Diagnostic Exercise

From The Davis-Thompson Foundation*

Case #: **169** Month: **July** Year: **2021**

Answer sheet

Title: *Autoimmune vesiculobullous disease in a dog*

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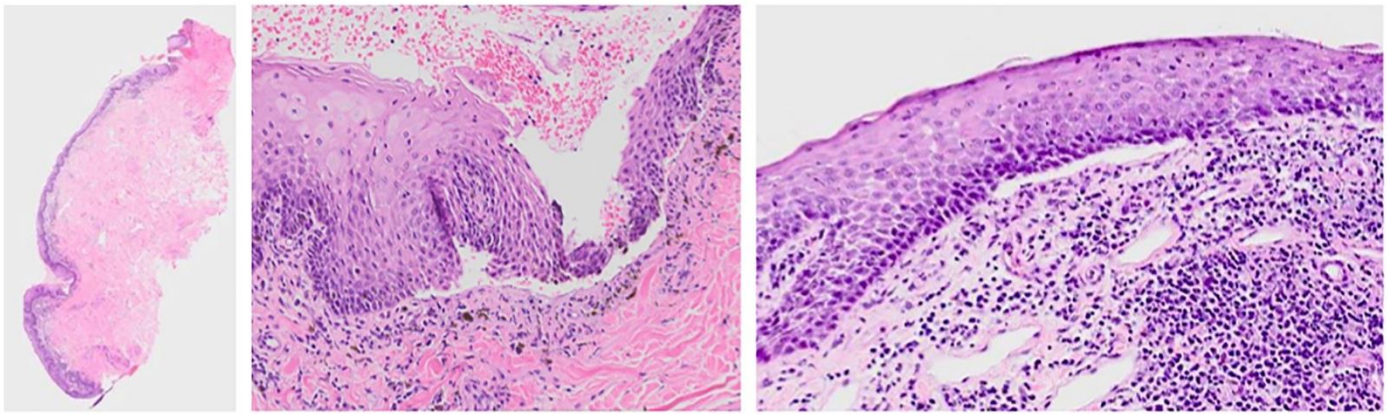
Clinical History:
This is a biopsy from an 11-year-old, male, intact, Labrador retriever dog.
The owners noticed waxing and waning halitosis approximately 6 months prior to presentation. The patient was taken to the referring veterinarian and prescribed antibiotics, then later, steroids. There was no improvement in the halitosis, and the patient developed increased signs of pain in the oral cavity. The patient began to exhibit ptyalism, and decreased interest in food unless soaked in water. At this time, the patient was referred to dental and oral surgery specialist service.
The physical exam revealed severe, generalized gingival hyperemia. There was ulceration of the ventral tongue, and multifocal ulcers along oral mucosa bilaterally, most prominent along buccal oral mucosa in contact with the right and left maxillary canines and premolars. Punch biopsies of the affected oral mucosa were acquired, and a complete dental cleaning was performed.

Microscopic Images:



Histopathologic Description:

Three sections of buccal mucosa are examined in which much of the superficial submucosa is infiltrated by a dense lichenoid infiltrate of lymphocytes and plasma cells, as well as smaller numbers of neutrophils, mast cells, and histiocytes. A similar infiltrate surrounds deeper submucosal vessels. Subepithelial clefts are present

multifocally throughout the samples, and occasionally, the epithelium is ulcerated completely. A moderate number of neutrophils are traversing the mucosal epithelium. Superficial vessels are lined by plump, reactive endothelial cells. Coarsely clumped melanin is present within the superficial submucosa of all sections.

Follow-up questions:
● *What is your morphological diagnosis?*
● *Given the physical exam and histologic findings, what are your differential diagnosis*
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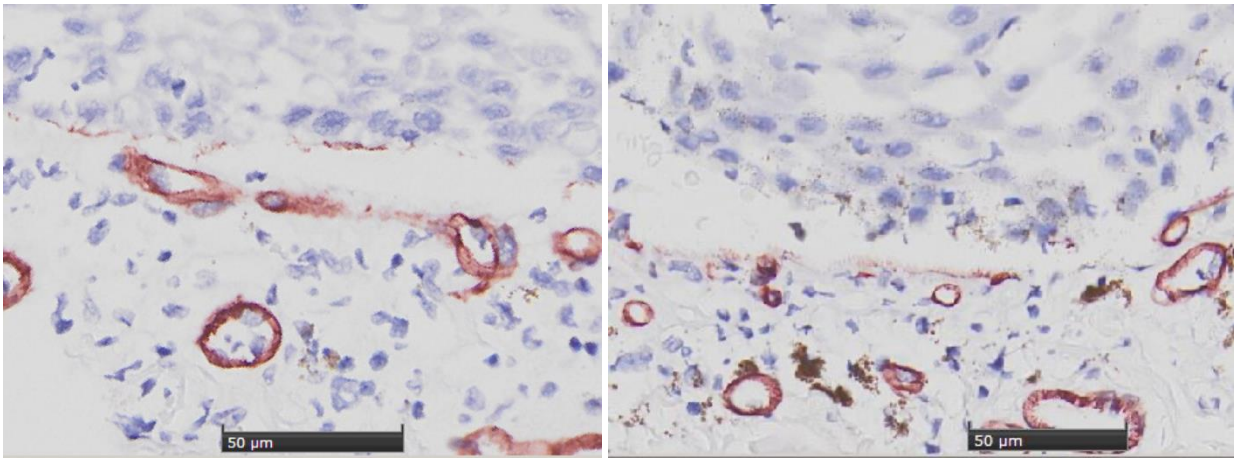
● *What ancillary diagnostic tests would be helpful to diagnose the cause?*

●Morphological diagnosis
Oral mucosa: Moderate to severe, chronic, lichenoid lymphoplasmacytic, ulcerative stomatitis with subepithelial clefts.

● Differential diagnosis?
Bullous pemphigoid (generic term for autoimmune vesiculobullous disease), Bullous drug reaction, pemphigus vulgaris, mucous membrane pemphigoid (specific disease)

● Ancillary diagnostic tests
Definitive diagnosis of mucus membrane pemphigoid vs. other requires immunologic studies such as direct or indirect immunofluorescence, and immunohistochemistry for IgG or laminin.



These figures demonstrate results from this case with immunohistochemistry for laminin. In the left-hand photo, clefting occured with the epithelium in short segments, but most of the immunohistochemistry demonstrated that, as is shown in the right hand photo, laminin lay on the DERMAL side of the clefts, which is expected in cases of MMP where the target is within the lamina lucida. The authors attempted to clarify the result with anti-IgG, but that was not enlightening. Based on the gross distribution, the histologic character, and the IHC results, a diagnosis of mucus membrane pemphigus was made.

Discussion:
Although rare in domestic species, mucous membrane pemphigoid (MMP) is considered to be the most common autoimmune disease of the basement membrane zone in dogs and cats (Gross, et al.). Although epidemiological data on canine MMP are scant, German shepherd dogs appeared to be an over-represented (Tham et al, 2016). The disease affects mucocutaneous junctions, and mucous membranes, and is characterized by ulcerative or erosive lesions, and/or intact vesicles. Circulating IgG autoantibodies target several different basement membrane elements, including collagen XVII, or laminin-5. The most commonly affected sites include oral cavity, lips, and planum nasale, but other locations also occur, including genitalia, and anus. In the oral cavity, the gums, hard palate, and tongue are most commonly affected.
Histologically, lesions are characterized by subepithelial clefting or bulla formation. Bulla are often devoid of inflammatory cells. Inflammation mostly develops after rupture of bullae and is characterized by a lichenoid infiltrate of lymphocytes, plasma cells, neutrophils, and in some cases eosinophils. Ulceration is often present, and associated with more intense neutrophilic inflammation.
Bullous pemphigoid and bullous drug reactions are histologically similar, and clinical distribution of lesions and clinical history are helpful for distinguishing between these entities. Definitive diagnosis of MMP requires immunologic studies such as direct or indirect immunofluorescence, and immunohistochemistry for IgG or laminin. In this case, immunohistochemistry for laminin was performed, and showed faint immunoreactivity on the dermal side of the clefts, which is expected in cases of MMP where the target is basement-membrane fixed within the lamina lucida. Additional immunohistochemistry for canine IgG was attempted but did not result in reliable control staining.

References:
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