CASE REPORT

Acquired immune-mediated myasthenia gravis in a cat associated with a cystic thymus

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ABSTRACT

Acquired myasthenia gravis was diagnosed in a five-year-old domestic shorthair, neutered, female cat with generalised muscle weakness, tremors, dysphagia and alterations in voice. Radiographs indicated the presence of a mass in the anterior thorax. A response to edrophonium chloride, and raised levels of anti-acetylcholine receptor antibodies in the serum, confirmed the diagnosis and indicated an immune-mediated aetiology. Clinical remission occurred following thymectomy and the use of immunosuppressive corticosteroids. This is the first fully-documented case of acquired feline myasthenia gravis associated with the presence of a thymic abnormality in the United Kingdom. The clinical features, laboratory findings and response to treatment are compared with those reported previously in cats and other species.

INTRODUCTION

Myasthenia gravis in man is a disorder of neuromuscular transmission caused by a relative reduction in the number of acetylcholine receptors (AChR) on the muscle membrane. It is thought to be immune-mediated primarily through IgG anti-AChR antibodies which bind at the neuromuscular junction and result in AChR loss via antibody induced modulation, enhanced by elements of the complement system (Drachman 1978, Engel 1984, Lindström 1985). It has been postulated that an infection with either a viral or bacterial agent may trigger development of the condition, perhaps as a result of molecular mimicry in susceptible individuals (Dwyer and others 1986, Schwimmbeck and others 1989), but at present there is little direct evidence for involvement of such a trigger in human patients. In addition an association with thymic abnormalities is recognised in approximately 75 per cent of cases. In 85 per cent of these cases the thymic abnormality is found to be hyperplasia while the remaining 15 per cent are classified as thymomas (Drachman 1978).

In the cat myasthenia gravis appears to be an uncommon condition and there have been few case reports (Indrieri and others 1983, Joseph 1988, Van Oosterhout 1989, Cuddon 1989, Scott-Moncrieff 1990). The purpose of this paper is to record the successful surgical treatment of a case of a cat with myasthenia gravis and a thymic abnormality.

CASE HISTORY

A five-year-old female neutered domestic shorthair cat was referred to the Feline Centre, Department of Veterinary Medicine, University of Bristol.

The referring veterinary surgeon described an eight-week history of hypersalivation, progressing to abnormalities in head posture, involuntary head tremor and ventroflexion of the neck, a 'crouching posture', dysphagia, and regurgitation of food. There had been some weight loss. An initial response to a combination of injectable corticosteroid (Betsolan; Glaxo) and antibiotic (Clamoxyl; SmithKline Beecham) was observed but subsequently the animal's condition had steadily deteriorated. A change in the cats 'voice' was also noted. At the time of presentation the cat had not received any treatment for two weeks.

On clinical examination it was slightly underweight (2·9 kg) but reasonably bright and alert at rest, with flaccid muscular tone. All four limbs exhibited normal pain sensation and tendon

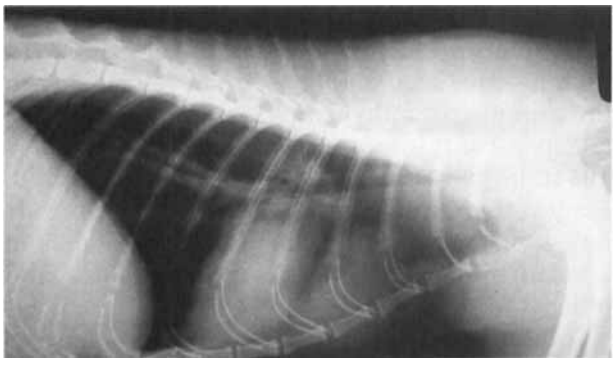

FIG 1. Lateral radiograph of thorax with soft tissue density visible immediately cranial to the heart

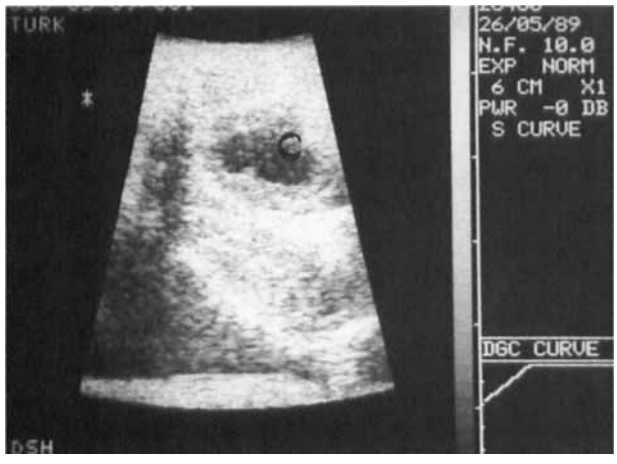

FIG 2. Ultrasound picture of thymic mass, showing multilocular cyst (C)

reflexes but conscious proprioception and withdrawal reflexes were reduced. The cat was reluctant to move from rest, and generally adopted a position with the head resting upon extended forepaws. The head was usually tilted slightly to one side, although no preference was shown to either side. When forced to move from rest the cat exhibited ventroflexion of the neck and mild head tremor and was able to walk only a few paces before collapsing. No other abnormalities were detected. Haematological and serum biochemical examinations were normal. The cat was FeLV (Leukassay/CITE), FIV antibody (CITE) and coronavirus antibody titre negative.

A tentative diagnosis of myasthenia gravis was made and 0·5 mg of edrophonium chloride (Tensilon; Roche), a cholinesterase inhibitor, was administered intravenously 15 minutes after subcutaneous injection of 300 µg atropine. The cat showed a dramatic improvement and was able to jump down from a chair and walk normally about the room for approximately 30 to 40 seconds.

Lateral and ventrodorsal radiographs of the chest were taken which indicated normal oesophageal position and shape, but a soft tissue density was visible in the anterior thorax, immediately cranial to the heart (Fig 1). Ultrasonography revealed that the mass consisted of well-defined solid tissue, interspersed with multilocular cysts of variable size (Fig 2).

Under general anaesthesia, a percutaneous biopsy of the mass was taken using a 'Tru-cut' (Travenol Laboratories Inc) needle under ultrasonic guidance. Fluid was also aspirated from the largest of the cystic areas. The fluid appeared slightly pink and cloudy on gross examination. Microscopic examination of the fluid sediment revealed a predominance of lymphocytes with some polymorphonuclear neutrophils and monocytes. Histological examination of the biopsy material detected both epithelial tissue and sheets of lymphoid cells divided by fibrous septa. These findings were considered to be consistent with a diagnosis of a cystic thymus.

The cat was treated initially with prednisolone orally at 2 mg/kg/day, divided into twice daily dosages, for two weeks before surgery and this resulted in an improvement in appetite and exercise tolerance.

A midline sternal thoracotomy was then carried out under general anaesthesia and intermittent positive pressure ventilation and a mass from the cranial mediastinum was removed. It appeared to be well encapsulated, and did not closely involve the heart, major blood vessels, or nerve trunks. The chest was closed routinely. A chest drain was inserted for 36 hours postoperatively and the cat's recovery was uneventful. Antibiotic (Ampfipen; Mycofarm) was given for ten days postoperatively and prednisolone therapy continued as previously. The dose of prednisolone was then reduced over the subsequent six weeks to 1·5 mg/kg on alternate days, at which time the cat was re-examined. The cat had made good progress, with a return to normal appetite and previous behaviour patterns, including exploration of outdoor territory. On clinical examination it was bright and exhibited no neuromuscular fatigue. However, there was no weight gain (2·7 kg), coat condition was poor, and it was treated for tapeworm infestation. Over the next two weeks the dosage of prednisolone was slowly reduced to zero. Appetite and

Table 1. Anti-AChR receptor antibody levels in a cat with acquired myasthenia gravis and related animals

Animal	Sample time	Anti-AChR Ab titre ($\times 10^{-10}$M)*	
Affected cat	1	At presentation	17
	2	immediately preoperatively	14
	3	immediately postoperatively	13
	4	6 weeks postoperatively	< 2
Dam	4		3
Sibling	4		18
Daughter	4		0

*A titre of $> 5 \times 10^{-10}$M is considered to be positive

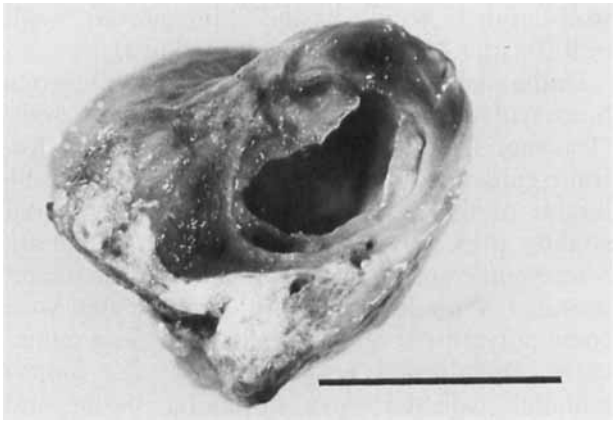

FIG 3. Transverse section of thymus following formalin fixation. A large cyst is present within the stroma. The dense white area represents adipose connective tissue. Bar, 1 cm

exercise capacity remained good, with weight gain and improvement in coat condition. The cat was reported to be in continued good health, with no further treatment, 16 months postoperatively.

Anti-AchR antibodies were measured retrospectively in sera from the dam, sibling, and one female offspring of the affected cat (Table 1). The results indicated a negative antibody for the offspring but a positive and equivocal result for the sibling and dam, respectively.

Pathological findings

The mass removed from the chest was triangular, measuring 3·3 cm long × 1·5 cm maximum width. Transverse sections revealed several cysts of variable size, up to 1 cm in diameter (Fig 3), the largest containing a yellow, floccular deposit. On microscopic examination no recognisable thymic medulla or cortex was seen. The cystic areas were lined with attenuated epithelial cells and in some areas a narrow, oedematous subepithelial space was present containing scattered plasma cells (Fig 4). The connective tissue stroma between the cystic areas contained normal lymphocytes. The cysts contained amorphous, eosinophilic material and a few macrophages. In the stroma, accumulations of eosinophilic material surrounded by epithelial cells, resembling Hassall's corpuscles, were present (Fig 5).

DISCUSSION

This is the first fully documented case of myasthenia gravis in a cat in the UK in which a thymic abnormality has been recognised. A previous case has been mentioned (Herrtage and McKerrell 1988) in association with a thymoma but no detail was given.

In dogs, both congenital and acquired forms of myasthenia are recognised. Unlike the congenital condition, all acquired cases are thought to be immune-mediated and have been associated with the presence of a thymoma in a small proportion (20 per cent) of cases (Aronsohn and others 1984). In humans, there is also some evidence to suggest that viruses such as herpes simplex may be associated with the initiation of myasthenia in a small proportion of cases (Schwimmbeck and others 1989).

In humans and dogs, circulating antibodies to acetylcholine receptors at the neuromuscular junction are detectable in approximately 90 per cent of cases. In five reported cases of myasthenia gravis in cats high levels of circulating antibody were demonstrated (Indrieri and others 1983, Joseph and others 1988, Cuddon 1989, Scott-Moncrieff and others 1990).

In the present case described here there was clear evidence of an immune-mediated basis as antibodies against ACh receptors were detected using a radioimmunoassay developed for use in man with human muscle as the antigen (Vincent

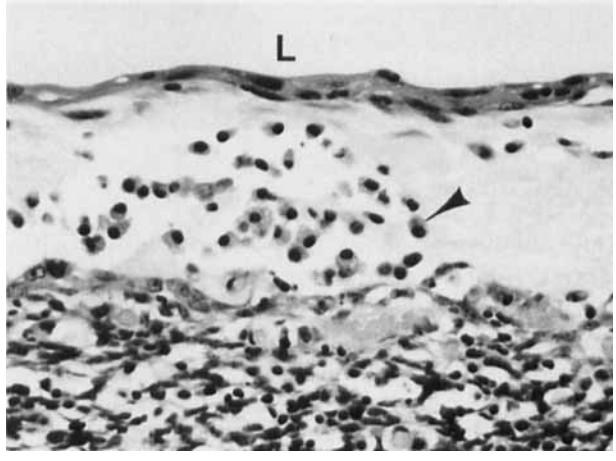

FIG 4. A cyst lined by attenuated epithelium with plasma cells (arrow), in a subepithelial space. L Cyst lumen. Haematoxylin and eosin × 230

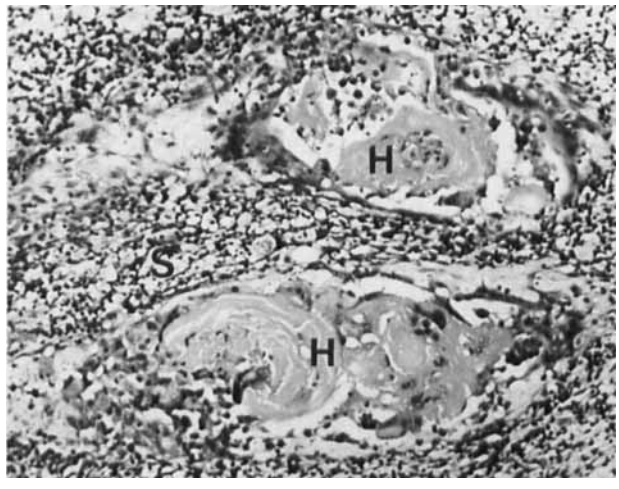

FIG 5. Two foci of amorphous material (H) within the thymic stroma (S) resemble Hassall's corpuscles. Haematoxylin and eosin × 100

and Newsom-Davies 1985). The reduction in antibody titre postoperatively correlated well with clinical improvement of the patient's condition.

In humans a familial predisposition is thought to occur in some cases (Drachman 1978). It is difficult to know if the results here (Table 1) represent a true familial predisposition or a common initiating agent such as a virus, as has been suggested to occur in humans (Schwimmbeck and others 1989).

In a description of 34 cats with thymomas (Carpenter and others 1987) signs indicative of polymyositis were reported in three cases, although it is not clear whether the possibility of myasthenia gravis was fully investigated. Thymic abnormalities are recognised in approximately 75 per cent of humans with myasthenia gravis (Drachman 1978) although in only 15 per cent of these is the thymic change classified as a thymoma. In the remaining 85 per cent the thymic changes are considered to represent hyperplasia with germinal follicles in the medulla (Henry 1978). In a series of 22 dogs with thymomas only one had evidence of cystic change (Bellah and others 1983). A review of reported cases of thymoma in the cat (Carpenter and others 1987) suggests that at least 50 per cent have a marked cystic component. There have been two well-documented reports of feline myasthenia gravis associated with thymic abnormalities (Van Oosterhout and others 1989, Scott-Moncrieff and others 1990). In these cases the thymic masses were described as thymomas. The authors feel that this present case probably represents cystic change in an enlarged thymus rather than a thymoma.

Recent work on the use of keratin antisera to characterise feline thymoma (Vos and others 1990) may be of value in the differentiation of thymic abnormalities.

The association of the thymus with the changes in the immune system which lead to the development of myasthenia gravis is not clear. There is a recognised antigenic similarity between the myoid cells of the thymus and the receptor-bearing muscle cells at the neuromuscular junction (Kao and Drachman 1977). It is postulated that some alteration of either the muscle cells or lymphocytes of the thymus may serve to break tolerance and thereby initiate an autoimmune response directed against ACh-receptors and other components of skeletal muscle.

The treatment of previously reported cases of feline myasthenia gravis, and those seen at our clinic, has been directed primarily at suppressing autoantibody production and supplying cholinesterase inhibitors. This cat responded well initially to corticosteroid therapy alone, similar to a recently reported case of acquired myasthenia gravis in a cat that showed clinical remission following long term immunosuppression with corticosteroids alone (Cuddon 1989). However, in this case, there was not a complete resolution of clinical signs and serum anti-ACh receptor antibody titres remained positive after two weeks of corticosteroid treatment.

Thymectomy is considered to be important in the treatment of human myasthenia gravis. In cases without a thymoma there is usually a clear benefit provided surgery is carried out early on in the course of the disease. However, if a thymoma is present the prognosis appears to be far more guarded. In humans, delayed and, or, poor response to thymectomy in some cases suggests that T-cells, controlling antibody formation by B-cells, continue activity in some extra-thymic site for some time after thymectomy. In these cases, it is thought that the use of immunosuppressive doses of corticosteroids may be as beneficial as, or even more so, than thymectomy. In humans, steroid therapy is always continued after the removal of a thymoma as this appears to improve survival time and nearly all patients require indefinite continuation of low level steroid maintenance therapy (Drachman 1978).

In the two previous fully reported cases of feline myasthenia gravis associated with thymomas, one died 24 hours postoperatively (Van Oosterhout and others 1989) and the other remained on corticosteroids and pyridostigmine (Mestinon; Roche) at the time of reporting (Scott-Moncrieff and others 1990). The clinical improvement seen in our patient, coupled with the reduction in serum anti-ACh receptor antibody, suggests that thymectomy, may be a useful adjunct to immunosuppressive therapy in the successful management of cases of feline myasthenia gravis associated with a thymic abnormality.

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ABSTRACTS

Hip dysplasia with bilateral ischiatic nerve entrapment in a dog

A FIVE-year-old spayed labrador had signs of bilateral hip dysplasia from one year of age. On clinical examination the following were found: marked hyperflexion of the right hip and stifle when walking; coxofemoral joint pain and crepitus; bilateral muscle atrophy of the hindlimbs; decreased range of hip movement. Hindlimb postural reaction deficits and decreased flexor reflex indicated ischiatic nerve involvement. EMG findings confirmed this. Exploratory surgery found the ischiatic nerve trapped between the sacrotuberous ligament and bone and soft tissue around the hip joint. The nerve was decompressed by resecting the sacrotuberous ligament. One year afterwards the dog was essentially normal.

SORJONEN, D. J., MILTON, J. L., STEISS, J. E., HAFCOCK, J. T. & DUNBAR, M. (1990) *Journal of the American Veterinary Medical Association* **197,** 495

Ivermectin toxicosis in a dog

A FIVE-year-old dobermann pinscher dog was found collapsed and unresponsive 24 hours after being given a tube of equine paste dewormer containing 115 g ivermectin. Pupils were dilated and unresponsive. Localised fasciculation of muscle groups occurred. Treatment consisted of intravenous fluids at two to three times maintenance, together with intravenous dexamethasone and flunixin meglumine. Intravenous diazepam controlled mild seizures and tremors. Two days later the animal began responding to its name. By the fourth day the dog could walk with difficulty. Treatment was continued with corticosteroids on a tapering dosage regime. Gradual improvement was made and the dog was clinically normal 12 days after the first signs.

HOPKINS, K. D., MARCELLA, K. L. & STRECKER, A. E. (1990) *Journal of the American Veterinary Medical Association* **197,** 93

Hepatic myelolipomas in a cat

A SIXTEEN-year-old spayed domestic shorthair was presented with an abdominal mass. Abdominal radiography revealed a large mass, containing areas of calcification. During exploratory laparotomy, two irregular masses were found (in the caudate and right lateral lobes of the liver, respectively). The affected liver lobes were removed. The masses were poorly separated from the surrounding hepatic parenchyma. In cross section they had a fatty appearance. Histological diagnosis was myelolipoma. The cat remained well until she died of unknown cause, 27 months after surgery.

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