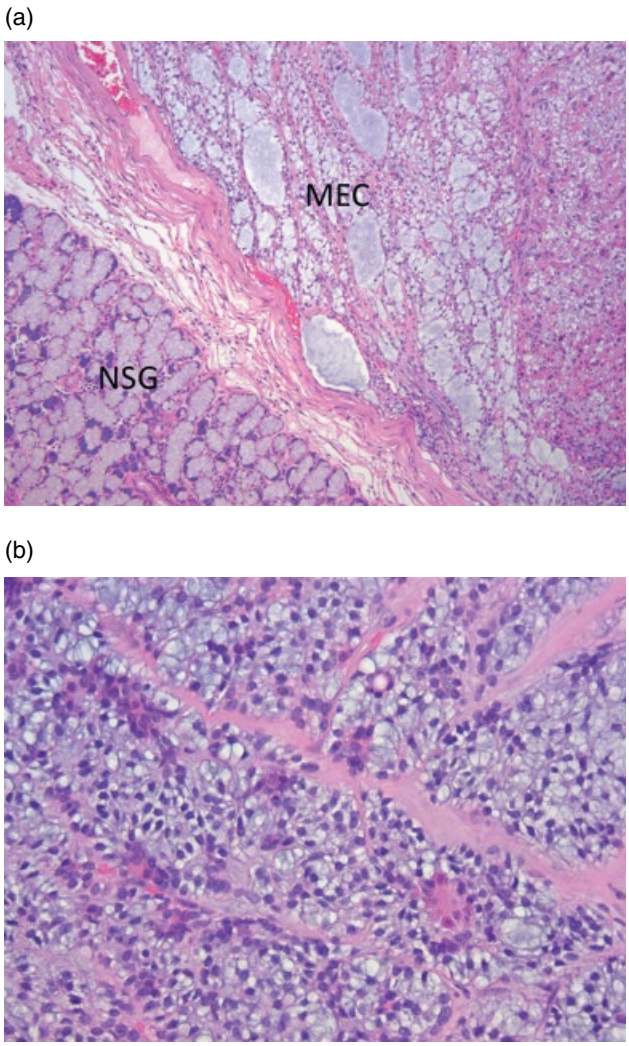


Figure 12.11 Histological images of mucoepidermoid carcinoma (MEC), submandibular salivary gland, 13-year-old miniature pinscher dog. (a) Normal salivary gland (NSG) is evident in the lower left corner, while the MEC is in the upper right. Numerous mucin-filled cysts are evident in this low-magnification image. (b) Mucus-containing epithelial cells form nests and lobules separated by fibrous stroma. In this MEC, the neoplastic epithelial cells have relatively bland cytological features. CT imaging revealed a concurrent pulmonary mass which was cytologically consistent with carcinoma.

general, the validity of these reagents has not been tested in lesions derived from domestic animals.

In a study of 30 cats with malignant salivary gland neoplasia, Siamese cats appeared to be overrepresented [5]. In this same study, median survival time for cats and dogs with malignant salivary gland tumors was 516 or 550 days, respectively. These investigators determined that histopathological features were not helpful in predicting survival times. This data supports our contention that the most important component of the diagnosis is whether or not the salivary gland tumor is malignant or benign (e.g. salivary gland carcinoma vs. adenoma).

12.5.4 Mucoepidermoid Carcinoma

Mucoepidermoid carcinoma (MEC) is a glandular tumor demonstrating varying degrees of mucin (mucus) production. This is one of the more common malignant salivary gland tumors in people, with a biological behavior ranging from low to high-grade [9]. The tumor readily metastasizes to local lymph nodes and distant sites. MEC has rarely been diagnosed in dogs and cats [8].

MEC is an invasive tumor that has a lobular architecture. Variably sized, mucus-containing cysts and

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microcysts are a common feature of the tumor (Figure 12.11). Mucus should stain positively with PAS, mucicarmine, or alcian blue. Ruptured cysts may result in a granulomatous reaction (mucin extravasation). The tumor is comprised of differentiated mucus-secreting cells and less differentiated epidermoid cells, and the proportion of these two cell types varies from lesion to lesion. The neoplastic epithelium also varies in state of differentiation; less differentiated tumors have less mucus production, higher levels of cellular pleomorphism, and increased numbers of mitotic figures. Infiltration into the adjacent normal tissue may be evident at the lesion margin. In people, small biopsy specimens of mucoepidermoid carcinoma have been mistakenly diagnosed as mucocele.

12.5.5 Adenocarcinoma

Although almost all of the primary malignant tumors of salivary glands are adenocarcinomas, the diagnosis of salivary gland adenocarcinoma in humans is restricted to those lesions lacking specific architectural, cytologic, and immunohistochemical features of the other salivary gland tumor subtypes. In humans, this type of tumor is referred to as *adenocarcinoma, not otherwise specified* (NOS) [6]. Salivary gland adenocarcinoma, NOS is rarely diagnosed in people but happens to be one of the most frequently diagnosed malignant salivary gland neoplasm in veterinary species [5]. Since most (almost all) of the malignant salivary gland tumors are actually adenocarcinomas, it does not really make sense to have a subcategory of malignant salivary gland tumor named *adenocarcinoma*. Going forward, it seems likely that salivary gland adenocarcinomas diagnosed in veterinary species will be divided into other subtypes (or maybe not, if a lumping approach to salivary gland taxonomy wins the day).

Salivary gland adenocarcinoma has been diagnosed in older dogs and cats (Figure 12.12), and a few cases have been reported in horses and cattle [7]. Adenocarcinoma is the most commonly diagnosed salivary gland malignancy in cats [7]. Adenocarcinoma of the salivary gland can be comprised of neoplastic epithelial cells forming acini, ducts, trabeculae, or solid sheets [8]. Some tumors can demonstrate cyst formation. Tumor cells span a wide range of morphologies including cuboidal, columnar, polygonal, clear, mucinous, oncocytoid, and plasmacytoid. Invasive growth at the lesion periphery, central necrosis and hemorrhage may be present. In dogs, metastases have been reported in the local lymph nodes and distant sites [7]. Grading has been shown to have a prognostic significance in humans, but did not predict survival in a study focused on dogs and cats [5].

Pathologists should bear in mind that adenocarcinomas from other anatomic sites (e.g. mammary gland, lung, ceruminous gland) have been known to metastasize to the oral cavity and jaws (areas where salivary glands would normally be found). A diagnosis of primary salivary adenocarcinoma should never be made without engaging the clinician in a conversation about the possibility of a metastatic lesion, particularly in animals that have a history of glandular neoplasia.

12.5.6 Acinic Cell Carcinoma

The serous acinar cell of the salivary gland is the namesake for the acinic cell carcinoma. In humans, acinic cell carcinoma occurs most frequently in the parotid gland, with a minority of tumors occurring in the minor salivary glands [12]. In human patients, these tumors can be associated with vague, intermittent oral pain, and facial paralysis in some [6]. In dogs, these tumors have been identified in both the major (parotid) and minor salivary glands, including the tongue [13]. Acinic cell carcinoma is considered to be a low-grade malignancy [7]. Although acinic cell carcinoma is the most commonly diagnosed salivary gland malignancy in dogs, it has rarely been reported in cats and horses [7].

Although the acinic cell carcinoma is named after the acinar cell of the salivary gland [6], the precise cell of origin for this tumor is a bit mysterious, as the tumor is comprised of multiple cell types forming several different architectural arrangements [12]. By definition, acinic cell carcinomas must contain at least some neoplastic cells with acinar differentiation – large polygonal cells



Figure 12.12 Gross image of salivary gland adenocarcinoma in the base of the tongue, 16-year-old DLH cat. *Source:* B. Hewitt, Cheyenne West Animal Hospital.

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Figure 12.13 Gross image of salivary gland basal cell adenocarcinoma, palatoglossal folds, 8-year-old DSH cat. *Source:* D. Nossaman, Dallas Veterinary Dentistry and Oral.

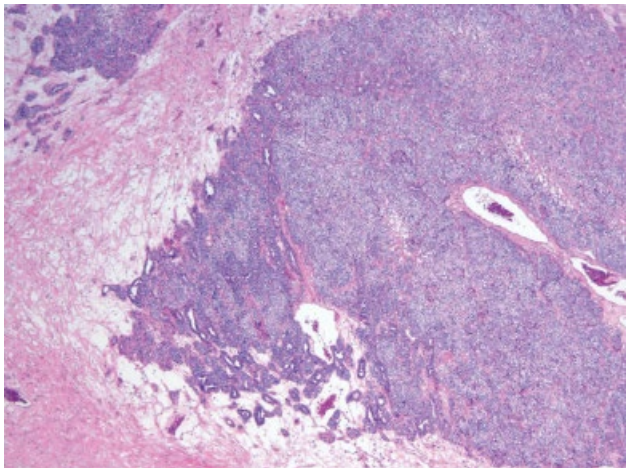
with granular cytoplasm. Mucin stains (PAS, alcian blue and mucicarmine) should positively stain this cytoplasmic material. Although the cytoplasmic granules are PAS-positive and diastase-resistant, PAS-positivity can be "patchy." In addition to the acinar cell type for which it is named, acinic cell carcinoma may also contain neoplastic ductal cells with vacuolated, clear, or oncocytic cytoplasmic features (oncocytes are cells with abundant granular eosinophilic cytoplasm thought to represent excessive numbers of mitochondria).

To further add to the complexity of this tumor type, acinic cell carcinomas can be organized into a multitude of architectures including solid sheets, nodules, microcystic, papillary cystic or follicular patterns (thyroid gland-like) [7]. Acinic cell carcinoma has rare mitoses, rare necrosis, and minimal cytologic pleomorphism. Acinic cell carcinoma is considered to be a low to intermediate grade malignancy in humans [9]. Poor prognostic features (in humans) include large size, incomplete resection, and multiple recurrences [6]. Variation in cell types and architectural features can lead to diagnostic confusion among pathologists. This is especially true considering how rarely this tumor is encountered.

12.5.7 Basal Cell Adenocarcinoma

Although basal cell adenocarcinoma of the salivary gland was not included in the 2003 veterinary-based WHO classification scheme of salivary gland tumors [7], the authors have identified several lesions histologically consistent with this entity in dogs and cats (Figures 12.13 and 12.14). Criteria for diagnosis of salivary basal cell adenocarcinoma have been

(a)



(b)

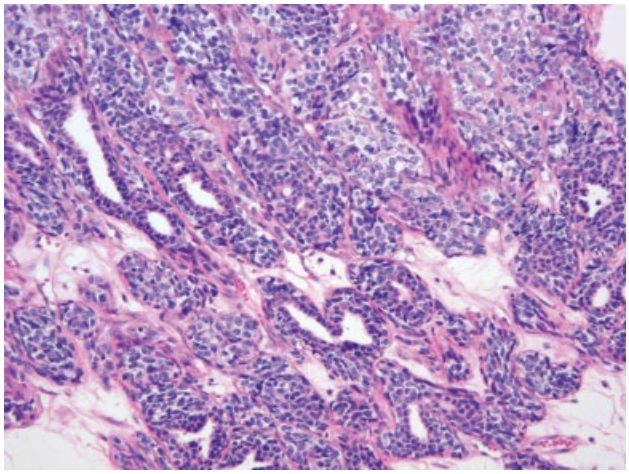


Figure 12.14 Histologic images of basal cell adenocarcinoma, submandibular salivary gland, 13-year-old Cocker spaniel dog. (a) Low- and (b) high-magnification images. The tumor is comprised of neoplastic basaloid cells arranged in solid nests, packets, and tubules. The neoplastic epithelial cells were positive for pancytokeratin expression, and negative for chromogranin A and synaptophysin by IHC. At the time of surgical biopsy this submandibular tumor was 8 cm in diameter and had been present for approximately two years. *Source:* F. Giannitti, California Animal Health & Food Safety (CAHSFS), Davis, CA.

well-described for humans [6, 9]. This lesion is considered to be the malignant counterpart to basal cell adenoma, to which it is histologically similar. However, unlike basal cell adenoma, basal cell adenocarcinoma exhibits an infiltrative growth pattern. In humans, this tumor is regarded to be a low-grade, minimally invasive malignancy [9].

Basal cell adenocarcinoma is primarily comprised of neoplastic basaloid cells with large round homogeneous nuclei forming nests, cords, and solid zones. Occasionally the basal cells may form ducts and

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tubules (this is an adenocarcinoma, after all). Smaller, compact basal cells may surround (palisade) larger polygonal cells. This tumor should be differentiated from basaloid squamous cell carcinoma and adenoid cystic carcinoma.

References

5 Hammer, A., Getzy, D., Ogilvie, G. et al. (2001). Salivary gland neoplasia in the dog and cat: survival times and prognostic factors. *J. Am. Anim. Hosp. Assoc.* 37: 478–482.

6 El-Naggar, A. K., Chan, J. K. C., Rubin Grandis, J., Takata, T., & Slootweg, P. J., International Agency for Research on Cancer. (2017). WHO classification of head and neck tumours. International Agency for Research on Cancer, Lyon.

7 Head, K. W., Armed Forces Institute of Pathology (U.S.), American Registry of Pathology., & WHO Collaborating Center for Worldwide Reference on Comparative Oncology. (2003). Histological classification of tumors of the alimentary system of domestic animals. Published by the Armed Forces Institute of Pathology in cooperation with the American Registry of Pathology and the World Health Organization Collaborating Center for Worldwide Reference on Comparative Oncology, Washington, DC.

8 Meuten, D.J. (2017). *Tumors in Domestic Animals*, 5e. Ames, Iowa: John Wiley and Sons.

9 Regezi, J.A., Sciubba, J.J., and Jordan, R.C.K. (2012). *Oral Pathology: Clinical Pathologic Correlations*, 6e. St. Louis, Mo: Elsevier/Saunders.

10 Speight, P.M. and Barrett, A.W. (2002). Salivary gland tumours. *Oral Dis.* 8: 229–240.

11 Seethala, R.R. (2009). An update on grading of salivary gland carcinomas. *Head and neck pathol.* 3: 69–77.

12 Barnes, L. and UniversitätsSpital Zürich. Departement Pathologie., International Academy of Pathology., & World Health Organization, International Agency for Research on Cancer (2005). *Pathology and Genetics of Head and Neck Tumours*. Lyon: IARC Press.

13 Brunnert, S.R. and Altman, N.H. (1990). Canine lingual acinic cell carcinoma (clear cell variant) of minor salivary gland. *Vet. Pathol.* 27: 203–205.

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Appendix

A.1 Processing Teeth Submitted as Biopsy Specimens

There are a number of reasons why a pathologist might receive one or more teeth for pathologic examination. Teeth might be submitted *in situ* within a resected jaw specimen, as the lesion in question might directly involve the teeth, the jawbone, or both. Individual teeth might be submitted if the clinician is interested in the attached periodontal tissues (e.g., so-called "tooth root abscess"), to determine the status of the pulp cavity, or to confirm the presence of crown or root resorptive lesions/ caries. Odontogenic cysts typically have a relatively specific anatomic relationship with either the tooth crown or root and may be submitted attached to the adjacent tooth.

Whatever the reason, it is likely that the submitting clinician has a specific question or questions. A careful reading of the submitted documentation is in order. The clinician may be concerned about the relationship of particular teeth and a lesion. Precisely identifying teeth during the grossing stage will allow this information to be included in the pathology report. Feline and canine dental charts posted at the pathology trim station will help in this process.

For most histology laboratories, the preparation of non-decalcified tissue sections of mineralized tissues such as teeth is not an option. It is important to realize that as a result of the decalcification process, lesions in the crown enamel (e.g., enamel hypoplasia) will likely not end up on the histology slide. Therefore, in order to document gross enamel lesions, photographing the tooth from at least two different angles prior to decalcification is advised. These gross images can be included in the pathology report.

Teeth should be fixed in an adequate volume of formalin (10 parts formalin to 1 part tissue) for at least 48 hours prior to decalcification. For most small animals, teeth can generally be processed intact in the decalcification solution of choice (see the next section, A.3 Recommended Best Practices, for more details on decalcification). The decalcification solution may need to be changed every two to three days. Depending upon the solution and strength, it may require up to a week of time. Monitoring the progression of decalcification (can the tooth be cut with a sharp knife?) on a daily basis is recommended.

If the clinician is interested in the status of the tooth pulp, we recommend that the tooth be sliced transversely into multiple round/ discoidal specimens. This will maximize the chance that the pathologist will get one or more good diagnostic sections on which to evaluate the pulp tissues for inflammation, necrosis, or other pathology. In teeth from older animals, the pulp cavity will generally be relatively narrow. As a result, longitudinal sections may miss the cavity completely. Even in transverse tooth sections, the difference in tissue density between the pulp cavity and surrounding dentin can result in artifactual separation and loss of the pulp tissues in histological sections. Having the opportunity to examine multiple transverse sections minimizes this eventuality. The attached periodontal ligament can also be evaluated from these transverse sections.

For large specimens such as equine teeth, pre-sectioning of the teeth using either a hand saw (hacksaw), oscillating saw (Stryker) or band saw prior to decalcification is recommended (see A.3, Best Practices, below). Pre-sectioning of the mineralized tissue to 3–4 mm thick will minimize the (often extensive) time required for decalcification. Equine incisors and cheek teeth can be quite large, much too large to fit in a standard-sized histology cassette. The specific feature of interest (hypercementosis, resorptive lesion, pulp/ infundibular necrosis) should be targeted. Even with pre-sectioning, equine teeth can take an inordinate amount of time to decalcify (give it a try, see how long it takes). Extensive decalcification times contribute to an eosinophilic "washed out" appearance and a general lack of differential staining. Pre-sectioning of the specimen, trimming the mineralized tooth to the size of the specimen cassette, using large volumes of decalcification solution, stirring the solution using an auto stirrer and frequently changing the solution can

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help to speed the decalcification process along. As always, the pathologist should charge for his/ her time and excellent diagnostic service.

A.2 Face Decalcification of Paraffin Blocks

Best histopathology practices involve adequate formalin fixation and decalcification *prior to* paraffin embedding. Despite best efforts, eventually some demineralized formalin-fixed paraffin embedded tissues will not be sectionable on a microtome. Fortunately, the technique of *face decalcification* can rescue these precious tissues.

Successful face decalcification of overly mineralized specimens is an art – experienced histology technicians use a delicately balanced iterative process of hot/cold water baths and various decalcification solutions to salvage the situation. During the "facing in" procedure (also known as "roughing into the block"), the technician will recognize that the tissue block cannot be adequately sectioned in its current state. Based on the specific situation at hand, the histotechnologist will select a rapid decalcifying agent such as Decal Stat (HCl + EDTA) or a less aggressive approach such as 5–15 % formic acid. The recalcitrant tissue block should be warmed for a few minutes in warm water bath (to aid uptake of the decalcifying agent), soaked in the decalcification solution for *a few minutes*, placed in an ice water bath for a minute or two (to harden the supportive paraffin) followed by another attempt to cut the section on a microtome. If the block continues to stubbornly resist sectioning, the process is repeated and tweaked (perhaps multiple times) as needed.

Successful paraffin block face decalcification requires both patience and perseverance. Pathologists should remember that the histology technician brings valuable skills to the diagnostic process, possibly skills that the pathologist does not possess. Recognition of these skills, praise for a job well done and perhaps even some form of remuneration for a patient and skilled histotechnologist will help to ensure high-quality histology sections.

A.3 Recommended Best Practices for "Grossing" Mandibulectomy and Maxilectomy Surgical Specimens

Partial to complete mandibulectomy and maxillectomy specimens are anatomically complicated and present a challenge on multiple levels for the examining pathologist. If processed correctly, such specimens can provide invaluable diagnostic information. However, trimming of such specimens, or "bone grossing," can be cumbersome, dirty, and physically demanding [1]. If precautions are not taken, sharp bone fragments and cutting instrumentation can present a real hazard.

The pathologist should bear in mind the information that the submitting clinician is likely to be interested in learning – (i) *what is this lesion* (what is the diagnosis and is it consistent with the prior incisional biopsy)?, (ii) *how does the histologic lesion associate with the clinical and radiographic findings?,* and (iii) *did I get it all?* For some of the more esoteric lesions in oral pathology, the clinician might actually be most interested in the answer to the third question.

The submitting clinician may also be interested in the relationship of the lesion to the jawbone, teeth, periodontal ligament, and soft tissues like the lips or tongue. The pathologist should take an interest in these details as well, as the diagnosis of a particular lesion may pivot upon the presence or absence of bone invasion and/or the relationship of the periodontal ligament and histological features of the teeth (is the pulp viable? is it inflamed?). To answer these questions, the pathologist must do a number of operations correctly and in the correct order.

The second chapter of the fifth edition of *Tumors in Domestic Animals* describes a simple and practical approach to approaching mandibulectomy and maxillectomy surgical specimens [2]. The chapter authors recommend an approach similar to that for amputated digits. First, the pathologist or technician should incise a wedge through a non-mineralized aspect of the oral lesion, ideally prior to decalcification. This sample should provide a high-quality specimen from which to address the *issue of diagnosis*. The authors recommend decalcifying the bulk of the surgical specimen (resected jaw) and to then cut *en face* sections at both the rostral and caudal surgical margins. In an attempt to address the "did I get it all" question of the submitting clinician, these sections should be marked with ink and placed into separate cassettes.

Although we are in general agreement with this approach to grossing jaw lesions, we recommend a few additional steps in order to maximize the diagnostic value of these very often difficult to obtain specimens. While it is true that a partially excised jaw represents a significant expenditure for the owner, such a submission represents a tremendous cost for the patient as well. Although our recommended approach to these submissions may require more time and effort, we believe this effort is justifiable. We support the pathologist who is willing to appropriately charge for excellent diagnostic service.

For pathology practices that receive specimens from elsewhere, the accepted processing strategy is most often fixation-section-decalcification [1]. However,

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sectioning-fixation-decalcification is also commonly performed, especially for samples obtained directly from necropsy procedures. The pathologist should bear in mind the zoonotic risks associated with using cutting instruments like band saws in cases where infectious agents are on the differential list (e.g., fungal infections, mycobacteria, other zoonotic microbes). In such cases, formalin fixation prior to sectioning is advised.

The authors of this textbook recommend the following general procedure as a best practice for grossing jawbone specimens. Of course, the ultimate strategy is always situation-dependent and should be made by the examining pathologist.

- Describe, measure, and photograph the gross features of the specimen.
- Obtain microbial cultures or fresh tissue specimens, if warranted.
- Appropriately mark the margins with tissue dye(s). Some pathologists may prefer to do this post-fixation.
- If not already performed, adequately fix the specimen in formalin.
- Section the specimen –
  - Cut a soft tissue wedge into the lesion along with sections adequate to evaluate soft tissue margins, submit for processing.
  - Cut one or more transverse section(s) through the oral lesion, bone, and associated teeth. This may be necessary to determine the extent of invasion and will guide selection of which section(s) will best represent the critical margins.
  - Cut in the rostral and caudal aspects of the resected jawbone.
- Decalcify the bony sections.
- Perform final trimming to the dimensions of the tissue cassette.
- Submit the samples for tissue processing.

Ideally, the resected tissue should have been submitted with clinical documentation including patient signalment and history, a working clinical diagnosis (perhaps based upon information from a prior incisional biopsy or fine needle aspirate), imaging results, and perhaps even digital photographs. The biopsy specimen may or may not have been inked prior to formalin immersion. The clinician may have particular concerns about the status of a specific surgical margin in addition to the rostral/ caudal aspects of the resected jawbone. The clinician may be interested in the relationship of the lesion to particular teeth, and perhaps interested in the histological status of particular teeth. As a result, a careful reading of the clinician's submission form is advised, as it will facilitate an approach to the case maximizing the chances of a positive outcome for all of the concerned parties.

The surgical specimen should be measured in three dimensions and the lesion, if grossly apparent, should be described. The relationship of the lesion to particular teeth should be recorded. To facilitate this, charts of the dental anatomy/ tooth numbering systems of companion animals could be posted near the trimming station for reference. The specimen should be photographed. There are several compelling reasons to photograph biopsy specimens – (i) the image can be incorporated into the report that is returned to the submitting clinician, (ii) the photograph can be diagnostically useful as a reference for the pathologist (especially if the pathologist was not involved in trimming the specimen), (iii) high-quality gross images can be useful for both teaching and eventual publication (if the pathologist is involved in these endeavors).

Although many pathologists choose to use a cellphone to photograph lesions, a better outcome will be achieved through the use of a dedicated digital camera. An appropriate camera for this purpose does not necessarily need to be expensive. Ideally, the pathologist should have the ability to mount the camera onto a stand with appropriate lighting. Several easy-to-clean colored panels should be available to provide appropriate contrast.

If not previously performed, the various surgical margins of the specimen should be inked. The Davidson Marking System (Bradley Products) and Cancer Diagnostics, Inc. provide a wide variety of high-quality tissue dyes for this purpose (Figure A.1). The dyes should be judiciously applied using cotton applicators and the anatomic locations of each dye recorded. A warning: excessive dye can quickly get out of control! The submitting clinician may be particularly interested in the status of certain margins like the lips, tongue, or palate in addition to the rostral/ caudal bone margins. If a soft tissue



Figure A.1 A set of tissue-marking dyes is essential for delineating surgical margins.

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oral mass is present, it should be sampled by wedge resection. In some jawbone resections, an oral mass may not be evident. This might be the case if an incisional biopsy procedure was recently performed, resulting in gross debulking of the oral lesion.

At this point, the pathologist (or technician) will need to make some decisions concerning sectioning of the mineralized specimen and decalcification. These decisions should be made on a case-by-case basis and reflect (i) the overall size and shape of the biopsy specimen, (ii) the presence of teeth, (iii) the relationship (or inferred relationship) of the lesion to the underlying bone and (iv) clinical imaging information.

Izak B. Dimenstein has an excellent web site entitled Grossing Technology in Surgical Pathology http://grossing-technology.com/grossing-technology-in-surgical-pathology/ (with many useful tips for grossing bony specimens). He has made the case that there are three main conditions that affect the success of obtaining diagnostic bone sections: specimen immobilization, the use of an appropriate cutting instrument, and orienting the specimen correctly [1]. Perhaps the most important of these is specimen immobilization.



Figure A.2 Vacuum base vices, such as this PanaVise, securely immobilize irregularly shaped biopsy specimens. A variety of materials can be inserted between the specimen and the jaws of the vice to prevent crushing of the specimen.

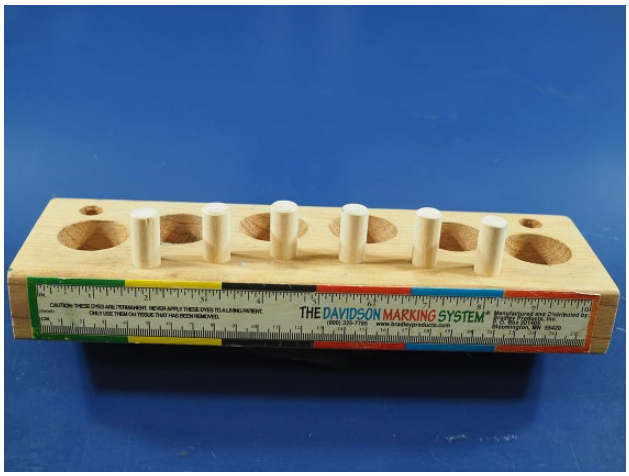


Figure A.3 The Davidson Marking System tray can be used as a "wooden immobilization gadget" to immobilize biopsy specimens for sectioning. Moistened cardboard or paper packed around the specimen will help hold it in place.

A.4 Specimen Immobilization

Proper immobilization of the specimen allows the pathologist or technician to make precise, well oriented cuts. Resected jawbone specimens are often oddly shaped and may include fragile components such as attached soft tissues or thin bony structures. As a result, there is no "one-size-fits-all approach" to immobilization, and a number of different options should be available in the trim room. A relatively inexpensive vacuum base vice, such as the PanaVise, facilitates specimen immobilization (Figure A.2). Bubble packing material, sheets of absorbent paper, or cardboard inserted between the jaws of the vice and the specimen prevents damaging of the specimen and facilitates immobilization.

Dimenstein argues persuasively for the use of hard pressed cardboard carton material as an inexpensive, disposable, and excellent stabilizer of irregularly shaped bony specimens [1]. This material is widely available, comes in a number of different shapes, and through the use of damp paper placed between the specimen and the cardboard, adequately immobilizes the specimen for cutting. Perhaps most importantly, the path of the cutting blade will not be impeded by the cardboard. This is not the case for a vice. The wooden Davidson Marking System dye rack can also be used as a "wooden immobilization gadget" to hold a complex bony specimen securely in place for cutting (Figure A.3) [1]. Immobilization is facilitated by packing moistened absorbent paper material around the surgical specimen to increase the frictional contact between the wooden rack and specimen. Cuts made through the specimen can pass into the wooden rack without consequence.

A.5 Cutting Instrumentation

Associated soft tissues (and perhaps the oral lesion itself) can be sampled using a scalpel blade or other sharp knife. However, no matter how sharp the blade, it will not adequately cut bony tissue that has not been previously decalcified. Cutting bone or mineralized tissue requires the use of a toothed saw. A number of different manual and power-cutting options exist. Although power band



Figure A.4 The Stryker Autopsy Saw has multiple blade options.

saws make short work of bone sectioning, some pathologists feel that they have no place in surgical pathology. These tools are relatively imprecise, are difficult to clean, may strip the adjacent soft tissue from the bone and can be dangerous to the operator (accidental cuts, thrown debris, noise, volatilized tissues). Although these deficiencies may exist, inexpensive table top band saws are available with small, relatively precise blades that result in the removal of less *kerf* (the width of material lost by the cutting action of the saw blade). Hand held oscillating surgical power saws, such as the Stryker Autopsy Saw (Figure A.4) are safer and offer a more precise cut. A disadvantage of these hand-held power saws is the limitation in the depth of cut introduced by the depth of the blade.

A variety of manual handsaws, such as inexpensive mini hacksaws and fretsaws (coping/ jigsaw) have disposable blades and offer perhaps the best solution to cutting bony tissues like jaws (Figures A.5 and A.6).



Figure A.5 Mini hacksaws are inexpensive, come in a variety of shapes, and can be equipped with disposable saw blades with varying teeth density (TIN).



Figure A.6 Coping saws are inexpensive and are ideal for delicate and precise cuts.



Figure A.7 The Mopec Dual Blade ZawBones has a jig to securely immobilize the bony specimen and two parallel mounted hacksaw blades to cut 2 mm wide transverse sections. Shandon sells a similar cutting system.

These light saws facilitate precise and relatively safe cutting. Mopec's Dual Blade ZawBones is a simple to use manual hacksaw device (https://www.mopec.com/product/zawbones-bd130-2) (Figure A.7). The stand holds irregularly shaped bones securely while the dual bladed hacksaw cuts neat, 2 mm thick sections.

The coarseness of the blade's teeth is the defining feature of the saw, as the finer and more precise the cut, the higher the number of teeth per inch (TIN) required [1]. For most blades, the TIN varies from 18–32, with small fragile specimens requiring both a light touch and high blade TIN. A blade with high TIN will require a longer cutting time but will reduce specimen damage due to crushing or tearing.

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A.6 Orienting the Specimen

Orienting the specimen for sectioning in an optimal manner is highly dependent upon the particular features of the anatomic structure and the particular lesion. Sectioning may require the use of a combination of perpendicular cuts (so that margins can be measured) and tangential sections (*en face*, to evaluate the entire marginal face).

During the grossing procedure, the pathologist should bear in mind the dimensions of the cassette and glass histology slide. Typical histology cassettes are approximately 3 × 2.5 cm and slightly less than 5 mm deep, while tissue capsules for small delicate specimens (Micromesh, Thomas Scientific) are substantially smaller. The sample should be sectioned with this constraint in mind. Samples less than 4 mm thick must be obtained.

What specific features of the lesion does the pathologist wish to capture on the histology slide? The interface of the oral lesion and the underlying bone or tooth? The relationship between the adjacent soft tissues and the osseous lesion? The extent of the lesion in the rostral-caudal plane? Whether the jawbone is cut in a longitudinal or transverse manner and how many sections are taken through the lesion should be dictated by these varying objectives.

A.7 Decalcification

Removal of the mineralized component of the jaw and lesion (decalcification) is generally required for obtaining high-quality histology specimens. Large specimens, especially those containing teeth, should be rough-sectioned using a power saw or handsaw prior to decalcification. Specimens such as equine teeth, highly mineralized odontoma lesions, and skull specimens including the petrous temporal bone can be particularly difficult to decalcify. Try to avoid the trap of initially rough-cutting a bony specimen into sections that are *too thick to fit into a cassette* (e.g. >5 mm wide) (see Figure A.8). After decalcification, these slices can be very difficult to precisely split to the dimensions of the embedding cassette.

For small specimens, such as partial jaw resections from a cat or small dog, the entire specimen can be immersed in the decalcification solution *prior to any trimming*. Of course, this should only occur after adequate formalin fixation has been achieved. For larger specimens or lesions associated with one or more large teeth (canine/ cheek teeth) the biopsy specimen should be thin-sectioned using an appropriate saw prior to decalcification, as large jaws that are decalcified *en block* will likely require an inordinate amount time for processing. This will delay the diagnostic turnaround time and may damage the histological features of the submission.

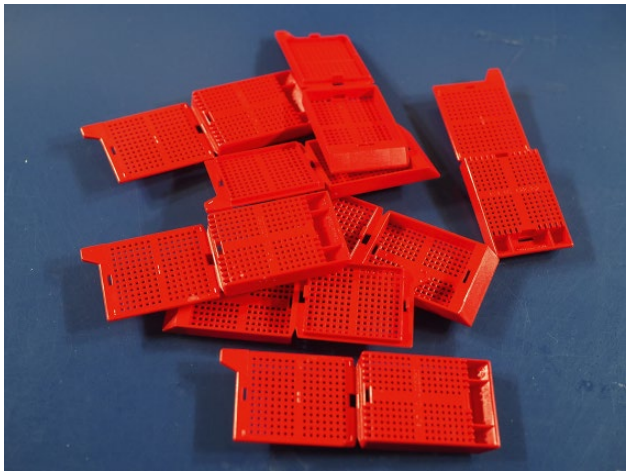


Figure A.8 During specimen sectioning, it is best to always keep cassette size in mind.

A variety of options for decalcifying solutions are available including various acids (formic acid, hydrochloric acid), EDTA solutions, and decalcification solutions and fixatives combined into one product. These solutions are available commercially and generally include buffering salts. Tissues exposed to strong acids should be rinsed prior to submitting them for tissue processing. Although an in-depth analysis of the various options that are available for tissue decalcification is beyond the scope of this chapter, a resolute and unwavering reliance on one approach for all situations is perhaps ill-advised. Pathologists should consider performing a decalcification trial using mandibular compact bone and the more delicate maxillary bone exposed to different decalcification solutions. A number of decalcification tutorials are available online through Leica Biosystems (https://www.leicabiosystems.com/pathologyleaders/an-introduction-to-decalcification) and IHC World (http://www.ihcworld.com/_protocols/histology/decalcification_solution.htm).

Changing the decalcification solution every two to four days will reduce the overall time required. Some pathologists prefer to change the decalcification solution on a daily basis. Some laboratories use automated stir bars during decalcification. Checking the pliability of the specimen every few days will help to determine the endpoint; the ultimate test is whether or not the tissue can be easily sectioned with an appropriate blade.

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Inadequately decalcified specimens will result in poor quality histology sections (sectional fragmentation, see A.2 Face Decalcification). One method to avoid under-decalcification is to soak the trimmed tissues in fresh solution for an additional 24 hours after sectioning. Over-decalcification should be avoided, as such specimens have a diffuse loss in the range of staining intensity.

References

1 Dimenstein, I.B. (2008). Bone grossing techniques: helpful hints and procedures. *Annals of Diagnostic Pathology* 12: 191–198.

2 Meuten, D.J. (2017). *Tumors in Domestic Animals*, 5e. Ames, Iowa: John Wiley & Sons.

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