Canine oral lesions: a decision-tree approach to ulcers, leukoplakia, and pigmented lesions

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ABSTRACT
Lesions in the oral cavity of dogs can be erythematous, leukoplakic, or pigmented in coloration. The diagnosis of oral erosions, ulcers, and white lesions in contrast to pigmented lesions in veterinary practice can be challenging. The most benign-looking oral ulcers can be associated with local malignant or systemic disease. Many factors are important in the evaluation and correct diagnosis of oral lesions, including medical and drug history, description of the lesion, number of lesions, depth of the lesion, biopsy technique, and correct histologic interpretation. The goal of this paper is to create a decision tree to guide the classification and proper diagnosis of canine oral mucosal lesions.

Keywords: oral lesions, diagnostic approach, red/erythema, white/leukoplakia, blue/pigmented

Introduction

Oral lesions are common in dogs, although they often go undetected. Unless there is halitosis, ptyalism, hemorrhage, a gross mass lesion, or inappetence, some lesions may persist unnoticed. For a head-shy or painful pet, it may be difficult for the veterinarian to perform a good awake oral examination. Common oral diseases such as periodontitis and endodontic disease may present with oral lesions, although erosions, ulcers, and pigmented or leukoplakic white lesions are the subject of this manuscript.

Diagnosis of mucosal lesions is difficult as the lesions may appear similar to other lesions and have vague clinical symptoms, and they are rarely diagnosed based on oral exam appearance alone. Critical to accurate diagnosis, a clinician must conduct a comprehensive historical and physical examination. A detailed description of the lesion should be recorded. Lesion descriptors include color, shape (regular or irregular), size (all dimensions), consistency, surface (smooth, granular, verrucous, papillomatous, pebbly, cobblestone), demarcation (homogeneous or not), duration of the lesion, how many lesions are present, has the lesion been present before and disappeared, has there been a change in the lesion over time, is the origin acquired or nonacquired, is there a temporal association with new medications, is there a travel history, are there toxins or foreign bodies in the environment, is it painful, and are there other parts of the body where the lesion is present or is there systemic disease.1,2

Two terms borrowed from the dermatology literature are primary lesions and secondary lesions. The term “primary” is used to describe a lesion as it first appears, for example, a plaque. A “secondary” lesion results from an alteration of the primary lesion either in the natural course of disease or as the result of manipulation or treatment. Essential morphologic terms, for nonblister form lesions, allow us to define and communicate about lesions. Primary lesions include macule, patch, papule, plaque, nodule, and tumor. Flat circumscribed lesions < 10 mm include macules and patches. A papule is a circumscribed, elevated, solid lesion that is < 5 mm in diameter. Whereas a plaque is a circumscribed, elevated, solid lesion that is > 10 mm in diameter and is usually broader than it is thick and appears pasted on.2,3 A nodule represents a palpable, solid lesion deep in the mucosa that is > 10 mm in diameter and is either sessile or pedunculated. A tumor is > 2 cm and may be above, level with, or below the mucosa. Secondary lesions include erosions, ulcers, fistulas, fissures, and scar formation.2 Fluid-filled lesions seen in the oral cavity might be hematomas, vesicles, bullae, pustules, abscesses, or cysts.2 These features will help to guide potential differentials, although histopathology will likely be necessary for a definitive diagnosis.4
Erosions and Ulcers

Erosions and ulcers in the canine oral cavity occur with unknown frequency. A proposed classification scheme to understand these lesions is based on the number of lesions and the duration of their occurrence. Human pathologists hold by the adage that erosions are red, and ulcers are yellow due to a fibrinous cover; however, this may not hold true for animals. Lesion location, although important in differential diagnosis, may not be as crucial in determining the causation of ulcers.

Five subgroups of ulcers are proposed: solitary acute, multiple acute, solitary chronic, multiple chronic, and solitary/multiple recurrent. A decision tree approach to canine oral lesions is presented (Figure 1). Definitions as per the human oral literature define acute ulcers as those with a < 2-week duration, chronic as those that last > 2 weeks, and chronic recurrent as being present with an intermittent episode of healing. Ulcers are depressed and below the plane of the mucosa. They should be characterized by number, outline (regular or irregular), margins (raised or smooth), depth (superficial vs deep), and diameter. Additionally, lesions can be separated into those with an infectious or immunologic etiology or those associated with systemic disease.

A recent publication has reviewed autoimmune disease affecting the oral cavity. Veterinarians are referred to that and other excellent articles in lieu of duplication here.

Solitary acute ulcers can be dramatic and are most often associated with trauma, whether that be from a thermal burn such as an electric cord injury, foreign body, or impingement of tissues. The source of the injury is generally identified, and when removed or treated, the ulcer will resolve within 7 to 14 days.

Multiple acute ulcers compromise more mucosal surface area and may be enigmatic and more debilitating. In addition, ulcers have different parts: the floor, the base, the margin, and the edge. In the feline species, various viral infections can cause deep ulceration of the mucosal surfaces of the tongue, palate, and caudal retropharyngeal area. In contrast to cats, viral-associated oral lesions in dogs are rare. Bacterial infections resulting in multiple ulcerations of the mucosa are more common. They include gingival erythema and ulcers secondary to mandibular osteomyelitis and actinomycosis. Acute necrotizing ulcerative gingivitis or “trench mouth” is a severe crater-like or blunt ulceration of the interdental gingival papilla due to Fusospirochete infections. Ulcerative stomatitis can also be a feature of leptospirosis secondary to thrombocytopenia. Bone marrow dyscrasias of various causes include adverse drug events and most forms of leukemia. Signs and local symptoms of leukemia in the oral cavity include paleness of the oral mucosa with gingival bleeding that develops into painless gingival hyperplasia, hemorrhages, and ulcerative necrotic lesions, which may appear similar to pyogenic granulomas.

Chemotherapy-associated oral adverse events are common and debilitating in human cancer.

Several excellent articles from the veterinary dental literature describe an approach to the diagnosis of oral lesions in dogs, including site-specific lesions of the tongue or lesions associated with systemic disease. Contributions from the pathology literature include descriptions of oral cavity tumors and tumor-like lesions, canine chronic ulcerative stomatitis, and eosinophilic oral disease. These articles will provide an important adjunct to the current evaluation of canine mucosal lesions.

Understanding normal oral anatomy, at the clinical and morphologic levels, is critical to understanding pathology. Veterinarians are referred to the exceptional text by Murphy et al, wherein the histologic features of normal and abnormal oral tissues are described. Clinically, we know what a normal incisive papilla looks like and where the major salivary glands and ducts are located. Morphologically, we know that there are keratinized tissues and non-keratinized tissues and that this is supported by an epithelium and basement membrane, lamina propria, and deeper connective tissue. Various oral pathologic lesions occur in different or site-specific locations and involve different layers of the oral mucosa, such that erosions only affect the superficial epithelium; however, ulcers affect the basement membrane and deeper connective tissue and can extend to underlying fascia, muscle, and bone. Specific to the oral mucosa, there are three distinct sites where lesions can occur. These are lining mucosa, which represents 60% of the total mucosa, is non-keratinized, and includes cheeks, alveolar mucosa, lips, soft palate, ventral tongue, and floor of the mouth. The masticatory mucosa represents 25% of the mucosa, is keratinized, and is made up of the gingiva and hard palate. Specialized mucosa including the papilla is present on the dorsal surface of the tongue and makes up only 15% of the total mucosa. Important guidelines for differential diagnosis of oral lesions include documentation of the size of the lesion as to site, clinical morphology (elevated, depressed, or flat), homogeneous or not, size, and consistency. Consistency relates to fixed lesions, which may be firm, freely moveable, fluid filled, or fluctuant. Many of our senses are involved in this documentation. Also critical to diagnosis is the ability to describe the lesion. This information should accompany the veterinarian’s histopathology report. For example, an ulcer is depressed below the normal plane of the mucosa and can be solitary or multiple (separate or coalescing), with raised or smooth margins, and have a regular or irregular outline. It is important to measure the size of the lesion at each time point the patient is examined.

The goal of this manuscript is to provide a decision tree to guide classification and proper diagnosis of canine oral mucosal lesions. Histopathology (including special stains and immunohistochemistry) may be crucial to definitive diagnosis, prognosis, and treatment until such time that biomarkers, immunodiagnostics (direct immunofluorescence and indirect immunofluorescence), and high-plex immunofluorescence imaging become mainstream.
patients leading to infection, discomfort, and inap- petence. All chemotherapeutics can cause oral ulceration and should be prevented and treated quickly. Mucositis, which is defined as inflammation of the oral and oropharyngeal mucosa, occurs in 20% to 40% of patients who receive chemotherapy for solid tumors and typically occurs within 5 to 14 days of receiving chemotherapy. In veterinary medicine, gastrointestinal and hematologic adverse events to chemother- apy are generally described and there is little mention of oral adverse events. A recent retrospective article describing severe adverse events observed in dogs during cancer chemotherapy did not include oral mucosal ulceration. However, these lesions are common and painful in neutropenic pets undergoing cancer chemotherapy. It is important to evaluate for these adverse events, so that humane treatments, such as “magic mouthwash,” can be prescribed.

Head and neck radiation therapy, particularly for oral squamous cell carcinoma, causes severe ulceration of mucosal tissues in 2% to 8% of people. Mucositis is one of the first acute toxicities that affect the patient. It appears within the first 2 to 3 weeks of treatment as erythema of the oral mucosa that proceeds to ulceration and pseudomembrane formation and affects the nonkeratinized oral mucosa more than the keratinized ones. The mechanics and exposure damage to the tissues in dogs receiving radiation therapy to the oral cavity are thought to be like those in people but depend on many factors such as total dose and type of radiation. Adverse events in dogs include acute mucosal ulceration and chronic necrosis with exposure of underlying necrotic bone. Lesions are generally found at the site of tumor irradiation or in the jaw closest to the irradiated tumor; however, contralateral lesions have been reported. Radiation oral adverse events, such as osteoradionecrosis, are influenced by the lack of general care of the teeth (for example, extraction of teeth affected by advanced stages of periodontal disease) before the course of radiation. Compliance with a comprehensive oral health assessment and treatment with extractions, as necessary, before chemoradiation and radiation therapy may be criti- cal to patient outcomes. Oral evaluations at each recheck are important for this patient population. A better awareness of oral toxicity is necessary in veterinary oncology.

Figure 1—Decision-tree approach to canine oral lesions. CC = Calcinosis circumscripta. CCUS = Canine chronic ulcer- ative stomatitis. MMP = Mucous membrane pemphigoid.
Oral hypersensitivity reactions can include entities such as contact allergy stomatitis, oral lichenoid reactions (discussed later), erythema multiforme, Stevens Johnson syndrome, and toxic epidermal necrolysis. Contact allergy is a form of cell-mediated hypersensitivity to small molecular antigens. Agents such as foods, oral hygiene products, and certain dental materials may be causative. The pathogenesis has been well described and briefly involves a primary exposure, T-cell sensitization, and recruitment and a second exposure, which then leads to cytokine release and mucosal hypersensitivity damage. Clinically, these may be difficult to separate from traumatic lesions. Most often there is erythema, edema, desquamation, and ulceration. In people as well as in dogs, the antibacterial rinse chlorhexidine may cause such reactions. Removal of the offending allergen will in most cases resolve the lesion. Histopathology and subsequent topical corticosteroids may be necessary if the lesion does not resolve.

Erythema multiforme is a complex hypersensitivity reaction with a wide range of causes from viral to bacterial and fungal, as well as numerous medication-related origins. In people, there is a 60% to 90% association with herpes virus. In dogs, sulfonamides and penicillins are highly suspected. Photographic representation of acute mucosal ulcers on the sublingual surface of the tongue is presented in erythema multiforme secondary to a course of sulfonamides (Figure 2).

A comparison study of dogs with oral erythema multiforme and epitheliotropic T-cell lymphoma revealed clinical similarity to canine chronic ulcerative stomatitis, although histology alone was not able to provide a definitive diagnosis. In this evaluation, 4/14 dogs required immunohistochemistry and clonality testing for T-cell receptor gamma-gene rearrangement to differentiate the disorders.

Solitary chronic ulcers comprise disorders such as those listed in the decision tree (Figure 1). Eosinophilic ulcers in dogs appear as raised, erythematous, fleshy masses with discrete borders and present typically on the palatal surface. Any oral tumor may become ulcerated and then necrotic, although extramedullary plasma cell tumors have a characteristic appearance and are raised, solitary mass lesions of the oral tissues with an indurated central ulcerative area.

Multiple chronic ulcers represent a long list of differentials from canine chronic ulcerative stomatitis to contact mucositis and from drug reactions to long-standing effects of toxins to various tumor types, including epitheliotropic lymphoma. In addition, various systemic diseases can result in multiple chronic ulcers and include uremia, hyperparathyroidism, hyperadrenocorticism, and nutritional disorders. Just as for multiple acute ulcers, autoimmune diseases may also cause chronic and recurrent ulcers. Deep fungal infections, such as blastomycosis, may occur in gingival and mucosal sites and be ulcerative in appearance.

Chronic recurrent ulcers, whether single or multiple, may include many of the differentials previously listed for multiple chronic ulcers. Additionally, cyclic neutropenia, a genetic disorder of gray collie dogs, results in cycles of neutropenia and susceptibility to fungal and bacterial infections. Neutropenia may present with features exclusive to the oral cavity such as overt ulceration. In addition, Cobalamin deficiency, whether congenital or acquired secondary to small intestinal disease, may also cause recurrent mucosal ulcers.

Autoimmune disorders are found within several categories of ulcers, multiple acute, multiple chronic, and chronic recurrent. Erosions and ulcers associated with autoimmune disorders of the canine oral cavity occur with relative frequency. Blister-formed lesions are those containing fluid such as vesicles, bullae, or pustules. Vesicles are < 0.5 cm and contain either mucin or serum. Bullae present as a larger lesion > 0.5 cm and contain mucin, serum, or blood. Pustules contain purulent material and can be any size. A positive Nikolsky sign, where the lesion epithelium easily separates from the underlying lamina propria, is seen with pemphigus vulgaris. Oral manifestations include short-lived vesicles/bullae, which lead to ulcers. Oral lesions of autoimmune etiology are represented by multiple and chronic ulcers, which can be recurrent with relapses to therapy. Ulcers affecting multiple sites and tissues are associated with autoimmune diseases such as systemic
lupus erythematosus, discoid lupus erythematosus, mucous membrane pemphigoid, pemphigus vulgaris, Wegener-like granulomatosis, and eosinophilic granulomatosis with polyangiitis. Subtle differences in the appearance and location of autoimmune oral lesions have been described recently. These lesions can be easily confused with more common causes of ulceration such as seen in canine chronic ulcerative stomatitis. Veterinary clinicians treating oral mucosal conditions must make this distinction. Unfortunately, veterinary pathologists do not have access to indirect and direct immunofluorescence, which hampers their ability to make an autoimmune diagnosis in some cases. Immunodiagnostics for veterinary oral medicine cases is on the near horizon. Photographic representation of the canine autoimmune disorder eosinophilic granulomatosis with polyangiitis is presented (Figure 3).

Figure 3—Present is a focal deep ulceration of the buccal mucosa including the mucogingival junction of the maxillary left canine tooth in a 4-year-old female spayed Australian Cattle Dog. The ulcer has a well-defined margin and is > 2 cm in size. Necrotic debris is present in the center of the lesion. Mesial to this ulcer is a generalized nonhomogeneous area of proliferative leukoplakia. Diagnosis is eosinophilic granulomatosis with polyangiitis.

### Leukoplakia

Oral leukoplakia is defined as a “white patch or plaque of questionable risk having excluded other (known) diseases or disorders that carry no increased risk for cancer.” Two forms of leukoplakia are present in people, localized leukoplakia, and proliferative ( verrucous) leukoplakia (proliferative leukoplakia). Proliferative leukoplakia includes a spectrum of diseases including lichen planus, hyperkeratosis, epithelial hyperplasia, epithelial dysplasia, verrucous carcinoma, and squamous cell carcinoma. Malignant transformation is seen with erythroleukoplakia (red and white lesions) and proliferative leukoplakia and depends on certain risk factors, histologic characterization, and immunoprofiling. However, the majority of leukoplakia lesions do not show evidence of epithelial dysplasia (in which the epithelium has cellular atypia), yet malignant transformation of these lesions is well recognized. These lesions have been referred to as “hyperkeratosis/hyperplasia, no dysplasia,” “keratosis of unknown significance,” and “hyperkeratosis, not reactive.” Hyperkeratosis represents an increase in the most superficial layer of the epithelium, the keratin. Some white lesions can be scraped off and include superficial oral burns, pseudomembranous Candidiasis, pseudomembrane of oral ulcers, and habitual biting of cheeks, lips, and tongue. All other white lesions cannot be scraped off.

Oral leukoplakia is not common in the canine oral cavity. However, lesions do exist and require documentation and further investigation. These lesions can be subclassified into solitary lesions, widespread leukoplakia, proliferative leukoplakia, and erythroleukoplakia. Leukoplakia is associated with canine chronic ulcerative stomatitis, papillomatosis, mucus membrane pemphigoid, eosinophilic granuloma, lichenoid reactions, foamy cell histiocytosis, calcinosis circumscripta, xanthoma, neoplasms, and idiopathic lesions which are common on the tongue. In veterinary medicine, we do not see features of dysplasia on routine histopathology with hematoxylin and eosin staining, and overt neoplasia is not a feature in these leukoplakia lesions. However, hyperkeratosis/hyperplasia is a common finding in oral histopathology. Considering the significance of hyperkeratosis in human oral medicine, perhaps further monitoring and scrutiny for the development of oral squamous cell carcinoma in dogs is appropriate. A table of canine oral leukoplakic lesions is presented (Table 1). Erythroleukoplakia describes a lesion that is both red and white. In people, these lesions may be precancerous. These lesions are rare in dogs and warrant histopathology. A generalized erythroleukoplakic lesion in a dog with severe periodontitis is shown (Figure 4).

Candidiasis, appearing as a white surface accumulation, is extremely common in the medically compromised human patient population causing significant morbidity and financial resources. It is not yet well understood why, even immunocompromised, cats and dogs do not develop oral candidiasis. Finally, various neoplasms including tonsillar lymphoma, amelanotic melanoma, and fibromas may have a white appearance.

### Pigmented Lesions

Pigmented oral lesions in people can be a normal variation, can represent endogenous change, or can be associated with pathologies such as malignant neoplasms. Certain dental materials, such as amalgam, can stain the gingiva and mucosa. As for ulcers and leukoplakic lesions, attention to location, color, shape, number, size, and surface texture is an important consideration for pigmented lesions. Melanocytes are regularly interspersed in the oral epithelium, and the number is species dependent. Oral nevi (moles) are common in women and the etiology is unclear. The types of nevi include intramusosal nevi, compound nevi, blue nevus, junctional, and combined nevi. In human oral medicine, persistent,
solitary-pigmented lesions require a biopsy to rule out melanoma. Multifocal and diffuse pigmentation may be a physiologic variation, drug induced, or appear secondary to an inflammatory process. Pigmentation may be induced by a wide variety of drugs; the main ones implicated include NSAIDs, phenytoin, antimalarials, amiodarone, antipsychotic drugs, cytotoxic drugs, tetracyclines, and heavy metals. Pigmentation can also occur due to systemic endogenous disorders such as Addison and Cushing disease.

The normal canine oral cavity can frequently have pigmentation and certain breeds are predisposed such as Chow Chows and German Short Haired Pointers. In general, acute inflammation often produces depigmentation, whereas chronic inflammation may lead to hyperpigmentation. Nevi have not yet been recognized in dogs. Malignant melanoma is a common reason for oral pigmentation in dogs. As in people, pigmentation can be seen with metabolic disorders, endocrine diseases, and hyper- or hypoadrenocorticism. Drug-induced oral pigmentation is uncommon in dogs. Differentials for fluid-filled blue discoloration of the oral mucosa can be seen with dentigerous and other cystic accumulations.

Changes in the number of pigmented lesions, or in the shape or surface texture, should prompt clinicians to rule out melanocytic neoplasms with histopathology and special stains. Canine oral melanoma is the most common tumor in the oral cavity of dogs and is characterized by aggressive local disease and metastasis.

The natural result of any approach to the definitive diagnosis of oral lesions is histopathologic interpretation. The more information that a clinician can offer, such as history, medications, lesion description, single or multiple, acute, or chronic, coloration, surface texture, margins, and extent, the more information will be forthcoming from the pathologist. Unfortunately, resources that discuss biopsy principles and techniques are limited.

**Conclusions**

To make a definitive diagnosis of erythematous erosions and ulcers, leukoplakias, and pigmented lesions, many components of each case are important. A complete and detailed history and physical examination are crucial to the process. In addition, the medications used and their potential side effects may reveal causation. A decision tree flow chart may help clinicians to organize their differential diagnoses. Histopathology is essential in most cases and is only as good as the representative biopsy and the information provided to the pathologist.

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<th>Table 1—Classification of canine oral leukoplakic lesions.</th>
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<td><strong>Localized leukoplakia</strong></td>
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<td>Lichenoid reactions</td>
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<td>Various cancers</td>
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<td><strong>Solitary leukoplakia</strong></td>
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<td>OLP</td>
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<tr>
<td>Lichenoid reactions</td>
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<td>CCUS</td>
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<td>Mucous membrane pemphigus</td>
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<td><strong>Proliferative leukoplakia</strong></td>
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<td>Foamy cell histiocytosis</td>
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<td>Papillomatosis</td>
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<td>Eosinophilic granuloma</td>
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<td>Xanthoma</td>
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<td>Calciosis circumscripta</td>
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<td>Candidiasis</td>
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<td><strong>Erythroleukoplakia</strong></td>
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<td>Malignancies</td>
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<td>Autoimmune</td>
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CCUS = Canine chronic ulcerative stomatitis. OLP = Oral lichen planus.
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