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Case Report

Lymphangiomatosis in the oral cavity in a mix breed dog

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ABSTRACT: A 12-year-old female spayed mixed breed dog presented with numerous firm proliferating, non-painful white/tan lesions on both the dorsal and ventral surface of the tongue. Initial clinical differentials include trauma, infection, and cancer. Histopathology revealed multifocal fibroangiomatous mucosal hyperplasia with foamy macrophages. Differential diagnoses included histiocytic foam cell nodules, xanthogranuloma (lipid-rich granuloma) or foam cell nodules containing lipid, cutaneous foam cell histiocytosis affecting the oral cavity, or systemic histiocytosis. Due to the presence of multiple lesions, medical therapy with tetracycline, and niacinamide was initiated, resulting in clinical improvement. Subsequent immunohistochemical staining identified branching and connecting CD31+ lymphatics throughout the sample, suggesting lymphagiomatosis. Lymphagiomatosis is an infiltrative disease affecting lymphatic vessels in one or multiple organs. This condition has not been previously reported in dogs. This case report is the first to describe lymphangiomatosis in a mixed-breed dog.

Keywords: Canine, Lymphangiomatosis, tongue, mouth, oral medicine.

INTRODUCTION

Lingual nodular lesions in dogs are relatively uncommon and are most often associated with neoplasm and glossitis secondary to trauma or infection. Retrospective studies reported that lingual biopsies represented 0.8% of all biopsy specimens received for histopathology studies (Dennis *et al*., 2006). Neoplasia was the most common diagnosis (54%), followed by glossitis (33.2%), and other diseases (12.2%). The most frequently diagnosed malignancies included melanoma, squamous cell carcinoma, hemangiosarcoma, and fibrosarcoma (Cornegliani *et al*., 2011). A case of histiocytic sarcoma was also reported. Non-neoplastic and non-inflammatory lingual lesions included immune-mediated disease, idiopathic disease (e.g., calcinosis circumscripta, canine eosinophilic granuloma), fibrosis, granulation tissue, hyperplastic tissue proliferation, generalized glossitis (burdock plant glossitis) and other degenerative or trauma-related lesions (Buelow *et al*., 2011).

Lymphatic anomalies, including lymphangioma, lymphatic malformation, and lymphangiomatosis, are rare congenital condition disorders of the lymphatic system, thought to arise from a failure of primitive lymphatic systems to separate from or communicate with the venous system adequately. These malformations lead to dilation and proliferation of lymphatic vessels in animals and humans (Park *et al*., 2023).

In humans, according to the International Society for the Study of Vascular Anomalies (ISSVA), lymphatic anomalies are classified as either cystic lymphatic anomaly or complex lymphatic anomaly, depending on whether they occur in solitary lesions or multiple organs (Park *et al*., 2023).

Lymphangioma is a lymphatic malformation which shows benign proliferation of lymph vessels, with the characteristic of submucosal tumours covered with normal mucosa. The disease can affect one organ or multiple organs concurrently (Hoang *et al*., 2020). It is a rare condition with a paucity of data in the literature. Differential

diagnosis in people includes Langerhans cell histiocytosis, hemangiomatosis, infection and multiple myeloma (Uribe *et al.,* 2018). Although lymphangioma is a benign tumour, most lymphangiomas do not cause symptoms and do not require treatment (Nason *et al*., 2012). It is not clear whether it is a neoplastic or a hamartomatous lesion that originates from lymphatic tissue sequestration and may or may not communicate with the rest of the system Neville *et al*., 2009). While Lymphangioma is a focal lesion, Lymphangiomatosis is a diffuse one showing infiltration by lymphatic channels varying in size and shape. The diffuse and infiltrative nature may lead to difficulty in differentiating this from malignant vascular/lymphatic lesions. The prognosis is dictated by whether or not one of the vital organs is involved (Chander *et al*., 2015).

Histologically, lymphangiomatosis consists of endothelial-lines spaces supported by connective tissue stroma of variable thickness containing lymphoid tissue, round cells and smooth muscle. Multiple organs such as the lung, liver, and spleen may be involved concurrently in approximately 75% of cases (Faul *et al*., 2000). Immunological staining of endothelial cells with lymphangiomatosis is positive for D2-40, CD31, and factors VIII-related antigen (Mehrnahad *et al*., 2020).

Current therapies for cases in people include surgery, interferon, radiotherapy, and glucocorticoids, but these therapies have side effects, and the treatment strategy remains controversial (Ozeki *et al*., 2011; Spencer *et al*., 2013; Júnior *et al*., 2023; Dimiene *et al*., 2021).

CASE DESCRIPTION

A twelve-year-old mixed breed, female spayed dog with several years long history of enlarging hemorrhagic tongue lesions was presented to Dentistry for Animals. The dog's lesions had been biopsied 5 years previously and was diagnosed as a nodular round cell infiltrate most consistent with histiocytic infiltrate. Interestingly, the patient's guardian reported no history of hyper-salivation but "she licks the air constantly". The patient did not have a cardiac murmur on auscultation, nor were there respiratory abnormalities at the time of presentation to Dentistry for Animals. She had moderate generalized calculus and gingivitis, multiple bullae lesions were present generally on the rostral lips, the dorsal tip of the tongue and the ventral aspect of the tongue. Complete blood count, chemistry profile and Antinuclear/antibody (ANA) test were performed showing an increase in ALT 500 (18-121 U/L), ALP 500 (5-160 U/L) and a negative ANA result. The elevated liver values were discussed with the owner and a recommendation was made to pursue a definitive diagnosis after evaluation and biopsy of the oral lesions, with the referring DVM or secondary referral to an internal medicine specialist.

The patient was anaesthetized with hydromorphone 0.05 mg/kg IM, dexmedetomidine 7 ug/kg IM, midazolam 0.5 mg/kg IV and alfaxalone 2 mg/kg IV to perform a Comprehensive Oral Health Assessment and Treatment (COHAT) and take biopsies from tongue and lips (Figure 1).

A dental evaluation under anaesthesia showed focal periodontal disease (PD): stage 2 PD for teeth 308 and 411, stage 3 PD at tooth 309, and stage 4 PD at teeth 109, 209 and 410. Oral evaluation revealed a 4 x 4 x 2 mm firm dark brown mass on the right maxillary and mandibular mucocutaneous junction. As well as multiple pale tan to beige colour, lobular and irregular bullae-like lesions affecting the ventral aspect of the tongue (Figure 1b). Biopsy sampling with a four mm punch was obtained from the two pigmented masses, as well as four of the sublingual masses. Biopsies sites were closed in a cruciate pattern using 4-0 Poliglecaprone 25. Tissue samples were fixed in buffered 10% formalin and submitted for routine histopathology with H&E staining.

Histological examination of the lesions from the right mandibular and maxilla mucocutaneous junction were diagnosed as well as differentiated low-grade melanoma.

Microscopic examination of the sublingual mucosa revealed a polyploid mass composed of hyperplastic surface epithelium and a core of edematous fibrovascular tissue with abundant macrophages (Figure 2). The surface epithelium was markedly thickened and multifocal covered by an increased layer of keratin. The fibrovascular core was loosely arranged, thick collagen bundles with abundant, anastomosing, dilated small vessels filled with clear space and/or erythrocytes, was infiltrated by numerous macrophages with abundant, foamy cytoplasm with variable-sized clear staining vacuoles. Macrophages had small, oval, hyperchromatic nuclei with pleomorphism. A diagnosis of multifocal fibroangiomatous mucosal hyperplasia with foamy macrophages was made. The histopathologist commented that the biopsy from the sublingual sites each had multifocal to coalescing nodules, and all had foamy macrophages within a hyperplastic tissue background. The lingual lesions were strongly analogous to histiocytosis foam cell nodules, and the microscopic findings along with presentation raised suspicion for a reactive, progressive histiocytic disorder.

Stage 3 and 4 periodontally diseased teeth were surgically extracted and closed with a simple-interrupted pattern using a 4-0 gut. The patient was prescribed tramadol 5 mg/kg PO BID for pain control. Given the melanoma diagnosis, the patient subsequently had a wider excision, and the second biopsy confirmed complete excision. A veterinary dentist with expertise in oral medicine was consulted about the lingual lesions and suggested a treatment of niacinamide 250 mg PO every 8 hours and tetracycline 250 mg orally every 8 hours. A recheck was scheduled in 1 month.

At recheck number one, medication compliance was poor, and the medications had not been given as

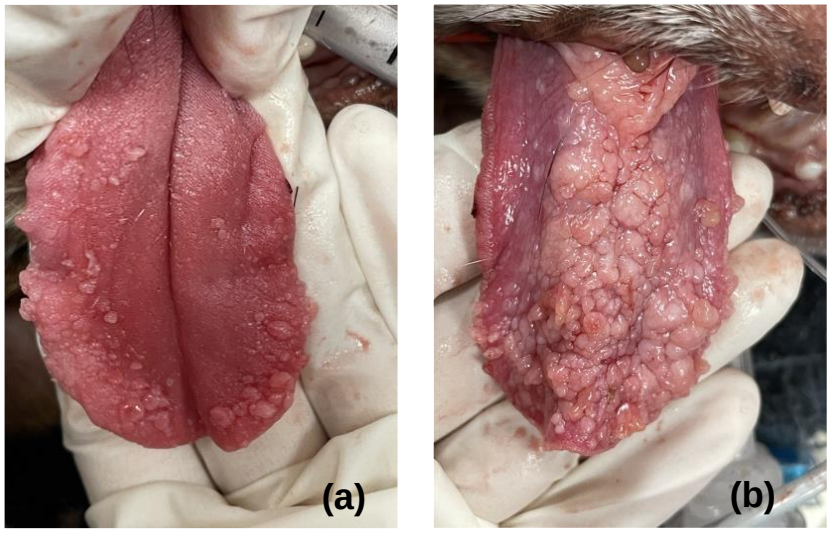

Figure 1. Clinical presentation of the (a) dorsal tongue, and (b) ventral tongue.

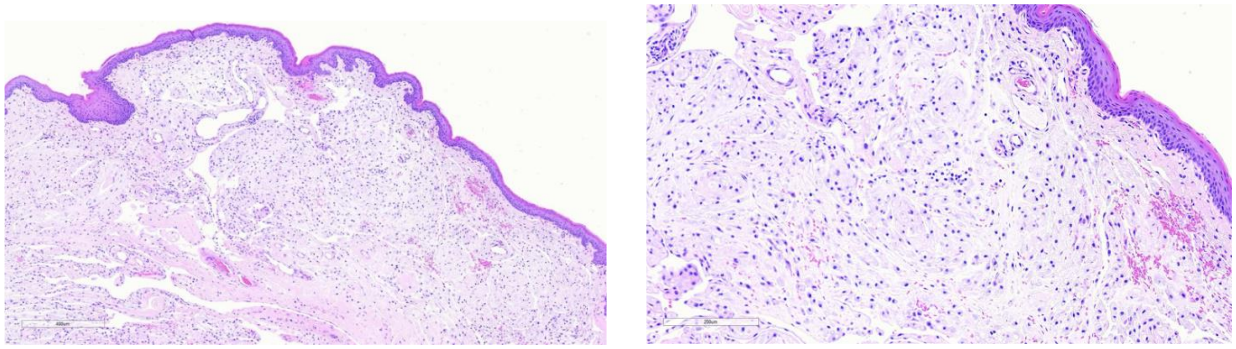

Figure 2. Photomicrographs of initial biopsy of the lingual lesions, initial biopsy 100x.

prescribed. The owner also advised that a dry cough had begun. The referring DVM (rDVM) started a tapering dose of oral prednisone of 0.5 mg/kg PO which helped the cough, though once off, the cough returned. At recheck number two, two months post-biopsy, the medication regimen was niacinamide 250 mg PO every 8 hours, and tetracycline 250 mg PO every 8 hours. An oral exam under mild sedation (dexmedetomidine 5 ug/kg and butorphanol 0.2 mg/kg IM), revealed a mild decrease in the size of tongue lesions and the owner reported less bleeding from the mouth. A local referral to an American College of Veterinary Internal Medicine (ACVIM) specialist was sought for the ongoing cough. The client declined all diagnostics including thoracic radiographs and thoracic ultrasound. A course of theophylline at 10 mg/kg PO twice a day was prescribed. Some resolution of the cough was noticed. Two months after the institution of theophylline, and taper of the tetracycline and niacinamide to twice a day, a third recheck evaluation revealed moderate worsening of bleeding from the tongue though the lesions were smaller and decreased in size compared to the time of biopsy. The owner shared concerns about the difficulty of giving medications three times a day and about the amount of medication her pet was getting.

A second opinion from a pathologist (V. Aftoler) with expertise in histiocytic disease, examined duplicate slides sent from the most recent biopsies. Utilizing immunohistochemistry (IHC), the staining revealed branching and connecting CD31+ lymphatics throughout that sample and reminiscent of lymphangiomatosis. Iba-1 identified variable numbers of cells between these branching lymphatics (Figure 3).

Based on the IHC findings and lymphangiomatosis, diagnosis it was recommended to switch from tetracycline to doxycycline at 5 mg/kg PO twice a day. Continuation of niacinamide therapy was advised, along with tapering the theophylline dose to 5 mg/kg PO once a day due to potential drug interactions between theophillyne and

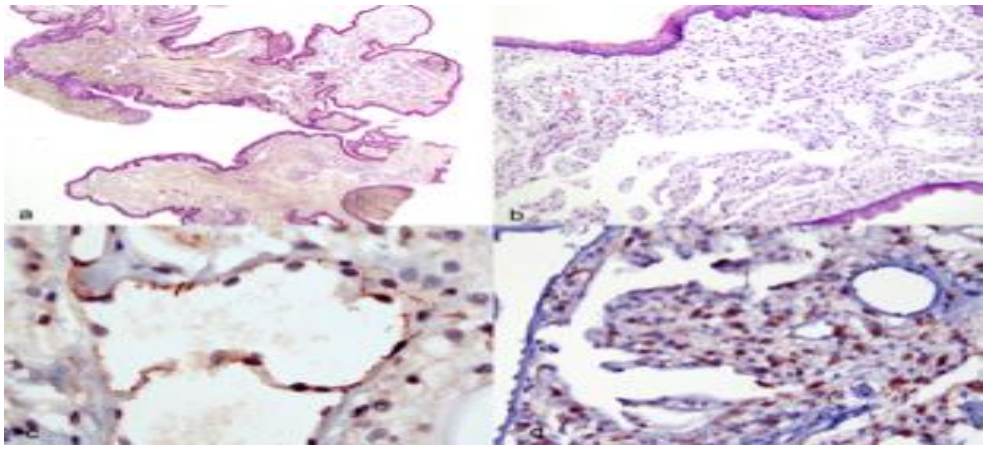

Figure 3. Histologic changes are characterized by a) Exophytic, markedly edematous mucosal tissue with papillated surface and interconnecting channels supported by variably dense stroma (20x; H&E). b) The channels are lined by flat spindle cells and lack luminal red blood cells, interpreted as lymphatic vessels. The supporting fibrovascular stroma is edematous and exhibits increased cellularity (100x; H&E). c) The cells lining the channels express CD31, consistent with endothelial cells. The absence of luminal red blood cells supports the interpretation of lymphatic vessels (400x; IHC anti-CD31). d) Numerous dispersed histiocytes are present within the supporting stroma (200x, IHC anti-Iba-1).

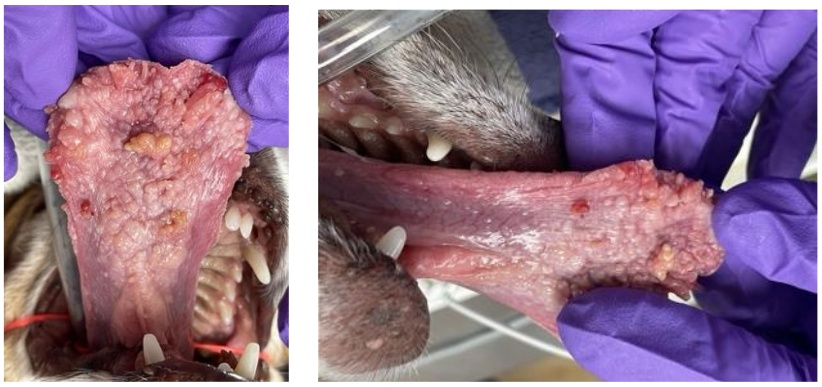

Figure 4. Clinical presentation of the tongue after two months of treatment with doxycycline and niacinamide. The amount of bullae-like lesions has decreased in size and numbe.

niacinamide. A recheck evaluation revealed improvement in the oral bleeding and lingual lesions (Figure 4).

Subsequently, the patient developed skin allergies and the rDVM prescribed oclacitinib. Oral lesions were reported to have recurred and there was no mention of concurrent medications. The patient was lost for further follow-up.

DISCUSSION

Lingual lesions are relatively uncommon in dogs, difficult to detect, and are most often associated with neoplasia. Lymphangiomatosis is a rare lymphatic development disorder, and its exact pathophysiology is not well understood, though the vascular endothelial factor receptor may play a role in the development of this disease (Bellows *et al*., 2019).

In human medicine, lymphangiomatosis refers to a lymphatic anomaly occurring in multiple organs. We suspect that our patient may have had a generalized form of lymphangiomatosis, given the development of cough after the tongue biopsy and the fact that empirical treatment for the cough (prednisone and theophylline) was unsuccessful. Although the patient may have had other medical issues, such as tracheal collapse or subclinical cardiac disease. These were ruled out based on the physical exam findings (no heart murmurs or arrhythmias

noted, even under anaesthesia). Thus, lymphangiomatosis affecting the lungs was strongly suspected due to his recurrent cough and the lesions noticed on his tongue.

In humans, lymphatic anomalies most commonly occur in the neck (75%) and ancillary sites (20%) and have rarely been reported in the mediastinum, omentum, mesentery, retroperitoneum, colon, pelvis and bone (Uribe *et al*., 2018; Mehrnahad *et al*., 2020; Júnior et al., 2023; Park *et al*., 2023). In dogs, lymphatic anomalies are most commonly been reported in the skin, soft tissue and retroperitoneum (Berry *et al*., 1996; Locker *et al*., 2021; Park *et al*., 2023). They rarely observed in parenchymal organs, with only two cases have been reported in the liver and spleen (Park *et al*., 2023). This case represents the first published case of IHC-confirmed oral lymphangiomatosis in dogs.

Treatment of lymphangiomatosis depends on the location and the severity of the disease. Most reports are single cases or small case series, predominantly in the orthopaedic and radiologic literature. In humans, a combination of surgery, radiotherapy and anecdotal use of medication like propranolol, corticosteroids and immunosuppressants have been recommended, but there is not a specific treatment that shows better outcomes than others (Spencer *et al*., 2013).

The combination of niacinamide, pentoxifylline and doxycycline has been used for the management of autoimmune and immune-mediated skin disease for many decades in animals and people (Cornegliani *et al*., 2011; Park *et al*., 2023). Doxycycline has been shown to disrupt inflammatory cytokine pathways (IL-1, IL-6, IL-8, TNF alpha), inhibit the function of matrix metalloproteinases, and reduce leukocyte chemotaxis and function of nitric oxide synthase. Niacinamide, a vitamin B3, inhibits multiple proinflammatory cytokines, neutrophil chemotaxis via reduced ICASM-1 expression and B cell differentiation, they have been used in several autoimmune/immune-mediated skin disorders. Pentoxifylline is a methylxanthine derivative with hemorrheologic and immunomodulatory properties, the major mechanism of action is believed to be nonselective phosphodiesterase inhibition. Recently the use of niacinamide and pentoxifylline in the medical management of CCUS has been a good option for this debilitating disease in dogs. So, based on their effect as immunomodulators, and the minimum side effects, the combination of these medications was chosen as a viable treatment for this case.

This case highlights an unusual presentation with a rare diagnosis in veterinary medicine. It also emphasizes the importance of IHC in diagnosing conditions that cannot be conclusively identified through histopathology alone.

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DISCLOSURE

The authors report no conflicts of interest in this work.

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