“Chug’s Chewing Conundrum”

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Introduction:

Masticatory muscle myositis is an autoimmune disorder that affects the muscles of mastication of the dog and other species[1,3,14,17]. The muscles of mastication function to close the jaw and chew food. Muscles of mastication include the temporalis, masseter, pterygoid, and rostral digastricus muscles, which are innervated by the mandibular branch of the trigeminal nerve, or the fifth cranial nerve. The digastricus muscle is composed of two separate muscles bellies with unique innervations. While the rostral digastricus is innervated by the trigeminal nerve, the caudal digastricus is innervated by the facial nerve, or cranial nerve 7. The masseter, temporalis, and pterygoid muscles are composed of a unique myosin isoform known as 2M muscles fibers[17]. This distinguishes masticatory muscles from limb muscles which are composed of type 1A and type 2A muscles fibers, also known as slow and fast twitch fibers respectively[12]. Masticatory muscle myositis has been known to affect any dog; however, young to middle aged large breed dogs are most afflicted. While any breed can be affected, Rottweilers, Golder Retrievers, and Labrador Retrievers are overrepresented[7,11,15]. The Cavalier King Charles Spaniel also appears to have a genetic predisposition to a "juvenile" form of masticatory myositis[10,15]. No sex predilection has been established. In recent years, the disease has been documented in other species including cats and minks[1,3,14]. The exact etiology of the disease process remains unknown. It has been theorized that the disease arises due to an infectious agent stimulating antibody production that subsequently cross reacts with endogenous antibodies. A second theory speculates that cytotoxic CD8+ T cells ultimately initiate the disease process producing antibodies against the unique 2M muscle protein fibers[9,17]. Focal disease involving the canine masseter muscles has been documented as early as 1920[17]. Originally this disease process was

termed eosinophilic myositis and atrophic myositis; however, this likely represents the acute and chronic forms of the disease respectively[4,9,12,15].

History & Presentation:

Chug is a 10-month-old, male neutered, Olde English bulldog that presented to Mississippi State University College of Veterinary Medicine Community Veterinary Service on March 19th, 2021. His presenting complaint was for a Cytopoint injection as well as not being able to open his mouth. Chug's owner noted that for approximately one week Chug had been acting inappropriately when eating treats. Chug was reluctant to open his mouth to take treats and would hide to eat them. The owner also noted an inability to play normally with his toys. Chug had a history of pyoderma and atopic dermatitis that flared up during warmer weather. His allergies have been historically managed with Cytopoint injects, with his last injection prior to presentation being on November 25th, 2020. Two weeks prior to presentation, Chug had presented to MSU-CVM Emergency Department for a 24-hour history of ocular discharge. Chug was determined to have conjunctivitis of the right eye and was treated with Neo-Poly-Dex ophthalmic solution applied to the right eye twice daily for five days and 50 milligrams of oral Benadryl twice daily as needed for allergies. Chug recovered uneventfully from this ocular episode. Chug was up to date on his vaccinations, he received Advantage Multi monthly for parasite prevention, and Chug's owner did not report any abnormalities in Chug's appetite, drinking, urination, or defecation. Chug lived in a household with one other dog, and he was reported to act otherwise happy and had been playing normally with his housemate.

On presentation, Chug was bright, alert, and responsive. He weighted 18.23 kilograms, with an ideal body condition of 5 out of 9. His vitals included a temperature of 101.1 degrees Fahrenheit, a heart rate of 132 beats per minute, and a respiration rate of 28 breaths per minute.

Cardiopulmonary auscultation revealed no crackles, wheezes, or irregular heart sounds. He appeared adequately hydrated, and his mucous membranes were pink and moist with a capillary refill time of less than two seconds. Chug had a type three malocclusion of his jaw. There were erythematous areas in his inguinal regions. Chug was offered treats throughout the physical exam but was unable to fully open his mouth when offered food or when manually manipulated. His jaw was unable to be opened more than approximately 1 inch. Chug's tongue was not visible throughout the exam, and he did not pant. No pain was elicited on deep palpation of his skull and masticatory muscles; however, the mass of his muscles of mastication seemed decreased.

Diagnostic Approach & Differential Diagnoses:

Masticatory muscle myositis of canines can be diagnosed in numerous ways based on a combination of clinical signs or physical exam findings, laboratory findings, serological testing, histopathology, and diagnostic imaging[1]. Chug presented for trismus, one of the hallmark signs of masticatory muscle myositis; however, further diagnostic testing was warranted to rule out other differentials.

Chug first had baseline bloodwork performed which included a complete blood count and serum chemistry panel. The complete blood count revealed a decreased red blood cell count of 5.16^6/ul (5.60-7.90), a mild anemia of 33.0% (34.0-60.0), and a decreased monocyte count of 85.1/ul (100.0-1700.0). The serum chemistry panel revealed a mildly elevated glucose of 134 mg/dL (75-125), a mildly decreased albumin of 2.4 g/dL (2.5-3.9), a mild hyperglobulinemia of 5.1 g/dL (2/1-4.3), an elevated phosphorus of 6.7 mg/dL (2.5-5.0), a mildly decreased magnesium of 1.5 mg/dL (1.7-2.4), and an increased creatinine kinase of 977 U/L (50-300). Hematologic changes that have been reported in canine patients diagnosed with masticatory muscle myositis include anemia, hyperglobulinemia, proteinuria, and an elevated creatine

kinase[12]. An eosinophilia has also been reported in several cases of animals with masticatory myositis; however, it is not a consistent finding[8,9,12]. Creatine kinase elevations are more commonly seen in the acute form of the disease and elevations are mild to moderate compared to those disease affecting a larger muscle mass[12]. A urinalysis was not performed during his visit to determine if proteinuria was present.

A serum blood test is available that tests for circulating antibodies against the 2M muscle fibers found in the muscles of mastication. The ELISA has a high sensitivity (80-90%) and specificity (100%) and is therefore used as a confirmatory test in cases with high clinical suspicion. It is easy to perform and widely available to general practitioners[1,2,3,12]. A negative ELISA result (<1:100) can be falsely obtained in animals on immunosuppressive doses of corticosteroids for at least 7 to 10 days prior to testing or in chronic stage disease. This ELISA is also not reliable for polymyositis or diseases affecting limb muscles. A borderline result (=1:100) or negative result requires additional testing, most often histopathology. Blood was obtained from Chug's jugular vein and transferred to a red top blood tube. The serum was sent off for serologic testing, and Chug tested positive with a lab result of 1:1000 (>1:100). The ELISA functions as a confirmatory test; however, it can be useful in disease monitoring to detect relapses or during tapering of immunosuppressants. To date there is not a feline specific ELISA available; however, the canine assay has been found to be reliable in diagnosing masticatory myositis in feline patients[1,3].

In those animals that test ELISA negative or inconclusive, biopsy and histopathology of the muscles of mastication is an appropriate next diagnostic step. A false negative ELISA may be obtained if an animal has received immunosuppressants prior to testing or during chronic stage disease when masticatory myofibers have been replaced by fibrosis[12]. Histopathology and

immunohistochemistry of muscle samples is useful as a confirmatory diagnosis and in determining long-term prognosis[6,12]. Immunohistochemistry staining is used to determine the presence of immune complexes in the biopsy samples. The biopsy provides insight to the degree of fibrosis, cellular infiltration present, and degree of normal 2M fiber population. The degree of fibrosis and number of normal muscle fibers present is critical in determining return to function of the jaw and surrounding muscles[3,6]. A muscle biopsy is a relatively simple surgical procedure that can be performed by the general practitioner. Samples are most commonly obtained from the masseter or temporalis muscle. Caution should be taken not to inadvertently biopsy the frontalis muscle. The frontalis muscle is not composed of 2M muscle fibers and is therefore not affected by masticatory myositis. A biopsy can also be useful in ruling out other myopathies even if MMM is suspected. If generalized muscle atrophy or abnormalities in gait are appreciated, biopsy of limb muscles should be considered[3.8.12]. Due to Chug's positive ELISA assay, a muscle biopsy was not performed.

Radiology and advanced imaging are useful to rule out numerous other causes associated with trismus including temporomandibular joint luxation, subluxations, fractures, retrobulbar abscesses, or foreign bodies[12]. Chug had sedated skull radiographs performed on March 22nd, 2021. The radiographs revealed foreshortening of the maxillary bones or prognathism which was an expected breed conformation. The temporomandibular joints were difficult to evaluate on lateral and oblique projections resulting in an asymmetric joint space. The joint space abnormalities may have been secondary to superimposition, but temporomandibular dysplasia was unable to be ruled out without cross-sectional imaging of the region which was declined. Computed tomography is desirable due to being more sensitive than traditional radiography in characterizing bony changes of the head and skull[9,17]. Both CT and MRI have been documented

to be useful in evaluating the soft tissue structures including size (swelling or atrophy), lesions, areas of attenuation or contrast enhancement, and surrounding lymph nodes. Advanced imaging also has proved useful in selecting the best areas to biopsy[3,2,6,9,17].

A final diagnostic tool that can be used in conjunction with others to diagnose masticatory myositis is electromyography (EMG). Spontaneous EMG activity is more commonly seen during the acute stage of the disease. EMG can be used to differentiate masticatory myositis from a polymyositis where the spontaneous activity would be generalized compared to the focal activity associated with MMM. EMG changes include moderate to severe fibrillation potentials and sharp, positive waves in the masticatory muscles. However, EMG changes are not specific for MMM and therefore need to be combined with confirmatory diagnostics[12,13].

Etiology & Pathophysiology:

Masticatory muscle myositis is a focal autoimmune disorder that exclusively affects the muscles of mastication[5,12]. The masticatory muscles include the masseter, temporalis, pterygoid, and rostral digastricus, all innervated by the mandibular branch of the trigeminal nerve[12]. Appendicular muscles are composed of a combination of type 1A (slow twitch) and type 2A (fast twitch) muscle fibers. In contrast, the masticatory muscles are composed of a type 1 muscle fiber variant and type 2M muscle fiber, which are unique to the masticatory muscles[5,12]. Type 2M muscle fibers were previously referred to as Type 2C fibers[18]. Electrophoresis has demonstrated differences in the heavy and light myosin isoforms of masticatory muscles compared to appendicular muscles[5,12,18]. A final target of the disorder is a newly discovered 150 kDa protein that is referred to as masticatory myosin binding protein-C, or mMyBP-C. The myosin binding protein-C is not only unique to the masticatory muscle fibers, but also has been determined to be located near their cell surface, perhaps making this protein more accessible to immune reaction[19].

Autoantibodies are formed against the 2M muscle fibers and mMyBP-C; however, the exact etiology that initiates autoantibody production remains unknown[5,9,12]. Some theorize that molecular mimicry is responsible for the production of antibodies. Antibodies are produced in response to an infectious agent; however, the bacterial antigens have a similar structure as a component of the 2M muscle fibers. Ultimately, antibodies produced against the infectious antigens cross-react with endogenous antigens[9,12]. A second theory hypothesizes that cytotoxic CD8+ T cells initiate the production of autoantibodies against 2M muscle fibers[9]. The antibody binding initiates an inflammatory response recruiting inflammatory cells, most commonly lymphocytes; however, plasma cells and other inflammatory cells may also be present[4]. The distribution of cellular infiltrates is most commonly perivascular[7]. During the inflammatory or acute phase of the disorder, there is often marked swelling and edema of the masticatory muscles. This creates restricted range of motion of the jaw and pain on palpation or manipulation[5,9,12,19]. The acute stage of the disease progresses to the chronic stage of disease as the 2M muscle fibers are destroyed and replaced with fibrous tissue. The chronic stage often results in severe muscle atrophy and permanent alteration in jaw movement[5,12].

Treatment & Management Options:

The hallmark treatment option for masticatory muscle myositis in both the acute and chronic phase is immunosuppressive therapy. An early and accurate diagnosis followed by aggressive immunosuppression yields the most favorable results in regard to regaining normal jaw function. The most common mistakes made when treating MMM is using an insufficient dose of an immunosuppressive agent or discontinuing immunosuppression too abruptly[12]. On March 22nd, 2021, Chug was prescribed prednisone (20 milligram tablets) at a dose of approximately 1.6 milligrams per kilogram orally twice daily. Ten days after beginning

prednisone therapy, the frequency of treatment was decreased to once daily dosing. Chug was maintained on this dose for an additional three weeks. On April 23rd, 2021, Chug's dose was reduced to 0.5 milligrams per kilogram orally once daily. Chug was maintained on this dose for one month until his recheck examination. During Chug's follow-up visit on May 19th, 2021, Chug's prednisone dose was tapered to every other day dosing. Chug was maintained on every other day dosing for two additional months before therapy was discontinued in late July of 2021. Chug was treated with prednisone for immunosuppression for a total of four months, during which time his dose was tapered three times.

Prednisone is a synthetic corticosteroid that is converted to its biologically active form, prednisolone, by the liver. Prednisone has both anti-inflammatory and immunosuppressive properties at low and high doses respectively. The mechanism of action of prednisone involves decreasing the migration of leukocytes and other inflammatory cells and decreasing capillary permeability[16]. Although prednisone is generally well tolerated in canine patients, the risk of adverse effects is higher at immunosuppressive doses. The most common side effects that owners should be prepared for include polyphagia, polyuria, polydipsia, and weight gain. However, more serious side effects include increased susceptibility to infections, delayed wound healing, and increased skin fragility. In cases where side effects are too severe or the animal is refractory to prednisone therapy alone, a second immunosuppressive agent may be added. The most common second line immunosuppressive agents to be added to refractory cases are Azathioprine (2 milligrams per kilogram, orally, every 24 to 48 hours) or Cyclosporine (5 milligrams per kilogram, orally, every 12 to 24 hours). Azathioprine has the potential to cause bone marrow suppression and hepatotoxicity; therefore, complete blood count and hepatic enzymes need to be monitored during therapy. Cyclosporine also requires extensive therapeutic

monitoring of blood drug concentrations or pharmacodynamic monitoring to account for individual variations.

Patients in the acute stage of disease tend to have a quicker and more complete response to corticosteroid therapy. However, patients in the chronic stage of disease may still benefit from corticosteroid therapy to prevent any further fibrosis of muscle fibers. Dexamethasone has also been shown to be safely used as an alternative to prednisone or in combination with other immunosuppressive agents at a starting dose of 0.2 milligrams per kilograms intravenously and tapered accordingly[8].

In addition to immunosuppressive agents, supportive care is required to ensure adequate nutritional intake. A softened or gruel diet can be used to increase caloric intake. Patients should also be encouraged to chew toys to promote use and exercise the muscles of mastication. Physical therapy including passive range of motion of the jaw and massaging the muscles of mastication can also be performed daily to help speed in recovery[13]. Chug had a normal appetite and was able to remain on his normal diet while maintaining his caloric requirements. Within the first few days of therapy, he regained enough mobility of his jaw to begin to play with his toys.

Expected Outcome & Prognosis:

The most reliable indicator in estimating long-term prognosis is a muscle biopsy at the time treatment is initiated. Histopathologic examination provides information regarding the amount of fibrosis present and population of healthy 2M muscle fibers remaining[1,3,12]. Dogs that are accurately and rapidly diagnosed in the acute stage of disease carry a good to excellent prognosis[6]. Those patients diagnosed in the chronic stage of disease have a more guarded and uncertain prognosis. However, the chronic stage of disease can still be treated with immunosuppressive agents and jaw function can be improved if extensive fibrosis is not already

present. Prognosis for return to normal jaw function decreases when inadequate doses of immunosuppressive agents are prescribed or discontinued without appropriate tapering and close monitoring for relapses of clinical signs[12]. Relapses are not uncommon when treating MMM; however, close monitoring should be observed as dogs that relapse are less likely to experience future remission[3,12]. It is possible for those animals that respond rapidly to immunosuppressive agents to experience muscle atrophy after treatment[6,12].

Case Outcome:

On May 19th, 2021, Chug received a follow-up exam from the MSU-CVM Community Veterinary Service, two months after his initial diagnosis. Chug was non-painful on deep palpation of the masticatory muscles and skull and manipulation of the jaw. He also had normal range of motion of his jaw and was able to accept and eat treats normally during the exam. Chug's jaw muscles were subjectively smaller than initial presentation in March, suggesting there may be a degree of muscle atrophy following treatment. Chug's owner reported he was doing well on prednisone therapy and was not experiencing clinical signs of polyuria, polydipsia, or polyphagia. Chug's prednisone was tapered for a final time, and it was recommended that Chug receive a follow-up exam at the end of his steroid treatment in approximately two months to reassess his progress.

Summary:

In summary, masticatory myositis is a focal, autoimmune disorder that affects the muscles of mastication of dogs and other species. The exact etiology of the disorder remains unknown. The disease is characterized by an acute or inflammatory phase and a chronic phase. During the inflammatory or acute phase of the disorder, there is often marked swelling and edema of the masticatory muscles. This creates restricted range of motion of the jaw and pain on

palpation or manipulation. If left untreated, the acute stage of disease can progress to the chronic stage resulting in severe muscle atrophy and permanent alteration in jaw movement. Masticatory myositis can be diagnosed using a combination of history, clinical signs, laboratory findings, serological testing, histopathology, and diagnostic imaging. A serum-based ELISA detecting circulating antibodies or biopsy and histopathology are most commonly used to confirm disease. The hallmark for treatment of both the acute and chronic phases is immunosuppressive therapy. A brisk and accurate diagnosis followed by aggressive immunosuppressive therapy yields the most favorable results.

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