Case Report Rapport de cas

Acquired myasthenia gravis in a poodle

Danielle Richardson

Abstract — An 11-year-old, spayed female, teacup poodle was evaluated for a chronic cough, lethargy, hindlimb weakness, and reluctance to exercise. Thoracic radiographs revealed megaesophagus and aspiration pneumonia. Serum antibodies against acetylcholine receptors confirmed the diagnosis of myasthenia gravis. The unusual clinical history and case outcome are discussed.

Résumé — Myasthénie grave acquise chez un caniche. Une chienne caniche miniature stérilisée qui était âgée de 11 ans a été évaluée pour une toux chronique, de l'abattement, une faiblesse des membres postérieurs et de la réticence à l'exercice. Des radiographies thoraciques ont révélé une pneumonie par aspiration et un mégacœsophage. Des anticorps sériques contre les récepteurs de l'acétylcholine ont confirmé le diagnostic de myasténie grave. L'anamnèse inhabituelle et les résultats du cas sont discutés.

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An 11-year-old, spayed female, teacup poodle was presented to the Ontario Veterinary College, Veterinary Teaching Hospital (OVC-VTH) in November 2007 for evaluation of a chronic cough and lethargy. The cough was originally noted 5 mo prior to presentation and was initially described as a "hacking" cough that had become moist and productive and was worse at night. Physical examination by the referring veterinarian in September 2007 revealed increased bronchovesicular sounds bilaterally with mild crackles and a possible heart murmur. Thoracic radiographs were concerning for cardiomegaly with left atrial enlargement and pulmonary edema. Subsequently, there was no response to treatment with enalapril (Enacard; Mérial, Montreal, Quebec), 1 mg, PO, q24h. Due to suspicion of concurrent chronic bronchitis, a combination of novobiocin, tetracycline, and prednisolone (Delta Albaplex; Pharmacia and Upjohn Animal Health, Orangeville, Ontario), 22 mg/kg body weight (BW), PO, q12h for 10 d, was prescribed and the cough was reported to have improved.

In October 2007, the dog was noted to be regurgitating clear fluid daily and the cough had increased in frequency and severity. Thoracic radiographs at that time revealed evidence of pneumonia and amoxicillin/clavulanate (Clavamox; Pfizer Animal Health, Kirkland, Quebec), 12.5 mg/kg BW, PO, q12h, and spironolactone (Aldactone; Pfizer Animal Health), 6.25 mg PO, q24h, were prescribed. During the 3 to 4 d prior to presentation, the patient had become progressively lethargic and had been regurgitating following ingestion of all food and water. Additional medical history included intermittent hindlimb weakness since 1 y of age and chronic reluctance to exercise that had been attributed to the dog's personality.

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Case description

On presentation to the OVC-VTH, the patient was dull, depressed, and recumbent. The dog was tachypneic (100 breaths/min) with a normal heart rate (100 beats/min) and temperature (39.2°C). The mucous membranes were tacky and the dog was estimated to be approximately 7% dehydrated. Thoracic auscultation revealed increased bronchovesicular sounds bilaterally with an increased expiratory effort. The patient appeared unable to blink and menace and palpebral reflexes were absent.

A complete blood (cell) count revealed an increased hematocrit [0.67 L/L; reference interval (RI): 0.39 to 0.56 L/L], leukopenia (3.7×10^9/L; RI: 4.9 to 15.4 $\times 10^9$/L) composed of a lymphopenia (0.15×10^9/L; RI: 0.8 to 5.1 $\times 10^9$/L) and a low-normal neutrophil count (2.96×10^9/L; RI: 2.9 to 10.6 $\times 10^9$/L) with a left shift (0.44×10^9/L; RI: 0.0 to 0.3 $\times 10^9$/L). Differential diagnoses for the increased hematocrit with normal total solids included catecholamine-induced splenic contraction and chronic hypoxemia secondary to pulmonary disease. The lymphopenia was consistent with a stress response and the mild left shift indicated possible inflammation. A serum biochemical profile showed elevations in urea (27.8 mmol/L; RI: 3.5 to 9.0 mmol/L) and alkaline phosphatase (ALP) activity (170 U/L; RI: 22 to 143 U/L). The increased urea was thought to be the result of pre-renal azotemia consistent with the history of regurgitation and the finding of clinical dehydration, but a urinalysis was not available to determine if the patient's urine

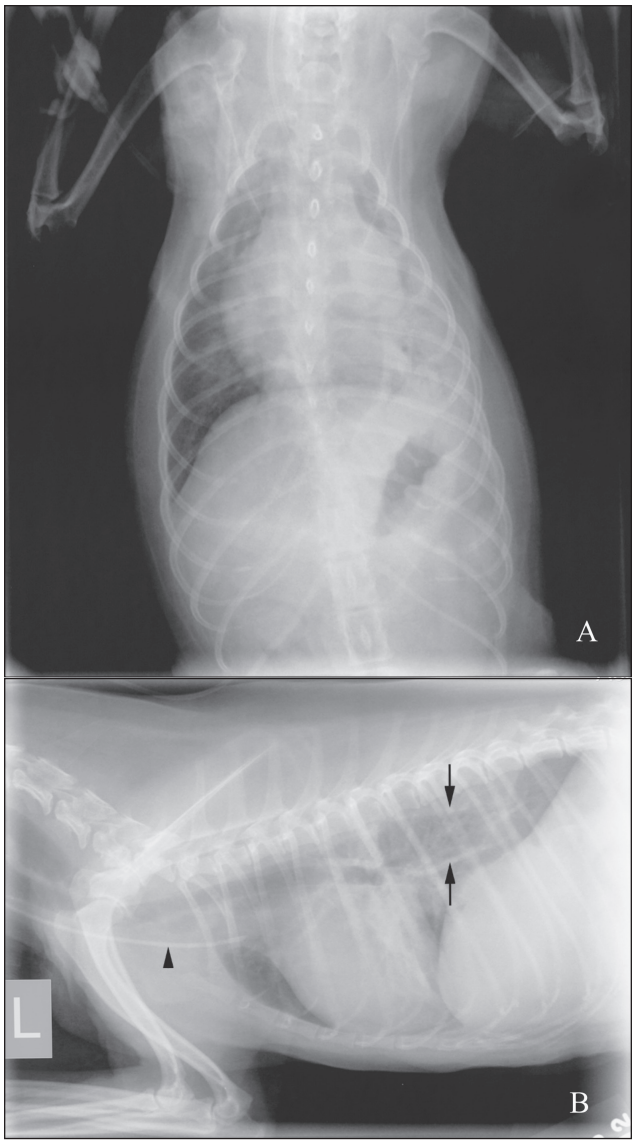

Figure 1. Dorsoventral (A) and lateral (B) thoracic radiographs demonstrating megaesophagus (arrows) and an asymmetric alveolar lung pattern affecting the left caudal and right middle lung lobes consistent with aspiration pneumonia. A jugular catheter is in place (arrowhead).

specific gravity was consistent with dehydration. The elevation in ALP was mild and differential diagnoses included cholestasis or corticosteroid induction secondary to the previous history of exogenous glucocorticoid administration. Thoracic radiographs revealed a moderate increase in soft tissue opacity in the caudodorsal lung field that partially to completely obscured the pulmonary blood vessels, silhouetted and summated with the heart and diaphragm and created air bronchograms. The pulmonary veins were mildly enlarged as was the cardiac silhouette. The esophagus was enlarged and gas filled. Differential diagnoses for the caudodorsal interstitial lung pattern included pulmonary edema or aspiration pneumonia secondary to megaesophagus. An abdominal ultrasound showed enlargement of the caudal vena cava and hepatic veins. In addition, decreased corticomedullary definition was noted bilaterally, consistent with chronic degenerative renal changes. Differential diagnoses for the hepatic congestion included dyspnea, congestive heart failure, or secondary to fluid therapy.

The patient was admitted to the intensive care unit and treatment was initiated with intravenous fluid therapy, oxygen supplementation as well as nebulized sterile saline and coupage. Broad-spectrum antibiotic therapy was administered to address the aspiration pneumonia and consisted of ampicillin (Ampicin; Novopharm, Stouffville, Ontario), 22 mg/kg BW, IV, q8h and enrofloxacin (Baytril; Bayer Animal Health, Etobicoke, Ontario), 5 mg/kg BW, IV, q24h.

Thoracic radiographs were repeated 24 h after admission and revealed persistent megaesophagus and progression of the pulmonary pathology (Figure 1). An asymmetric alveolar pattern was noted affecting the left caudal and right middle lung lobe. A cardiology consultant advised that, based on thoracic auscultation and evaluation of thoracic radiographs, cardiovascular disease was unlikely. A neurologist noted bilateral facial weakness with decreased palpebral reflexes. The patient was observed to have generalized weakness with the pelvic limbs being more severely affected. The spinal reflexes were adequate but the flexor reflexes were decreased due to weakness. The results of the neurologic examination were consistent with a neuromuscular cause for the observed weakness. Potential differential diagnoses included paraneoplastic syndrome, metabolic disorders (hypothyroidism, hypoadrenocorticism), or myasthenia gravis. Serum was submitted for determination of an acetylcholine (ACh) receptor antibody titer. Hypoadrenocorticism was ruled out on the basis of a normal response to an adrenocorticophin hormone stimulation test.

On day 4 of hospitalization the patient became acutely dyspneic and despite aggressive therapeutic interventions, succumbed to respiratory failure. The ACh receptor antibody titer was obtained after the patient had died and was positive (4.13 nmol/L; considered positive at $>$ 0.6 nmol/L).

Discussion

Acquired myasthenia gravis (MG) is an immune-mediated disorder in which antibodies are directed against postsynaptic nicotinic acetylcholine (ACh) receptors of skeletal muscle, resulting in impaired neuromuscular transmission that is manifested clinically as weakness. The disease is common in dogs; however, unlike the Akita, Scottish terrier, German shorthaired pointer, and Chihuahua, the poodle is not considered to be a breed at increased risk (1). The dog in this report had several non-specific historical and clinical findings that had not initially been attributed to myasthenia gravis. As a result, this unusual case should alert clinicians to the broad spectrum of clinical signs that may be associated with this condition.

Clinical signs of myasthenia gravis depend on the muscle groups affected and there can be a wide variety of presentations. The reason for the selective involvement of particular muscle groups is not known, but proposed explanations include differences in safety margin for neuromuscular transmission between muscle groups or antigenic differences between ACh receptors of muscle groups (2). Three main clinical forms of acquired MG have been described: focal MG in which weakness affects

pharyngeal, esophageal, laryngeal or facial muscles without appendicular muscle weakness; generalized MG with appendicular muscle weakness that is often accompanied by concurrent megaesophagus; and acute fulminating MG in which there is a rapid onset of severe appendicular muscle weakness, collapse and megaesophagus (1,3). The classic presentation of a dog with acquired MG is episodic, appendicular muscle weakness that is exacerbated by exercise and relieved by rest. Megaesophagus causing regurgitation and aspiration pneumonia is common in dogs with acquired MG because of the large proportion of skeletal muscle in the canine esophagus (1,3).

The dog in this report had an unusual history that illustrates the wide variety of clinical syndromes of acquired MG in dogs. There is little literature documenting the duration of clinical signs before arriving at a definitive diagnosis in canine myasthenic patients. In a case series of 5 dogs with acute fulminating myasthenia gravis, the duration of illness ranged from 2 d to 3 wk (4). The dog in this report is unusual in that the condition of the patient at the time of referral was consistent with the acute, fulminating presentation of the disease; however, the dog had a history of chronic hindlimb weakness and reluctance to walk that is common in myasthenic patients. Because this symptom had been present for years, it is not possible to ascertain whether it was a manifestation of MG or an incidental finding. Also of interest is that, unlike the dog in this report, there is usually no history of chronic regurgitation or exercise intolerance in patients presenting with the acute fulminating form of the disease (1,3). In addition, the dog had a history of a persistent cough that was attributed to chronic bronchitis, a common disease of geriatric, small breed dogs (5). Whether the cough was in fact a symptom of chronic aspiration secondary to megaesophagus is unknown.

The "gold standard" for the diagnosis of immune-mediated myasthenia gravis is the demonstration of serum autoantibodies against muscle ACh receptors by immunoprecipitation radioimmunoassay. The assay is both sensitive and specific and false positive results are rare (6). Rarely, affected dogs may be negative for circulating ACh receptor antibodies. Possible explanations include the presence of high-affinity antibody that remains bound to the ACh receptor and is not detected in circulation or of antibodies directed against junctional antigens other than the ACh receptor (1). Other testing procedures for acquired MG include administration of the short-acting anticholinesterase drug edrophonium chloride (Tensilon). Improvement in muscle strength following administration of the drug is suggestive of MG; however, improvement in muscle strength may be found in other neuropathic and myopathic disorders. Electromyography may also be used to obtain a presumptive diagnosis of MG. A decrement in the amplitude of the compound muscle action potential in response to repetitive nerve stimulation is observed. A limitation of this test is the need for general anesthesia in a potentially critical patient at risk for aspiration (6). Although EMG and Tensilon administration may provide a presumptive diagnosis of MG while awaiting confirmative antibody testing, the tests are neither sensitive nor specific and may result in false-positive or false-negative results (6).

Myasthenia gravis may be associated with other immune-mediated and neoplastic disorders, necessitating a thorough investigation for concurrent illness. Acquired MG may be associated with hypothyroidism, hypoadrenocorticism, thrombocytopenia, or hemolytic anemia. Myasthenia gravis has also been reported as a paraneoplastic syndrome associated with thymoma, osteosarcoma, and cutaneous lymphoma (6). To the author's knowledge, polycythemia has not been associated with MG and was attributed to chronic hypoxia in this case.

The optimum treatment protocol for MG has not been established. Anticholinesterase agents are the first line of treatment and act by prolonging the action of acetylcholine at the neuromuscular junction resulting in enhanced neuromuscular transmission. Anticholinesterase drugs have no effect on the immune response in acquired MG and may be ineffective as a sole therapy. Immunosuppressive treatment is indicated when weakness is not adequately controlled by anticholinesterase drugs. Prednisone, azathioprine and cyclosporine are immunosuppressive agents that have been associated with a positive clinical response in the treatment of acquired MG (3,6–8). Common side effects of prednisone therapy include polyuria, polydipsia, and polyphagia. Canine myasthenics are often at an increased risk of aspiration pneumonia, making polydipsia and polyphagia undesirable side effects. Additionally, immunosuppressive doses of prednisone may cause transient worsening of MG and their use in patients with aspiration pneumonia is contraindicated (6). Azathioprine and cyclosporine are relatively specific for T-lymphocytes and because acquired MG is a T-cell dependent disease, their use in the treatment of MG may be warranted (7,9). The rate of spontaneous remission of MG has been reported to be as high as 88.7% in patients treated with anticholinesterase therapy alone (10). This high rate of spontaneous remission must be considered when evaluating the efficacy of immunosuppressive treatment.

Antibiotic therapy is often indicated in MG due to the presence of concurrent aspiration pneumonia. Aminoglycosides and ampicillin may have detrimental effects on neuromuscular transmission and should be avoided (6). In a report of 5 dogs with acute fulminating MG (4), it was speculated that the administration of these antibiotics for the treatment of aspiration pneumonia may have contributed to clinical deterioration. However, similar to the dog in this report, it is unclear whether or not the deterioration seen in these patients resulted from antibiotic administration or progressive worsening of MG. As a result, the role of ampicillin in the clinical outcome of this case is unknown.

The prognosis for recovery from acquired MG is guarded. Aspiration pneumonia can be a fatal, acute event or a chronic, recurring problem that results in debilitation and eventual euthanasia often within 12 mo of diagnosis (1). Respiratory failure resulting from aspiration pneumonia or weakness of the diaphragm or intercostal muscles may be the most common cause of death in dogs with acute, fulminating MG as was suspected in the dog in this report (5). Severe aspiration pneumonia, persistent megaesophagus, acute fulminating MG, and the presence of thymoma are associated with a poor prognosis for recovery (1,11).

The dog in this case illustrates the wide spectrum of clinical signs of acquired MG that often resemble a variety of clinical

conditions that may result in a delay in arriving at a definitive diagnosis. The dog had a history of chronic hindlimb weakness and reluctance to exercise. In addition, the dog had originally presented for a chronic cough that was attributed to chronic bronchitis or cardiac disease and at that time, no radiographic evidence of aspiration pneumonia or megaesophagus was identified. Furthermore, the clinical condition of the dog in this report was initially attributed to the morbidity associated with severe aspiration pneumonia and MG was not immediately considered. The high mortality rate reported for MG might be related to delay in arriving at an accurate diagnosis and clinicians should be aware of the wide range of clinical presentations for this disease. CVJ

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Book Review
Compte rendu de livre

Clinical Signs in Small Animal Medicine

Schaer M. Manson Publishing Ltd., London, 2008. ISBN 978-1-84076-093-4, 288 pp.

This book was fun to go through; it is rare that I can say that about most veterinary texts. The book contains countless photographs of clinical syndromes (over 800), all of excellent quality. Most of the images are of clinical signs that are evident when examining a patient though radiographs, intraoperative photos and necropsy images are also represented. As the author points out, a picture is worth a thousand words (or potentially ten thousand words) and with this atlas of images, it is easy to realize that you can often learn a lot more by seeing than by just reading about something.

There are a total of 13 sections on such topics as dermatology, ophthalmology, infectious disease, cardiovascular disorders, endocrinology, and neurologic disorders to name a few. Each chapter is prefaced with some of Dr. Schaer's clinical pearls. These pearls contain useful clinical information learned through years of practice such as "prostate inflammation can cause the prostatic shuffle" or "mammary tumors — don't stick it, cut it." Some of these pearls are ideal guides for how to practice successful medicine.

Given that this is an image atlas of clinical signs, coverage in each chapter will not be complete for every disease or sign possible. The signs covered range from common to rare — of ccourse rare is at times determined by geographic location. Given that Dr. Schaer is located in Florida, certain diseases that are seen there such as pythiosis or cycad poisoning are seldom or never seen in Canada. By and large, however, the book does cover most of the clinically relevant signs seen in small animal patients.

This book is of interest to students and veterinarians as a reference image atlas. It is worthwhile to go through the whole book as you can pick up quite a few tidbits in this manner. It would also be very useful in practice in some cases to show owners illustrations of disease conditions you think their pet may have. As an example, there are good images of diabetic neuropathy, cushingoid dog, pyometra, eosinophilic granuloma complex, and dogs with hyperestrinism that could be shown to owners. Naturally not all images are suited for owners to see given that some are quite graphic.

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