Diagnosis of breed specific polymyositis in two Hungarian vizslas

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CASE REPORT

ABSTRACT

Two unrelated Hungarian vizslas were referred to university teaching hospitals in Australia with histories of dysphagia, regurgitation, ptyalism, lethargy and weight loss. Physical examinations revealed significant atrophy of the masticatory and skeletal muscles. Both dogs had elevated serum creatine kinase activities. Thoracic and abdominal imaging was unremarkable. Serum *Toxoplasma gondii* and *Neospora caninum* titres were within normal limits. For both dogs, muscle biopsies were taken from the masticatory and skeletal muscles for light microscopy, and serum was submitted for 2M antibody titres. The 2M antibody titres were negative for masticatory myositis. Light microscopy examination of all muscle biopsy samples identified a generalised inflammatory myopathy consistent with breed specific polymyositis recently identified in Hungarian vizslas in North America and the United Kingdom. The dogs were immunosuppressed with prednisolone and azathioprine. Treatment side effects were seen in both cases and each has been maintained on a single drug with owners reporting the dogs have a good quality of life. *Aust Vet Pract* 2013;43(3):471-474

INTRODUCTION

This report describes the diagnosis and treatment of a breed specific form of polymyositis in two unrelated Hungarian vizslas. Previous descriptions of breed specific polymyositis have been restricted to Newfoundlands, boxers and German wirehaired pointers.[1-3] Recent cases of Hungarian vizsla polymyositis have been identified in the United Kingdom and North America.[4,5] Hungarian vizslas diagnosed with the condition have all displayed similar clinical signs, including dysphagia, ptyalism and masticatory muscle atrophy.[4] Other clinical signs reported are reduced exercise tolerance, regurgitation and generalised skeletal muscle atrophy with weight loss.[4] Serum biochemistry analysis commonly shows increased serum creatine kinase (CK) activities.[1-3] The disease is definitively diagnosed by observation of characteristic findings on light microscopy examination of biopsies from skeletal and masticatory muscles. Immunosuppression with oral prednisolone and or azathioprine appears to slow down or stabilise the disease.[4] The exact aetiopathogenesis for polymyositis in dogs is poorly understood,[4] however the genetic basis to the disease in Hungarian vizslas is currently under investigation.[5,6] The aim of this report is to describe the features in two cases in Australia, to alert veterinary practitioners in Australia to this disease, previously only described in dogs outside this country.

CASE REPORTS

Case 1

A five-year-old neutered male Hungarian vizsla presented with a one-week history of regurgitation, ptyalism, lethargy, exercise intolerance and collapse whilst exercising. Physical examination revealed bilateral atrophy of the masticatory muscles (Figure 1). There was an impression of a generalised reduction in muscle mass (Figure 2). A mild to moderate decrease in the gag reflex was present but no oral abnormalities were visualised. The left prescapular lymph node was prominent, but all other lymph nodes were of normal size. The dog demonstrated pharyngeal dysphagia when offered food.

Figure 1. Masticatory muscle atrophy in a 5-year-old neutered male Hungarian viszla presented for regurgitation, ptyalism and exercise intolerance. Note the severe atrophy of the masseter and temporalis muscles.

The referring veterinarian performed fine needle aspirates of the enlarged prescapular lymph node and cytology was consistent with reactive inflammation. Serum biochemistry analysis and a complete blood count revealed increased alkaline phosphatase activity (902 IU/L, reference interval 1-150 IU/L) and a mild neutrophilia (16 x 10^9/L, reference interval 3.5-12 x 10^9/L). Thoracic and abdominal radiographs as well as endoscopy were considered within normal limits. There was no evidence of megaoesophagus.

Serum CK activity was increased (in house laboratory 518 u/L, reference interval 10-200 u/L; external laboratory 653 u/L,

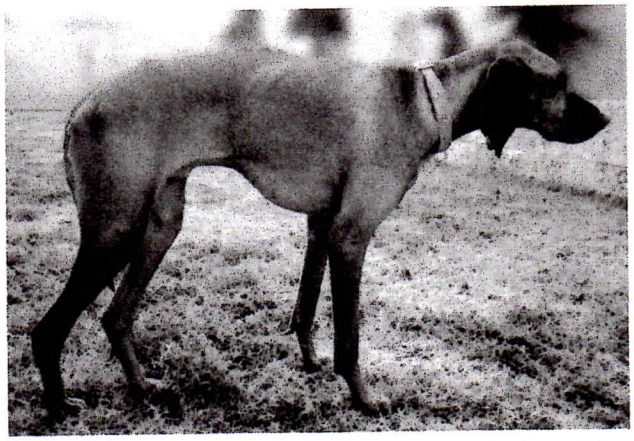

Figure 2. Generalised muscle atrophy and poor body condition noted in a a 5-year-old neutered male Hungarian viszla presented for regurgitation, ptyalism and exercise intolerance.

reference interval 60-500 u/L). Serum cortisol concentration (62 nmol/L, reference interval 15-120 nmol/L) and serum total thyroxine concentration (12.7 nmol/L, reference interval 6.7-35 nmol/L) were within reference intervals, excluding hypoadrenocorticism and hypothyroidism, respectively.

Serum *Toxoplasma gondii* and *Neospora caninum* titres were negative, thus eliminating a protozoal cause for muscle weakness and or a peripheral neuropathy. Serum acetylcholine receptor antibody titre was within reference intervals (0.11 nmol/L, reference interval <0.6 nmol/L normal serum titre, >0.6 nmol/L positive serum titre), ruling out myasthenia gravis as cause for oesophageal dysmotility, oropharyngeal dysphagia and generalised weakness. Structural causes of oropharyngeal dysphagia and oesophageal dysmotility were excluded with fluoroscopy and visual examination.

A serum 2M antibody assay was negative for masticatory myositis (<1:100, reference interval <1:100 negative, =1:100 borderline, >1:100 consistent with masticatory myositis). The assay measures autoantibodies directed against the myosin of the masticatory muscle type 2M fibres, with positive titres associated with masticatory myositis.[7] Biopsies of the right temporal, masseter and triceps brachii muscles were performed under general anaesthesia and fresh and 10% formalin fixed samples were submitted to the Comparative Neuromuscular Laboratory (California, USA) for light microscopy examination. Sections were stained with haematoxylin and eosin, modified trichome, periodic acid-Schiff, adenosine triphosphatase at pH 9.8 and 4.3, esterase, nicotinamide adenine dinucleotide dehdrogenase-tetrazolium reductase, acid phosphatase, alkaline phosphatase, oil red O and staphylococcal protein A-horseradish peroxidase. Light microscopy examination of the muscle showed moderate generalised myofibre atrophy of the temporalis and masseter muscles with atrophic fibres having a round shape and both type 1 and 2 fibres. Myofibre size was appropriate within the triceps muscle. Fibre type grouping was not observed. Several type 2C fibres were present, which suggested regeneration. Multifocal areas of mild lymphocytic infiltration were present in the temporalis and triceps muscles with an endomysial distribution. Fibrosis was not observed. The cellular infiltrations were considered to be only mild, but the fact that they were multifocal and in at least two of the muscles supported a diagnosis of generalised inflammatory myopathy or polymyositis. The microscopic findings, combined with the dog's signalment, history and clinical signs were sufficient to make a diagnosis of breed specific Hungarian vizsla polymyositis.

Immunosuppression was initiated with prednisolone and azathioprine, both at 2 mg/kg PO daily for two weeks with the aim to taper the prednisolone to 1 mg/kg PO every other day. However, the dog's muscle atrophy worsened with prednisolone administration, so the prednisolone was discontinued. Azathioprine alone at 1 mg/kg PO every one to three days stabilised the disease and the dog appeared to subjectively regain some muscle mass (Figure 3). The dog is now fed liquefied food and rarely has episodes of regurgitation and dysphagia.

Figure 3. Improved physical appearance of a 5 year-old neutered male Hungarian viszla one year after immunosuppressive treatment for breed specific polymyositis.

Case 2

A 15-month-old neutered male Hungarian vizsla was referred with a history of lethargy, hindleg lameness and weight loss. Initial physical examination revealed a thin body condition (score 3/9). A complete neurologic examination was within normal limits. Serum biochemistry analysis showed increased alanine aminotransferase activity (633 u/L, reference interval 21-142 u/L) and aspartate aminotransferase activity (424 u/L, reference interval 10-60 u/L). Serum CK activity was also increased (9618 u/L, reference interval 47-228 u/L). Ultrasonographic examination of the abdomen was within normal limits except for enlarged mesenteric and medial iliac lymph nodes, considered consistent with juvenile lymphoid hyperplasia. Thoracic radiographs were within normal limits. A percutaneous liver biopsy showed a nematode in a granulomatous region of one section, consistent with visceral larval migrans. Fenbendazole (150 mg/kg PO once daily for five days) was administered.

The dog continued to show regurgitation, dysphagia, ptyalism, hindleg lameness and progressive muscle atrophy. Four months after the first examination, significant masticatory muscle atrophy was observed. Serum titres for *Toxoplasma gondii* and *Neospora caninum* were negative ruling out infectious protozoal causes of muscle weakness and atrophy. The dog's serum creatine kinase activity had increased to 13361 u/L (reference interval 47-228

u/L), consistent with an ongoing, active myopathy. Muscle biopsies of the vastus lateralis, triceps brachii and temporalis muscles were collected under general anaesthesia. The samples were submitted fresh and fixed in 10% neutral buffered formalin to the Comparative Neuromuscular Laboratory for light microscopy examination. Light microscopy examination of the muscle showed a moderately severe, inflammatory myopathy involving a multifocal endomysial distribution of mixed mononuclear cell infiltrates typical of the polymyositis seen in Hungarian vizslas.

Immunosuppression with prednisolone (2 mg/kg PO daily) and azathioprine (2 mg/kg PO daily) was commenced. The dog developed pancreatitis, suspected to be secondary to the azathioprine, so azathioprine was discontinued. Prednisolone was tapered to a maintenance dose of 1 mg/kg PO once daily with ranitidine at 2 mg/kg PO twice daily. The owners currently consider the dog has stable disease and a good quality of life.

DISCUSSION

This report describes characteristic clinical features and microscopic changes of Hungarian vizsla polymyositis in two unrelated Hungarian vizslas in Australia. These cases, and those previously reported, have all presented with very similar clinical signs. Dysphagia has been reported in every confirmed case to date.[4,5] Males appear to be over-represented, however conclusions about gender and age predisposition cannot be made as the size of the reported cohort is still small.[4,5] The dogs in this report were five years and 15 months old at diagnosis. The first case was a similar age to dogs reported in North America (2, 5 and 9 years of age).[4]

A thorough history and physical examination is essential to making a diagnosis of breed specific Hungarian vizsla polymyositis. Other conditions with similar clinical signs must be excluded with laboratory testing before a definitive diagnosis can be made. Polymyositis is an immune-mediated disorder which is characterised by a number of specific diagnostic criteria.[1] Criteria can include clinical signs of muscle weakness and atrophy, increased serum CK activity, abnormal electromyography, negative serologic testing for infectious diseases including *Toxoplasma gondii* and *Neospora caninum*, and lymphocytic infiltrates of skeletal muscle on microscopic examination.[1]

Both Hungarian vizslas in this report had increased serum CK activity and this is typical of dogs diagnosed with polymyositis. Evans recorded 96 of 140 mixed-breed dogs diagnosed with polymyositis as having increased serum CK activity.[1] Other Hungarian vizslas diagnosed with breed specific polymyositis had increased serum CK activity.[4] It is important to note that serum CK activity is not always increased in muscle conditions but it should be part of every minimum database for dogs with neuromuscular disease as increased serum CK activity may be one of the first indicators of muscle disease.[3]

Endocrinopathies such as hypothyroidism, hyperadrenocorticism and hypoadrenocorticism have been documented as causing muscle weakness, exercise intolerance, muscle atrophy, megaoesophagus and regurgitation.[3,8-11] The Hungarian vizsla described in the first case had a normal serum total thyroxine concentration and normal resting serum cortisol concentration which eliminated hypothyroidism and hypoadrenocorticism, respectively, as causes for the generalised weakness and regurgitation. Other reported cases in North America have also had normal serum thyroxine and cortisol concentrations.[4]

An infectious cause of myositis should also be considered if generalised clinical signs are present and more than one muscle group is affected.[3] *Toxoplasma gondii* and *Neospora caninum* have both been reported as causes of generalised inflammatory myopathy in dogs.[1,12] It is recommended that serologic testing for both *Toxoplasma gondii* and *Neospora caninum* should form part of the minimum database for all dogs diagnosed with an inflammatory myopathy on light microscopy examination.[1] All currently reported cases in North America have had negative serologic titres for both these infectious protozoa.[4]

Congenital or acquired myasthenia gravis should be considered in any young dog with weakness that is exacerbated by sustained exercise.[13] Approximately 90% of dogs with acquired myasthenia gravis will have oesophageal dilation, which can lead to regurgitation.[13] Clinical signs may be focal in nature and limited to regurgitation, dysphagia and multiple cranial nerve abnormalities.[13] Autoantibodies to acetylcholine receptors are rare in healthy dogs and in dogs with other diseases such as polymyositis, but are present in the majority of dogs with acquired myasthenia gravis.[3] Cases with congenital myasthenia gravis generally present in the first months of life and are characterised by their clinical abnormalities being present from birth. Hungarian vizslas with breed specific polymyositis should not have elevated serum acetylcholine receptor antibody titres. Titres were evaluated in the first case as part of the workup but were not measured in the second case, where biopsies were performed earlier in the workup and proved definitive.

Light microscopy examination of masticatory muscles and skeletal muscles is necessary for the definitive diagnosis of Hungarian vizsla polymyositis and also to eliminate masticatory myositis as a possible differential diagnosis. Biopsies should be taken from the masseter and temporalis muscles for testing for masticatory myositis and from at least one skeletal muscle (for example triceps brachii, vastus lateralis, cranial tibial, biceps femoris or gastrocnemius) for investigation of generalised inflammatory disorders.[1] Hungarian vizslas with breed specific polymyositis should have evidence of lymphocytic cellular infiltrates in both the masticatory muscles and skeletal muscles.[1,4] The histologic characteristics typically show an endomysial or perimysial distribution of mixed mononuclear cells typical of polymyositis.[1,4] In contrast, dogs with masticatory myositis alone will have cellular infiltrates that are commonly distributed perivascularly, and limited to the muscles of mastication.[1,3] Masticatory muscles contain a unique muscle fibre type known as 2M which differs from skeletal muscles both biochemically and histochemically.[1] A serologic assay for antibodies against 2M fibres is also available for confirming or excluding a diagnosis of masticatory myositis.[1,3]

Immunosuppression with oral azathioprine and prednisolone is used to treat the disease.[4] Disease responsiveness to immunosuppressive medication is in keeping with an immune-mediated aetiology, a theory that has been supported by the recent association of the disease with a major histocompatibility complex Class II haplotype.[5] As with many immune-mediated disorders, possession of a specific risk haplotype along with other genetic and

environmental factors are likely to, together, promote expression of clinical disease in the Hungarian vizsla. Typically dogs are started on 2 mg/kg PO daily for both azothioprine and prednisolone with the aim to taper down to a maintenance dose of 1 mg/kg PO daily.[4] Some dogs may have lasting dysphagia due to muscle fibrosis. These dogs may require their food to be fed in small ball or liquefied form.

The Hungarian vizsla specific form of polymyositis has only recently been confirmed in Australia and around the world. These two cases show the typical clinical features with confirmation of the diagnosis based on light microscopy examination of multiple muscle biopsies. It is important that veterinarians are aware of the disease, as early diagnosis and treatment can improve the quality of life and stabilise the disease in affected dogs.

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