Ginger's Weakness (Other than Catnip)

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Tori E. Fields

Mississippi State University

College of Veterinary Medicine

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Advisor:

John Thomason DVM, MS, DACVIM

Introduction

Myasthenia gravis (MG) is a disorder of neuromuscular transmission affecting cats and dogs that has historically been classified as congenital or acquired.[7] Congenital MG, now referred to as a congenital myasthenic syndrome, presents in the first weeks to months of life and results from either a deficiency or functional disorder of the nicotinic acetylcholine (ACh) receptor.[7,9] Acquired MG is an immune-mediated disorder in which antibodies (mostly IgG) are formed and directed against nicotinic ACh receptors, resulting in decreased numbers of postsynaptic receptors in skeletal muscle.[2] With either form, failure of neuromuscular transmission results in clinical signs of paresis.[10] Acquired MG is a relatively common disease in dogs but is reported less frequently in cats.[4] It can occur spontaneously, can be drug-induced, or occur in association with a variety of diseases including neoplastic conditions, endocrine disorders, and autoimmune diseases.[6] MG can occur as a paraneoplastic syndrome in association with a thymoma or other thymic abnormalities.[6] Studies that analyzed cases of acquired MG in cats and dogs reported that the incidence of a mediastinal mass was higher in cats with 52% of affected cats having a mediastinal mass, compared to only 3.4% of affected dogs.[4,6]

Acquired MG is further characterized as focal, generalized, or acute fulminating depending on the muscles affected.[8] The most common clinical presentation in the feline patient, accounting for up to 80% of cases, is generalized MG which manifests as generalized appendicular weakness that often worsens with exercise and improves with rest.[2,6] A diagnosis is suspected based on clinical abnormalities along with improvement following administration of an anticholinesterase drug and is confirmed by demonstrating ACh receptor antibodies via serology.[1] Treatment may include the use of a longer-acting anticholinesterase drug, immunosuppressive therapy, or a combination of the two. In the case of a thymoma or drug-

induced MG, removal of the inciting cause is warranted. The prognosis for acquired MG in cats is generally good.[8] One study found that the 1-year mortality rate in cats (15%) was much lower than in dogs (60%), suggesting a better long-term prognosis.[6] The following case report outlines current literature in the context of a cat seen at Mississippi State University, College of Veterinary Medicine, who developed MG as a paraneoplastic syndrome.

History and Presentation

Ginger, an approximately 10-year-old female spayed domestic shorthaired cat, presented to the MSU-CVM Emergency Service on December 9th, 2021 for anorexia, neurological issues, and for further investigation of a thoracic mass. Ginger was suspected to have endured an outdoor injury on December 5th and was taken to an emergency clinic where a cranial thoracic mass was revealed on radiographs. While visiting Mississippi on December 8th, Ginger's owner noticed that Ginger was tremoring and seemed stiff in the hindlimbs. Her owner noted that she was not acting like herself and had not eaten in three days. Additionally, although she had always eaten dry kibble, recently, she seemed to only be able to consume canned soft food.

Upon presentation, Ginger was quiet, alert, and responsive. She weighed 5.18 kg and appeared mildly overweight with a body condition score of 6/9. Her vital parameters included a heart rate of 220 beats per minute, a respiratory rate of 32 breaths per minute, and a rectal temperature of 100.0º F. Her mucous membranes were pink and tacky with a capillary refill time of less than 2 seconds which estimated her to be approximately 5% dehydrated. Fleas were noted throughout her haircoat. A neurological exam revealed decreased menace and palpebral reflexes bilaterally and normal tendon reflexes. A short, choppy gait, particularly in the forelimbs was appreciated as well as intermittent generalized muscle tremors. Focal tremors of the ear and foot were seen intermittently as well. When provoked to move around for a prolonged period, Ginger

became noticeably fatigued. It became difficult for her to walk in a straight line. She began to knuckle over in the forelimbs and eventually rolled to lateral recumbency. When placed in standing position on all four paws, she would immediately fall into sternal recumbency.

The signalment, history, and clinical findings were strongly suggestive of a neuromuscular disease process. The presence of a thoracic mass led to suspicion of a thymoma and acquired MG. A bimodal age distribution is seen in cats with acquired MG with the majority of reported cases affecting those aged 2-3 years or older 9–10-year-old cats.[8] Clinical findings of MG in cats commonly include a gait that is stiff, short, and choppy, appendicular weakness that becomes more pronounced after exertion, and sometimes cervical ventroflexion.[8] Some cases will demonstrate depressed or fatigable palpebral and menace reflexes.[2] Unlike in dogs where focal MG is commonly seen, signs localized to the esophagus or pharynx only are relatively uncommon in the cat, accounting for only 10% of cases in one study.[4] This is most likely due to the smaller proportion of striated muscle in the esophagus in cats versus dogs. Other causes of muscle weakness including hypoglycemia, hyperthyroidism, thiamine deficiency, hypokalemia, and other myopathies/neuropathies were not excluded from the differential list at this time.

Diagnostic Approach

A minimum database including CBC, serum chemistry, coagulation profile, and FeLV/FIV snap test was performed. CBC and coagulation values were within normal limits. Snap test was negative for FeLV and FIV. Serum chemistry revealed a mildly elevated ALP, mild hyperalbuminemia, and mildly elevated creatine kinase which had all normalized at a subsequent visit.

Thoracic radiographs confirmed a cranioventral mediastinal mass. The top two differential diagnoses at this time were thymoma or lymphoma, although ectopic thyroid tissue, chemodectoma, or a benign thymic cyst could not be excluded. While thymoma and lymphoma can occur in cats at any age, thymomas are usually seen in older FeLV negative cats, and lymphoma is often seen in younger cats that may or may not be FeLV positive.[8] Thoracic ultrasonography is a great tool to evaluate for effusion, better visualize a mass, and guide aspirates. Thymomas may appear heterogeneous with cystic cavities while lymphoma may appear more homogenous.[5] Cytologic examination via fine needle aspirate is considered minimally invasive and may aid in the diagnosis of mediastinal masses, although distinguishing between thymoma and lymphoma can be difficult.[11] Both type of tumors may contain small lymphocytes, and in the case of a thymoma, the lymphoid component exfoliates more readily than do the neoplastic epithelial cells.[5,11] Ginger was sedated with a mixture of dexmedetomidine (4 mcg/kg) and butorphanol (0.2 mg/kg), and four ultrasound guided fine needle aspirates of the mass were obtained. Cytologic exam revealed a heterogenous proliferation of lymphocytes composed predominantly of small and intermediate sizes and few scattered mast cells. The results were suggestive of a hyperplastic lymph node, but a poorly exfoliating lymphocyte rich thymoma could not be ruled out. In one study, cytologic examination was suggestive of thymoma in only 23% of confirmed cases.[11]

A common screening test performed in cases of suspect acquired MG is through the use of a short-acting anticholinesterase drug (historically edrophonium chloride, recently neostigmine methylsulfate) which after administration, may temporarily relieve clinical signs of weakness. The results of this test must be interpreted with caution as false positives can occur due to other myopathic and neuropathic disorders as well as false negatives for unknown

reasons.[1] A 0.02 mg/kg dose of neostigmine (suggested dosing 0.02 – 0.05)[1] was administered intravenously to Ginger while in sternal recumbency. Within 60 seconds, she was ambulating normally, even jumping onto vertical surfaces. This positive response strongly supported the clinical suspicion of MG. While this can be a beneficial screening tool for generalized MG, there is often no detectable improvement in cases of focal MG.[2] Ginger experienced mild hypersalivation for approximately 30 minutes which is a common side effect of an anticholinesterase drug. Other possible cholinergic side effects include vomiting, diarrhea, and lacrimation. An anticholinergic drug such as atropine should be administered if these signs are noted and some clinicians even choose to premedicate with such drug.[1] Due to the mild nature of Ginger's hypersalivation, the use of an anticholinergic drug was not warranted.

The gold standard diagnostic test for acquired MG is demonstration of serum ACh receptor antibodies via immunoprecipitation immunoassay. This assay is highly specific and sensitive and should be performed prior to initiating therapy.[1] The test is species specific; titers greater than 0.6 nmol/L in the dog and greater than 0.3 nmol/L in the cat are considered diagnostic for acquired MG. A blood sample was collected from Ginger prior to her screening test and therapeutic intervention and submitted for testing. Her titer was 5.56 nmol/l which was above normal reference range. One study showed a significant correlation between higher ACh receptor antibody titers and decreased survival time in cats with MG.[4]

Computed tomography provides better information than survey radiographs for determining the extent of mediastinal abnormalities.[11] A CT scan was performed when Ginger re-presented for surgical planning which confirmed an approximately 2.6 x 1.9 x 3.4 cm mass within the cranioventral mediastinum as well as mildly enlarged sternal and cranial mediastinal lymph nodes.

Surgical Approach

On January 6, 2022, Ginger was prepped for surgery for removal of the cranial mediastinal mass. A median sternotomy was performed from the manubrium to cranial of the xiphoid. The rib cage was retracted, and the mass was easily visualized. It appeared well encapsulated and was not thought to have invaded any important surrounding structures. The left lateral thoracic artery was located along the mass, so it was carefully freed and retracted using a vasculature loop. The mass was carefully excised from the mediastinum using cautery and blunt dissection. Upon excision, an enlarged sternal lymph node became apparent and was removed. The thoracic cavity was copiously lavaged with warm sterile saline. A chest tube was placed through the skin of the right lateral thorax into the thoracic cavity and secured in place with a purse string and finger trap. The sternum was closed with an interrupted figure 8 pattern. The thoracostomy tube was aspirated to remove any air and fluid from the thoracic cavity. The musculature, subcutaneous tissue, and skin were closed. The incision and tube site were covered with a non-adhesive bandage. The mass and sternal lymph node were submitted for histopathology.

Diagnosis

Histopathology of the mass revealed a mixed population of small mature lymphocytes and a neoplastic population of epithelial cells, confirming a diagnosis of thymoma. The lymph node contained cells within the medullary spaces that resembled the epithelial cell population within the mass. Thymoma is a slow growing, epithelial tumor of the thymus infiltrated with benign, mature lymphocytes arising from the cranial mediastinum. The median age of affected cats is 9.5 years and domestic short-haired and Siamese cats appear to be overrepresented.[8] Whether a thymoma is benign or malignant is based on the degree of tumor invasiveness and

pattern of growth rather than histopathologic features.[8,11] Malignant tumors do not necessarily metastasize but may be invasive and difficult to remove surgically. Metastasis has been reported to occur in 20% or less of feline cases.[8] Clinical signs may occur as a direct result of a mass within the thoracic cavity or may be paraneoplastic. Paraneoplastic disorders associated with thymoma in the cat include MG, polymyositis, myocarditis, hypogammaglobulinemia, and exfoliative dermatitis.[5] Because of the close association of MG and thymoma, it is recommended to measure ACh receptor antibody levels in all animals upon recognition of a cranial mediastinal mass.[6] Histopathology is needed for definitive diagnosis. Immunohistochemistry can help further subtype thymoma; lymphocyte-rich thymoma was a positive prognostic indicator for long-term survival.[5] Ginger's thymoma was further classified as Type B2 with a heavy lymphocyte population. Thymectomy is generally curative for cats with noninvasive, resectable tumors. In one retrospective study, the median survival time for cats treated with thymectomy was 1,825 days with a 1-year survival rate of 89% and 3-year survival rate of 74%.[11] Radiation and chemotherapy are options for those with non-resectable tumors, although the efficacy of these in feline patients have not been well defined.

Pathophysiology

The nicotinic ACh receptor plays a central role in neuromuscular transmission in skeletal muscle. ACh, released from a presynaptic nerve terminal, binds to a postsynaptic ACh receptor leading to flux of cations and ultimately muscle contraction.[9] In acquired MG, autoantibodies are formed and recognize epitopes on the extracellular surface of the ACh receptor. These epitopes are located in the main immunogenic region, which is in close proximity to the ACh binding site.[2] These autoantibodies alter receptor function by one of three mechanisms: (1) antibodies may bind directly to the receptor, blocking ion channel opening, (2) antibodies may increase the

degradation rate of receptors, (3) antibody binding may lead to complement-mediated lysis of the muscle endplate.[2] Regardless of the mechanism, disruption of normal neuromuscular transmission results in skeletal muscle weakness.

The association between thymic neoplasia and myasthenia gravis is complex. The thymus gland contains antigen-presenting cells, T-cells, and B-cells. T-cell mediated activation of B lymphocytes leads to synthesis of pathogenic autoantibodies. Because there is antigenic similarity between the neurofilaments of the thymic myoid cells and the nicotinic ACh receptors, cross reaction may occur.[3]

Treatment and Management

Anticholinesterase drugs are the cornerstone of therapy for acquired MG, although cats may respond better to immunosuppressive therapy or a combination of the two.[9] These drugs inhibit degradation by acetylcholinesterase, therefore prolonging the availability of ACh for binding to ACh receptors.[2] Pyridostigmine bromide is the most commonly prescribed drug for long-term control in veterinary patients as an oral form is available. The dose is often started at the lower end of the dosing range and titrated to achieve the best clinical response while avoiding cholinergic side effects. There is some variability between patients in response to anticholinesterase therapy, and the reasoning behind such is poorly understood.[2] Approximately twelve hours after the positive neostigmine challenge, Ginger was started on pyridostigmine (2.6 mg/kg) which she received orally every twelve hours. Her clinical signs improved mildly, and no cholinergic side effects were noted.

If optimal clinical response to therapy is not achieved with anticholinesterase drugs, immunosuppressive therapy can be added. Corticosteroids are often used alone or in conjunction

with pyridostigmine in cats with MG. These drugs reduce autoantibody levels and decrease the ACh receptor reactivity of circulating lymphocytes.[6] The use is controversial in dogs as it may worsen muscle weakness and exacerbate aspiration pneumonia; however, cats tend to tolerate the drug well and some suggest it is superior to anticholinesterase therapy.[2,6,9]

In the absence of immunosuppression, performing serial ACh receptor antibody titers is a good indicator of disease status.[9] Levels that return to the reference interval are indicative of resolution and thus can be used to determine duration of medical management.[6]

In cases of acquired MG in which an underlying cause is apparent, treatment of such cause is crucial. Administration of methimazole can uncommonly cause secondary MG in cats. Hyperthyroid cats receiving this medication should therefore be monitored closely and stop treatment if signs of MG develop. In cases where neoplastic conditions including thymoma, osteosarcoma, lymphoma, and bile duct carcinoma cause paraneoplastic MG, the cancerous process must be addressed. While Ginger's condition was initially managed medically, the primary goal was removal of the presumptive source, the mass. Clinical signs of MG often present prior to detection of a thymic mass, although MG has developed post-thymectomy in some cases.[11] The overall rate of spontaneous remission appears to be low in cats compared to dogs. In one study, 34/35 cats required medical management to control signs of MG post-thymectomy.[4] Complete remission has been reported in a small number of cases, however incomplete resection or regrowth of the tumor can result in persistent clinical signs and elevated antibody titers.[9]

Case Outcome

Ginger recovered from surgery in the intensive care unit where she was maintained on intravenous fluids, pain medications, and anti-inflammatory medications. Her thoracostomy tube was utilized to remove fluid and air and was removed two days post-operatively due to minimal production. She was discharged to continue recovery at home on January 9, 2022 with instructions to continue medical management with pyridostigmine. She was additionally prescribed buprenorphine and gabapentin to control any post-operative discomfort. She returned to the hospital for a recheck on January 18, 2022. At this time, her owner reported that her clinical signs had improved significantly as her activity level had returned to normal and she was able to eat hard kibble again. On physical exam, her palpebral and menace reflexes had improved from initial presentation. Occasional mild ear and foot twitching was noted but she was able to ambulate normally, and no gait deficits were appreciated. Her incision site was healing well with no evidence of infection or dehiscence. A blood sample was collected and submitted for ACh receptor antibody testing. Ginger was discharged with instruction to continue pyridostigmine while awaiting antibody titer results. Approximately one week later, results showed her ACh receptor antibody titer was 1.88 nmol/l, which was significantly decreased from her initial titer of 5.56 nmol/l. While her antibody levels were still above normal reference range, Ginger had shown major clinical improvement per her owner. It was recommended she continue medical management and recheck titer levels in one month.

Upon histopathology results and due to apparent lymph node involvement, chemotherapy was discussed with the owner as an option moving forward. However, clinical data supporting the use of chemotherapy in cases of thymoma is lacking. The owner elected not to pursue chemotherapy at this time. It was recommended that Ginger be actively monitored for evidence of metastasis or tumor regrowth with thoracic radiographs every few months.

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