Indy's Jaw Dropping Story

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Class of 2021

Clinicopathologic Conference

5 March 2021

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Introduction

Inflammatory myopathies are a group of conditions characterized by non-suppurative inflammatory cellular infiltrate into skeletal muscle due to an idiopathic, immune-mediated, or infectious cause.[1-4] One of the most common inflammatory myopathies in dogs is the fairly specialized focal inflammatory myopathy, masticatory muscle myositis (MMM).[1-3] MMM is an auto-immune disease in which autoantibodies attack the specific 2M muscle fibers found in the muscles of mastication (temporalis, masseter, medial and lateral pterygoid, and rostral portions of the digastricus muscles).[1-5] Since MMM exclusively affects the muscles of mastication, clinical signs are restricted to this muscle group and include trismus, pain upon mastication, swelling of the masticatory muscles, exophthalmos, and atrophy of the masticatory muscles, among others.[1-3, 5]

History and clinical signs help guide the clinician to a clinical diagnosis of MMM. A definitive diagnosis may be achieved using an antibody titer test or histopathology from an inflamed masticatory muscle.[2,3, 6-9] Diagnostic imaging in the form of CT and MRI have also proven useful in further characterizing this disease process.[7-9] Treatment and management of the disease primarily rely on immunosuppression.[1, 3, 10] Prognosis for return to normal jaw function is good, and some animals go into remission.[1, 3, 10] Prompt diagnosis and treatment are key to help prevent fibrosis from chronic MMM.[1, 3, 8, 10] While this disease typically presents bilaterally, unilateral presentations do occasionally occur and must be differentiated from other causes of unilateral facial disease.[11] The following case will discuss a unilateral presentation of MMM and the path taken to find a diagnosis.

History and Presentation

Indy, a 1-year-8-month-old, neutered male Golden Retriever, was presented to the Mississippi State University College of Veterinary Medicine (MSU-CVM) Small Animal Emergency Service on November 29, 2019, for left-sided facial swelling and muscle quivering that began around his eye. Approximately 6 weeks prior, he was noticeably chewing his treats and toys less. His referring veterinary performed skull radiographs which had no significant findings. Indy was prescribed an anti-inflammatory drug and antibiotic, but no improvement was seen. He was then given a dexamethasone sodium phosphate injection that transiently helped his clinical signs of muscle swelling. A 2M antibody serum test for masticatory muscle myositis was subsequently performed and was negative. Indy had a history of frequently chewing on toys, sticks, and bones. His owner and referring veterinarian were concerned that a foreign body was causing his clinical signs. He was referred to MSU-CVM for further diagnostics and work-up.

On Indy's initial presentation to MSU-CVM, his unilateral clinical signs along with his history of a potential foreign body and a negative 2M serum antibody test resulted in an exploratory surgery to help explain his atypical presentation. Prior to surgery, a CT revealed a fluid-attenuating pocket in the retropharyngeal region with surrounding muscle inflammation. Mandibular ultrasound was consistent with a possible granuloma or abscess. However, no granuloma or abscess was discovered.

Exploratory surgery of the left mandible and mandibular ramus showed a region of disorganized muscle fibers. This region was biopsied and submitted to MSU-CVM's Pathology Department. Muscle tissue was elevated to relieve his restricted jaw movement. At time of discharge, he could open his jaw approximately 4 cm.

Indy was represented to MSU-CVM's ER Service on December 27, 2019. He had progressively worsened since the onset of clinical signs and drastically declined since time of

discharge. He had an increase in salivation, anxiety, and pain when eating or when his mouth was touched. The right side of his face was moderately swollen, and he had submandibular lymph node enlargement, particularly of the right lymph node. He could only open his mouth approximately 2 cm, whereas it had been 4.8 cm under sedation at his referring veterinarian the day before.

Differential Diagnoses and Diagnostic Approach

Unilateral muscle atrophy of the head is an infrequent clinical presentation with limited differential diagnoses.[11] Neoplasia of the trigeminal nerve is thought to be the most common cause of unilateral facial muscle atrophy.[11] Other differentials include a neuropathy (i.e. trigeminal neuritis), myopathy (i.e. MMM or a generalized inflammatory myopathy), trauma, or an extra-axial mass invading into the brain.[11]

The diagnostic approach for MMM varies depending on the clinical signs and differential diagnoses at time of presentation. CBC and chemistry typically have no significant abnormalities or non-specific findings, such as an elevated serum CK that may be present with any canine myopathy.[3, 5, 8,9] Advanced imaging through CT and MRI are useful diagnostic tools for this disease process as they help characterize the degree of muscle inflammation and aid in ruling out other diseases.[7-9] They may also be used to guide biopsy selection sites for a more promising diagnostic yield.[7-9] Imaging characteristics from these modalities have been described in MMM patients and may be used to monitor disease progression or response to treatment.[7-9] Similarly, described changes for electromyography in MMM are present in the literature and may help support a diagnosis of MMM.[3,8]

The gold standard tests for definitively diagnosing MMM include a 2M antibody titer test and muscle biopsy to characterize cellular infiltrate, assess fibrosis, and identify autoantibody

complexes in masticatory muscles.[1,2,7,8] The 2M antibody test capitalizes on the unique nature of MMM in only attacking the muscles of mastication. 2M autoantibodies are exclusively found in patients with MMM, making this test 100% specific.[2,6] Additionally, this well-established ELISA has a high sensitivity of 85%.[8] In addition to the 2M antibody test, histopathologic characteristics of masticatory muscles involved in this disease process have been thoroughly described.[2-5]

Lastly, a therapeutic and diagnostic treatment trial with an immunosuppressive dose of corticosteroids may be attempted. Since the dose needed for treatment is immunosuppressive, infectious causes of disease must be ruled out prior to steroid administration. Furthermore, in cases of unilateral facial muscle atrophy, it is not recommended to perform a diagnostic steroid trial if a diagnosis of disease is not made.[11]

Differential diagnoses for Indy's trismus included trauma with subsequent abscessation and fibrosis of muscle tissue, MMM, other inflammatory myopathy, temporomandibular joint disease, retrobulbar abscess, neoplasia, ear disease, and tetanus.[7, 9-11] Trauma due to a penetrating injury with subsequent abscessation and fibrosis of affected tissue was the first differential given the unilateral presentation and history of a potential foreign body. MMM was considered less likely due to the negative 2M serum antibody titer test and unilateral signs. Neoplasia was considered less likely since Indy was young; however, it could not be ruled out after physical exam alone. Further diagnostics were warranted to diagnose Indy.

During Indy's first visit in November, a CBC had no clinical abnormalities; chemistry revealed a mildly elevated CK (539 U/L), a mild hypercholesterolemia (423 mg/dl), and a mild hyperglycemia (128 mg/dl). A CT was performed and showed a contrast-enhancing, fluid attenuating region in the left pterygoid muscle. His left medial retropharyngeal and mandibular lymph nodes were enlarged. Consideration was given to an abscess in the pterygoid muscle with

reactive lymph nodes. Cytology of this area was performed and was non-diagnostic due to heavy blood contamination but could not rule out an abscess. An aerobic and anaerobic culture and sensitivity showed no growth after 48 hours. A musculoskeletal ultrasound supported evidence of a possible granuloma or abscess in the region of the left pterygoid and digastricus muscles. A surgical exploratory of his left ventral mandible was performed for biopsy of the abnormal tissue identified on CT and ultrasound. Biopsy of the affected area demonstrated myositis with mild multifocal neutrophilic inflammation and myocyte degeneration. During the surgical exploratory, fibrotic muscle was released from the medial aspect of the caudal half of the left body of the mandible and the ventral half of the ramus of the mandible. Post-operatively Indy could open his mouth approximately 5 cm. He was sedated to have his mouth stretched daily until discharge 6 days following surgery. He was discharged with a broad-spectrum antibiotic (Clavamox), a pain medication (acetaminophen with codeine), and a non-steroidal anti-inflammatory drug (carprofen).

Several diagnostics were repeated when Indy was seen again in December. He had a stress leukogram on CBC and continued to have a mild elevation in CK (415 U/L) on chemistry. Given the worsening trismus and right-sided facial clinical signs, MMM was now considered the top differential diagnosis. A recheck CT of the head was performed and showed marked atrophy of the left temporalis muscle with thickening of the masticatory muscles on the right. The masticatory muscles had patchy, heterogenous, contrast enhancement, and the mandibular and retropharyngeal lymph nodes were moderately to severely enlarged. The top differential diagnosis from the CT report was MMM. Indy had an electromyography (EMG) performed on the muscles of mastication, but no abnormalities were noted on EMG. Open surgical biopsies of the left and right temporalis muscles, to be submitted to the UC San Diego School of Medicine

Comparative Neuromuscular Laboratory, were performed for diagnosis of MMM. Additionally, the 2M antibody titer test was repeated and sent to the same laboratory. A temporary tracheostomy was performed prior to surgery due to advanced trismus preventing endotracheal tube passage through the oral cavity.

Pathophysiology

MMM is one of the most common canine inflammatory myopathies, more frequently seen than polymyositis.[1-3,10] MMM was previously thought to be only a domestic canine myopathy but has now been documented in a cat and a gray wolf.[12,13] No breed, sex, or age predisposition exists; however, young adult, large breed dogs, such as German Shepherds and Golden Retrievers, tend to be overrepresented.[1,3,4] The exact etiology for MMM is unknown. Speculation for a bacterial cause of antigenic stimulation leading to an immune-mediated reaction has been reported but not proven.[1] Even though the etiology of MMM is unclear, this disease process has been very well characterized.

The temporalis, masseter, pterygoid, and rostral portions of the digastricus muscles of carnivores contain a unique 2M muscle fiber type that is not found elsewhere in the body.[1-6] In MMM, autoantibodies form against the 2M myosin heavy and light chains contained in masticatory muscle fibers and lead to non-suppurative inflammation.[2,5,6] The inflammation seen with MMM is typically a mixed mononuclear cellular infiltrate comprised of lymphocytes, macrophages, dendritic cells, and occasionally eosinophils.[2-5] Furthermore, cell populations contain prominent numbers of B cells with fewer T cells.[2,4] Of the T cells that are present, TCR$\gamma\delta$ T cells are the most numerous, followed by CD4+ T cells and CD8+ T cells.[2-4] This is unlike other generalized inflammatory myopathies, such as polymyositis, that do not contain B lymphocytes or TCR$\gamma\delta$ T cells (TCR$\alpha\beta$ T cells are present in other inflammatory myopathies).[4]

Major histocompatibility complex class I and II are also expressed on muscle fibers associated with MMM with or without cellular infiltrates.[2,4,5]

The clinical signs of painful and swollen masticatory muscles correlate with the infiltration of inflammatory cells into the muscles and makes up the acute form of the disease.[2,5,10] The chronic form of MMM occurs later in the disease process and is characterized by myofiber loss and fibrosis of affected masticatory muscles with or without inflammatory cellular infiltrates present.[2,10] The chronic form has a more guarded prognosis for return to functional jaw range of motion.[10]

Treatment and Management Options

Treatment of MMM relies on immunosuppressive drugs to remove autoantigens and prevent antibodies from attacking the 2M muscle fibers.[6] When the treatment course is finished and the patient is in remission, if possible, autoantibodies for 2M muscle fibers are no longer detected.[6] Therefore, an immunosuppressive dose of prednisone is the mainstay of treatment.

Prednisone is a commonly used immunosuppressive drug in veterinary medicine due to its rapid onset of action and systemic effects on innate and acquired immunity.[14] Prednisone has several well-known systemic side effects that must be managed in conjunction with clinical disease.[14] While these side effects can be detrimental, other immunosuppressive agents have more severe side effects and are typically more expensive.[10] When a second immunosuppressive agent is used in the management of MMM, it is usually to taper the prednisone due to adverse effects, help manage a concurrent immune-mediated disease, or treat patients refractory to prednisone therapy.[10]

Signs of improvement and remission include further ability to open the jaw, reduced pain associated with masticatory muscle palpation or opening of the jaw, and decreased lethargy.[10]

Vertical mandibular range of motion (vmROM) was a measurement used in one study to compare improvement in return of normal jaw function.[10] Decreased vmROM was typically the first clinical sign associated with a relapse of MMM.[10] Remission of disease is possible but many patients require long term low-dose corticosteroid administration.[3,8,10] It is currently unknown which patients will achieve remission or relapse, forcing owners and clinicians to rely heavily on the patient's clinical signs for disease progression. However, dogs that do have a relapse in clinical signs become well controlled again after restarting prednisone or increasing their dose.[10]

MMM does not yet have a proven treatment plan. Tapering off prednisone is largely based on clinical signs and the results of 2M antibody titers or advanced imaging when utilized.[9,10] Clinical improvement after treatment can begin as early as 1 to 3 days.[10] Jaw function does not immediately become restored but has a progressive return to function.[10] This occurs most quickly over the first month of therapy and then slowly over the next several months until a plateau in improvement is reached.[10] Immunosuppressive doses of steroids are recommended initially for 1 month or until maximum vmROM has been reached.[10] They may then be tapered every several weeks by 25-50% depending on the patient's clinical signs.[10]

Expected Outcome and Prognosis

Dogs diagnosed with MMM have a good to excellent prognosis for return of jaw function, particularly when diagnosed and treated at an early stage.[1,8,10] A key indicator of prognosis is the degree of fibrosis present.[10] Therefore, histopathology is a useful prognostic tool. Additionally, prognosis depends on the patient's and owner's ability to manage the adverse effects of prednisone or other immunosuppressive agents.[10]

Case Outcome

Following recovery from surgery, Indy's tracheostomy tube was removed. His recovery occurred uneventfully. He received a dexamethasone injection immediately following muscle biopsy and blood serum collection for testing. He was started on an immunosuppressive dose of oral prednisone (1 mg/kg PO q12h) and was transitioned, 10 days later, to an immunosuppressive dose based on body surface area (20 mg/m2 PO q12h) to help control unnecessary side effects of prednisone administration.

Indy began to clinically improve following immunosuppressive steroid administration. He began opening his mouth and was transitioned from a food slurry to a dry kibble 10 days post treatment. At the time of discharge, 2 weeks after muscle biopsies, Indy could pick up an approximately 5 cm diameter toy. His masticatory muscles remained non-painful.

A definitive diagnosis of MMM was made when the result of the serum 2M antibody titer test was reported positive (1:500) one week post-operatively. The muscle biopsy results followed and indicated that Indy had mild to moderately severe MMM with no fiber loss or fibrosis present. The cellular infiltrate was of mixed mononuclear origin, primarily lymphocytes and macrophages.

Indy's initial 2M antibody titer test performed by his referring veterinarian was negative; however, the serum sample for the test was acquired 4 days after dexamethasone SP administration. False negative results are possible within the 85% sensitivity reported of the 2M antibody titer test, and it is speculated that the dexamethasone injection increased his likelihood of a false negative result. Additionally, as the sample was acquired early in the disease process, Indy may not have had a sufficient number of autoantibodies for a positive titer.

Indy's initial prednisone dose (40 mg daily) was scheduled to be reduced by 10 mg every 3 weeks until a 20 mg every other day dosing schedule was achieved. It was recommended to

keep Indy on this low dose for a minimum of 6 months to ensure his clinical signs were well controlled and maximum range of jaw motion was restored. Indy's treatment management following discharge has been performed with his primary veterinarian. However, through follow-up it was learned that Indy began having relapse of clinical signs when attempting to taper to a lower effective dose (10 mg of prednisone every other day). A 2M antibody titer was resubmitted at the time of relapse and showed a "low positive titer" (exact titer unknown). Azathioprine was added to Indy's treatment in addition to his low dose prednisone, as prednisone side effects were becoming difficult to manage. Currently, he receives azathioprine every other day with prednisone administered on days azathioprine is not given. His clinical signs are largely controlled apart from continued atrophy of his masticatory muscles and occasional, transient trismus. Indy appears to be a patient that will require lifelong treatment for management of MMM.

Conclusion

Masticatory muscle myositis is a disease process unique to the muscles of mastication (temporalis, masseter, medial and lateral pterygoid, and rostral portions of the digastricus). Clinical signs may be unilateral, as in this case initially, or bilateral and are specific for this disease process. Advanced imaging techniques and EMG may help support a diagnosis of MMM, but a 2M serum antibody titer and muscle biopsy are the definitive diagnostics needed. MMM is a manageable disease process that has a good to great prognosis of return to normal jaw function along with a good long-term prognosis, if medication side effects can be well-managed and kept to a minimum. MMM is a focal inflammatory myopathy that should be identified, diagnosed, and treated as soon as possible to help minimize the long-term effects of the disease and provide a higher likelihood of successful medical management.

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