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Case Report Rapport de cas

Glossitis in an older non-corgi dog: Diagnosis and long-term follow-up

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Abstract — A 9-year-old spayed female 18.8 kg mixed breed boxer dog was referred for evaluation of a 7-month history of difficulty swallowing and prehending food, regurgitation, hypersalivation, and an abnormal dorsiflexion of the tongue. Prior to referral, a barium study was performed, which revealed a mildly dilated esophagus. Treatment with sucralfate, cisapride, and prednisone was initiated.

Physical examination revealed bilateral, symmetric atrophy of the temporalis muscles, dorsiflexion of the distal aspect of the tongue with concurrent muscle atrophy, and a reduced gag reflex. Electrodiagnostic examinations revealed spontaneous electrical activity in the muscles of mastication and tongue. Biopsies from the right temporalis, tongue, and biceps femoris muscles were collected. An immune-mediated myositis with fibrosis, scattered CD3, CD4, and CD8+ T-lymphocytes, and upregulation of markers for major histocompatibility antigens were observed in the tongue and temporalis muscles.

The dog was treated with a tapering course of prednisone over 2 months and cyclosporine long-term. The dog was maintained on cyclosporine alone for > 2 years and clinical signs remained static, although multiple episodes of aspiration pneumonia occurred. Ultimately, euthanasia was performed due to chronic kidney disease with associated anemia, lethargy, and anorexia.

Résumé — Glossite chez un chien âgé non-corgi : diagnostic et suivi à long terme. Une chienne boxer de race mixte de 18,8 kg stérilisée âgée de 9 ans a été référée pour l'évaluation d'une histoire de 7 mois de difficulté à avaler et de préhension des aliments, de régurgitation, d'hypersalivation et d'une dorsiflexion anormale de la langue. Avant la référence, un examen baryté a été réalisée et a révélé un œsophage légèrement dilaté. Un traitement par sucralfate, cisapride et prednisone a été initié.

L'examen physique a révélé une atrophie bilatérale et symétrique des muscles temporaux, une flexion dorsale de la face distale de la langue avec atrophie musculaire concomitante et un réflexe nauséeux réduit. Les examens électrodiagnostiques ont révélé une activité électrique spontanée dans les muscles de la mastication et de la langue. Des biopsies des muscles temporaux droits, de la langue et du biceps fémoral ont été recueillies. Une myosite à médiation immunitaire avec fibrose, des lymphocytes T CD3, CD4 et CD8+ dispersés et une régulation positive des marqueurs des principaux antigènes d'histocompatibilité ont été observées dans la langue et les muscles temporaux.

Le chien a été traité avec une posologie décroissante de prednisone sur 2 mois et de cyclosporine à long terme. Le chien a été maintenu sous cyclosporine seule pendant > 2 ans et les signes cliniques sont restés stables, bien que plusieurs épisodes de pneumonie par aspiration se soient produits. En fin de compte, l'euthanasie a été pratiquée en raison d'une maladie rénale chronique associée à une anémie, une léthargie et une anorexie.

(Traduit par Dr Serge Messier)

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Case description

A 9-year-old, 18.8 kg spayed female mixed breed boxer dog was referred to the University of Wisconsin — Madison Veterinary Care (UWVC) with a 7-month history of difficulty swallowing and prehending food, regurgitation, hypersalivation, and an abnormal positioning of the tongue. At the time of the initial onset of clinical signs, a barium study was performed by the primary veterinarian which revealed a mildly dilated esophagus. The dog was prescribed famotidine 10 mg (0.5 mg/kg, PO, q12h), cisapride 5 mg (0.25 mg/kg, PO, q8h), and prednisone 5 mg (0.25 mg/kg, PO, q12h). Feedings from an elevated platform were recommended for home care. The owners reported marked improvement with these treatments. The prednisone dosage was tapered over the course of 20 d and was subsequently discontinued 5 mo before admission to our hospital. The frequency of cisapride was decreased from q8h to q12h, but clinical signs of regurgitation worsened and q8h administration was reinstituted. The dog was referred to a local internal medicine specialist for additional examination and diagnostic tests. No abnormalities were seen on complete blood (cell) count (CBC), serum biochemical analysis, urinalysis, and thyroid panel. An acetylcholine receptor antibody titer was within the reference range. No neurologic deficits were identified at that visit and the preliminary diagnosis was dysphagia of unknown cause, muscular atrophy of the tongue, and tongue weakness. The dog was referred to the UWVC for a videofluoroscopic swallow study.

Upon presentation to the UWVC, physical examination revealed bilateral, symmetric atrophy of the temporalis muscles. The rostral half of the tongue showed symmetrical severe atrophy and dorsiflexion (Figure 1). The rostral portion of the tongue did not appear to have motor function present, and the caudal portion of the tongue appeared to have normal movement. A complete neurologic examination revealed no additional abnormalities except for a reduced gag reflex. Results of a CBC and serum biochemical analysis were within the respective reference ranges including creatine kinase activity [219 U/L (reference range: 22 to 491 U/L)]. A videofluoroscopic swallow study and thoracic radiographs revealed oropharyngeal and esophageal dysphagia, gastroesophageal reflux, megaesophagus and aspiration without evidence of current pneumonia. The dog was continued on cisapride and famotidine at the previously prescribed doses as well as upright feedings until returning 3 mo later for further diagnostics including electrodiagnostic testing and muscle and nerve biopsies. At that time the dog was reportedly doing well at home and was being treated only with cisapride as previously prescribed. Physical and neurologic examinations were unchanged from the previous evaluation.

Electromyography (EMG) was performed on all major muscle groups, including epaxial and appendicular muscles, which revealed moderate to severe spontaneous activity (fibrillation potentials and positive sharp waves) in the masseter muscles and diffuse changes within the rostral part of the tongue (Figure 2). Motor nerve conduction velocities and sensory nerve conduction velocities were performed on the left sciatic and peroneal nerves and were overall within normal limits. Unfixed chilled and formalin-fixed biopsies from the right temporalis, tongue, and biceps femoris muscles were obtained and submitted by a courier service to the Comparative Neuromuscular Laboratory, University of California, San Diego. The unfixed biopsies were immediately frozen in isopentane precooled in liquid nitrogen and stored at −80°C until further processing. The fixed biopsies were routinely processed into paraffin.

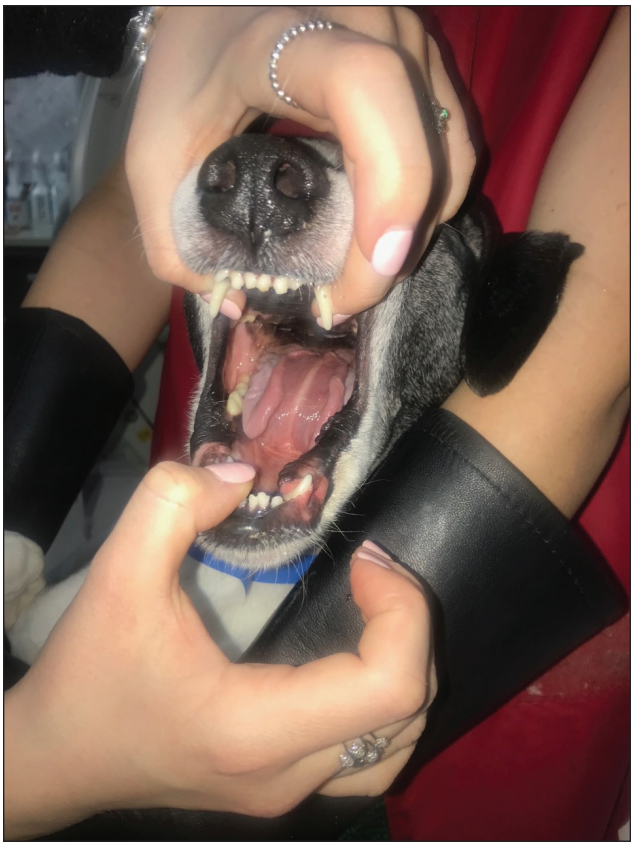

Figure 1. At the time of presentation, the rostral half of the tongue was severely atrophied and continuously maintained in a dorsiflexed position.

Biopsies from the temporalis and tongue muscles showed generalized myofiber atrophy with marked fiber loss, fibrosis, and fatty infiltration in the tongue (Figure 3). Scattered (tongue) or clusters (temporalis) of mixed mononuclear cell infiltrations were present having an endomysial and perimysial distribution. Intramuscular nerve branches were normal in appearance. No abnormalities were seen in the biceps femoris muscle. No evidence of infectious disease was present in any of the biopsy samples.

To further characterize the mononuclear cell infiltrations and determine if upregulation of major histocompatibility complex (MHC) antigens was present, cryosections from the tongue muscle were incubated with monoclonal antibodies against the MHC antigens MHC-I and MHC-II, the T-cell markers CD3, CD4, and CD8, the macrophage/dendritic cell marker CD11c, and the B-cell marker CD21 (Figure 3; all antibodies were from the laboratory of Dr. Peter Moore, University of California Davis). Additional antibodies were used against developmental myosin heavy chain (dMHC; NCL-MHCd) for regenerating fibers and dysferlin (NCL-Hamlet) for a form

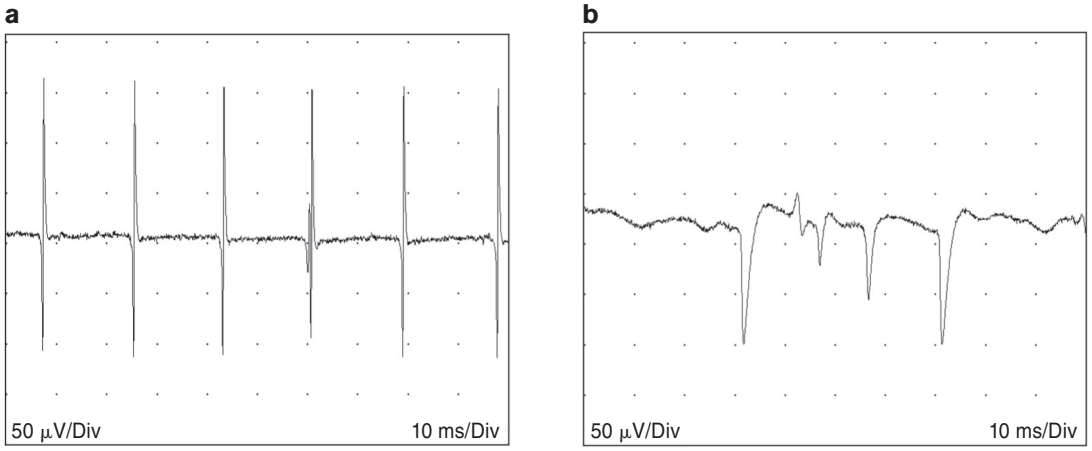

Figure 2. Electromyography (EMG) of the tongue (a) and temporalis muscles (b) revealed fibrillation potentials and positive sharp waves, respectively.

of muscular dystrophy (both from Novocastra Laboratories, Newcastle, UK). Scattered CD3+, CD4+ and CD8+ T-cells were present in the endomysium (Figure 3). No CD21+ B-cells were observed. Scattered CD11c+ macrophages were present in the endomysium, perimysium and within necrotic myofibers. MHC-I+ staining was markedly increased in the sarcolemma of some muscle fibers. Sporadic MHC-II+ staining was observed within inflammatory cells. Sporadic dMHC regenerating fibers were present. Dysferlin antibody staining was normal, ruling out a form of muscular dystrophy. Based on these findings and histopathological changes, a chronic immune-mediated inflammatory myopathy with fibrosis and fiber loss was diagnosed.

Treatment with cyclosporine (5.3 mg/kg, PO, q12h) and a 2-month tapering course of prednisone (1 to 1.5 mg/kg per day) was initiated. A cyclosporine (CSA) pharmacodynamic assay testing for activated T-cell mRNA IL-2 expression was recommended 3 to 4 wk after initiating cyclosporine to ensure efficacy of treatment. The assay was performed approximately 11 mo after diagnosis when the dog showed signs of gingival hyperplasia, suspected to be secondary to cyclosporine administration. Results of the assay revealed moderate IL-2 suppression with the recommendation to increase the dose of cyclosporine to 6.6 mg/kg, PO, q12h. However, the owner elected to continue with the original dose to minimize side effects.

In the 18 mo following diagnosis, the dog had 2 episodes of aspiration pneumonia, one of which occurred during recovery from anesthesia for surgical removal of dermal lesions. Megaesophagus was not present on thoracic radiographs. Approximately 24 mo after diagnosis, the dog developed a left-sided head tilt and left-sided facial nerve paralysis, which improved without any additional treatments. The diagnosis was ideopathic facial and vestibular neuropathy. The dog was seen and treated by the referring veterinarian for this episode, but a complete neurologic examination was not performed. Therefore, central or paradoxical vestibular neurolocalization cannot be completely ruled out. At 28 mo after initial diagnosis of immune-mediated glossitis, the dog was evaluated for anorexia and lethargy. Severe azotemia with secondary nonregenerative anemia was diagnosed and the dog was humanely euthanized. At the time of euthanasia, the temporalis and tongue muscle atrophy remained static and partially controlled with continued use of oral cyclosporine.

Discussion

Inflammatory myopathies are characterized by infiltration of inflammatory cells into striated skeletal muscle (1). Inflammatory myopathies can be infectious, immune-mediated, or paraneoplastic in origin (2). Infectious etiologies include parasitic, bacterial, rickettsial, or viral disease; immune-mediated etiologies primarily include examples such as masticatory muscle myositis (MMM), idiopathic polymyositis, extraocular myositis and familial canine dermatomyositis. Paraneoplastic inflammatory myopathies have been described in dogs and cats with thymomas and round cell tumors (1). Standard diagnostic criteria to further characterize an inflammatory myopathy includes i) an increase in CK activity; ii) EMG changes associated with muscle membrane instability; and iii) histologic evidence of inflammation in muscle (1). However, all 3 criteria do not need to be met for the diagnosis of an inflammatory myopathy. Also, magnetic resonance imaging (MRI) can help in diagnosing inflammatory myopathies (3). The dog herein had normal CK activity and underwent electrodiagnostic testing and muscle biopsies to diagnose an inflammatory myopathy. The normal CK activity in this case may represent the stage of the disease (may be normal in end-stage disease with fibrosis) or if only small groups of muscles are affected such as in glossitis, masticatory myositis and extraocular myositis. In addition, the dog had received a 20-day tapering course of prednisone approximately 5 mo before presentation to our hospital, which also could have resulted in a normal CK.

Electrodiagnostic testing is often used to diagnose and confirm the presence and distribution of muscle disease, as well as to concurrently exclude alternative diagnoses, such as motor neuron disease (neuropathies) or neuromuscular junction disorders (4). Electromyography has been useful in veterinary and human medical practice to characterize the functional integrity of muscle by testing the stability of the muscle membrane (1). However, EMG changes can be nonspecific, as abnormal discharges may be present in myopathies, neuropathies, or disorders of neuromuscular transmission. In cases in which the clinical

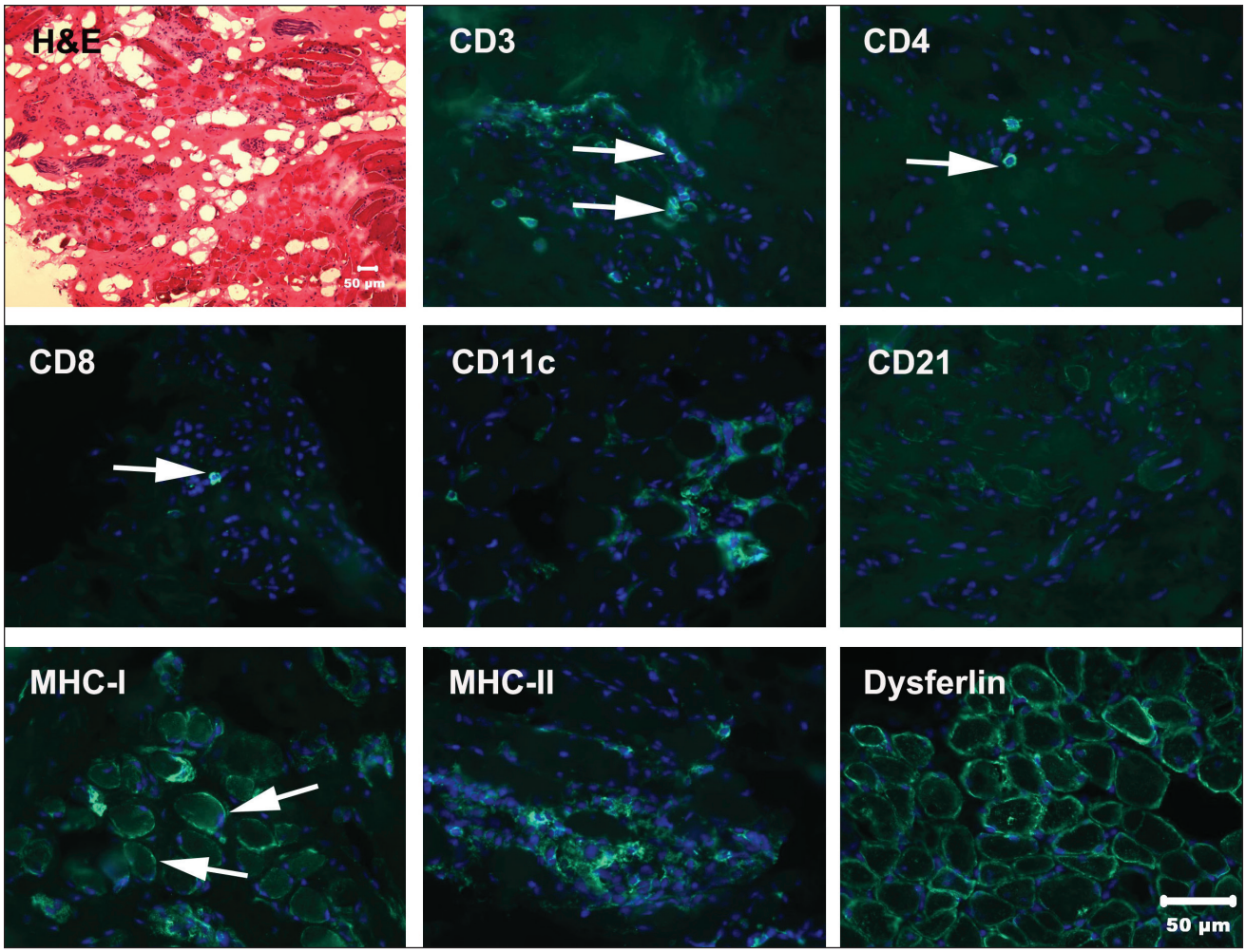

Figure 3. Histopathology and immunofluorescent staining of cryosections from the tongue. H&E staining showed muscle fiber loss and replacement with fatty tissue and fibrosis. Scattered and multifocal areas of mononuclear cell infiltrations were present. Immunofluorescent staining for CD3+, CD4+, CD8+ T-lymphocytes showed small numbers of positive cells (green, arrows). No CD21+ B-cells were identified. Scattered CD11c+ macrophage/dendritic cells were highlighted. Sarcolemmal staining of myofibers was identified with an antibody against MHC-I (arrows) and inflammatory cells were highlighted with the antibody against MHC-II. Staining for the muscular dystrophy associated protein dysferlin was present ruling out a form of muscular dystrophy.

suspicion is high, corroborated with a persistently increased serum CK activity, it could be considered reasonable to skip electrodiagnostic testing and go straight to muscle biopsies as that is the only way to definitively diagnose a myopathy (4). In this case, electrodiagnostic testing showed marked changes to the tongue and muscles of mastication, further increasing the suspicion of a neuromuscular disease.

Additional immunofluorescent staining was done to identify CD3, CD4, and CD8+ T-lymphocytes, CD21+ B-lymphocytes, and to confirm upregulation of the major histocompatibility (MHC) antigens Classes I and II. Normally MHC Class I and Class II antigens are not expressed on the muscle sarcolemma. However, in both humans and animals, MHC-I and II antigens are regulated in inflammatory myopathies, even in areas remote from the inflammation (5–7). Given the strong sensitivity, specificity, and negative predictive value, MHC Classes I and II are frequently used to discriminate immune-mediated inflammatory myopathies from other muscle diseases with inflammation (6); however, this information comes primarily from the human medical literature. Major histocompatibility Class II is less sensitive than MHC Class I, but if positive, it can also help to exclude the presence of other neuromuscular disorders.

Cyclosporine was the chosen treatment in this case due to mode of action for immunosuppression and the potential for less systemic adverse effects compared to long-term corticosteroid administration. The most common side effect of cyclosporine is mild gastrointestinal upset with more severe and less common adverse effects including gingival hyperplasia, opportunistic infections, hepatoxicity, and lymphoproliferative disorders (8). In this dog, gingival hyperplasia was observed but was not affecting quality of life. Eleven months after initiating cyclosporine therapy, a CSA pharmacodynamic assay (T-cell function *via* IL-2 qRT-PCR) was performed to determine the level of immune-modulation present to decide if dose adjustments were needed. This panel revealed moderate suppression of T-cells with a dose

increase was recommended. However, the owners elected to keep the dose the same to avoid additional side effects from the medication.

Although a similar disease process has been reported in corgi dogs (2,9) the age at onset, breed, very focal clinical signs related to the tongue and temporalis muscles, and partial response to immune-modulating medications are unique to the present case. A single case series followed 7 corgi dogs with tongue atrophy and diffuse muscle involvement affecting ambulation (2). These dogs were younger with an average age of onset of clinical signs at 3.4 ± 2.14 y at presentation and partially responsive to immunosuppressive therapy. Another case of an inflammatory canine myopathy was described in a 3-year-old female Welsh corgi who exhibited similar signs to the dog herein including: symptomatic tongue atrophy, crinkling of the tip of the tongue, and dysphagia (9). However, that dog did not respond to prednisone treatment and at necropsy had generalized muscle atrophy, involving both the masticatory and quadriceps muscles. Lastly, a case of inflammatory myopathy in a 14-month-old intact female pitbull terrier with similar clinical signs that began at 6-months-old, included dysphagia and a dorsiflexed tongue that did not respond to prednisone (10).

In the present report, the dog had signs consistent with dysphagia, gastroesophageal reflux, and esophageal dysmotility, which were diagnosed by a videofluoroscopic swallow study and megaesophagus on thoracic radiographs on initial evaluation at UWVC. On thoracic radiographs reviewed by a Board-certified radiologist taken 24 mo later for a suspected episode of pneumonia, the megaesophagus had resolved. Given the dog's concurrent reflux at the time of megaesophagus diagnosis and later radiographic resolution of megaesophagus, it is likely that the megaesophagus was transient and secondary to esophagitis (11). It is also possible that the esophageal dysmotility was part of the immune-mediated myositis, as these muscles were not evaluated by EMG or biopsy. If part of the disease, resolution of the megaesophagus would not have been expected, as no other clinical improvements were noted during the follow-up period. Although previous reports of focal myositis in dogs have listed dysphagia as a clinical sign, megaesophagus and esophageal dysmotility have not been described. Finally, it is possible the esophageal dysmotility was secondary to another underlying disease, such as polyneuropathy associated with laryngeal paralysis given the dog's signalment (12).

The dog herein developed signs at a much older age (9 y old at initial presentation), did not display generalized muscle weakness or difficulty walking, and was partially responsive to immune modulators. Therefore, an immune-mediated inflammatory myopathy should be considered in older non-corgi dogs presenting with focal symmetrical tongue atrophy and dysfunction. The partial response may be a result of the chronicity of the myopathy with myofiber loss and fibrosis evident in the muscle biopsy. Earlier diagnosis and treatment may have resulted in a more complete response to immunosuppressive therapy. To our knowledge, this is the first case of immune-mediated glossitis in an older, non-corgi dog with long-term follow-up. CVJ

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