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Clinical presentation, MRI, histopathology and outcome in a cat with immune-mediated masticatory myositis

Marco Armellini[1], Lluís Sánchez[2], Andrea Lorek[3], G Diane Shelton[4] and Luisa De Risio[5]

Abstract

Case summary A 4-year-old female spayed domestic shorthair cat was presented with facial swelling, ocular discharge and intermittent bilateral exophthalmos. Haematology revealed mild eosinophilia. Serum biochemistry showed a markedly elevated creatine kinase activity. MRI of the head revealed diffuse and severe changes of the masticatory muscles, including irregular areas compatible with fluid or necrosis within the abnormal muscle tissue. Cytological analysis of the left temporal muscle revealed eosinophilic and macrophagic inflammation. Bacterial and fungal cultures were negative. Serological titres against *Toxoplasma gondii* were compatible with previous exposure. A canine ELISA against masticatory muscle type IIM fibre proteins was positive at 1:4000 (reference interval <1:100). Histopathological examination of the left temporalis muscle revealed moderately severe and multifocal myositis. A diagnosis of immune-mediated masticatory myositis was made and immunosuppressive therapy was started. The cat initially responded to tapering doses of prednisolone, but subsequent relapses required therapy modulation. At the time of writing, 27 months after the initial diagnosis, the cat was in remission, but was diagnosed with diabetes mellitus, probably secondary to chronic glucocorticoid use.

Relevance and novel information To our knowledge, this is the first case report to describe the MRI appearance of masticatory myositis in a cat and the second to describe the clinical presentation, histopathology, response to treatment and outcome in a cat with this condition.

Keywords: Masticatory; myositis; magnetic; resonance

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Case description

A 4-year-old female spayed domestic shorthair cat weighing 6.9 kg was presented with a 2-week history of intermittent bilateral exophthalmos, facial swelling and serous ocular discharge. Food prehension, the ability to open the mouth and pre-referral intraoral radiographs were unremarkable. Owing to a lack of visible clinical improvement following clindamycin (Zodon; Ceva) treatment, amoxicillin–clavulanic acid (Noroclav; Norbrook) and meloxicam (Metacam; Boehringer Ingelheim), the cat was referred to the neurology and neurosurgery service at the Animal Health Trust.

At presentation, generalised facial swelling, extending to the neck and cheeks, mild exophthalmos, third eyelid protrusion, chemosis and bulbar conjunctival hyperaemia were detected bilaterally (Figure 1). The left eye was more severely affected than the right. Aqueous flare was absent and intraocular pressure, menace

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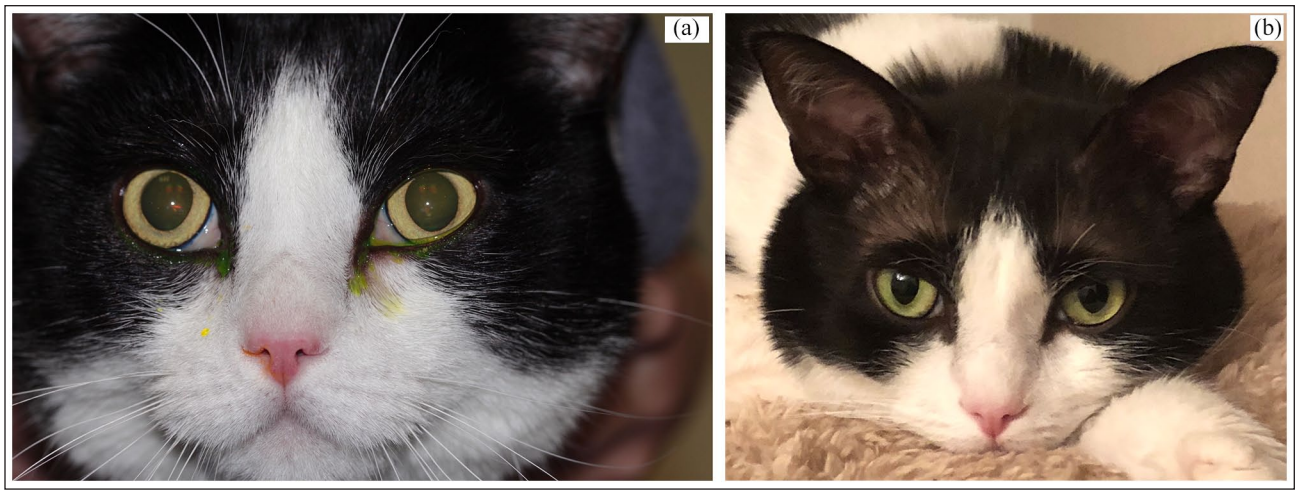

Figure 1 (a) The cat's face at the time of presentation; (b) image of the cat's normal facial characteristics prior to developing masticatory myositis

response and pupillary light and dazzle reflexes were unremarkable. Fluorescein staining was negative bilaterally and the Jones test was positive in the right eye only. Performing complete physical and neurological examinations was not possible given the uncooperative nature of the cat; however, the remainder of the physical examination under general anaesthesia was unremarkable. A disease affecting the retrobulbar area or the masticatory muscles, including masticatory myositis (MM), was suspected.

Haematology and serum biochemistry revealed mild eosinophilia (3.38×10^9/l; reference interval [RI] 0.10–2.00) and a markedly elevated creatine kinase (CK) activity (5959 IU/l; RI 70–190). Serological titres against *Toxoplasma gondii* were consistent with previous exposure.

MRI of the head was conducted with a 1.5 T scanner (Signa EchoSpeed; GE Healthcare). Transverse, dorsal and sagittal T2-weighted (T2W) (repetition time [TR] 3975–6221 ms/echo time [TE] 84–87 ms; field of view 140 mm, matrix 512 × 512) sequences, transverse precontrast T1-weighted (T1W) (TR 521 ms/TE 6.6 ms) images, and transverse and dorsal postcontrast T1W sequences – after the administration of an intravenous gadolinium-based agent (Gadovist; Bayer) – were obtained. Additionally, transverse short tau inversion recovery (STIR) (TR 8344 ms/TE 39 ms/TI 150 ms) and transverse postcontrast T1W images with fat saturation (TR 732 ms/TE 6.6 ms) were acquired. Slice thickness was 3 mm.

The temporal, masseter and medial pterygoid muscles were diffusely thickened bilaterally and showed multifocal-to-coalescing areas of marked hyperintensity on T2W and STIR images relative to normal muscle (Figure 2a). There were subtle hyper- and hypointensities on T1W images, producing an ill-defined striated appearance. The affected muscles showed strong and heterogenous contrast enhancement, with multiple embedded, non-contrast-enhancing areas (consistent with fluid or necrosis) within the abnormal muscles (Figure 2b,c). The digastricus, extraocular and cervical muscles appeared to be unaffected. Significant mandibular and medial retropharyngeal lymphadenopathy was detected. The MRI was suggestive of severe infectious or immune-mediated MM.

As a feline-specific assay has not been established, a canine ELISA was used to detect serological titres against type IIM muscle fibre proteins and was positive at a dilution of 1:4000 (RI <1:100 in dogs). Cytological analysis of ultrasound-guided fine-needle aspirates of the left temporal and masseter muscles, including the suspected necrotic regions on MRI, revealed eosinophilic and macrophagic inflammation. Bacterial and fungal cultures were negative. Lack of evidence supporting active infection coupled with positive serological titres against type IIM muscle fibres supported the diagnosis of immune-mediated MM.

Electromyography (EMG) was performed using digital electrodiagnostic equipment (Medelec Synergy; Oxford Instruments). The temporal, masseter, epaxial and pelvic and thoracic limb appendicular muscles were assessed. Normal insertional activity was recorded and no electrical activity abnormalities were identified.

Open muscle biopsy samples were obtained from the left temporal muscle. Both fresh refrigerated and formalin fixed samples were sent to the Comparative Neuromuscular Laboratory at the University of California, San Diego, by a courier service, for complete histopathological examination. The biopsies showed a moderate variability in type IIM myofibre size with scattered atrophic fibres having a round shape. Fibre type grouping was not observed and intramuscular nerve branches appeared normal. Multifocal areas of mononuclear cell infiltrations (lymphocytes and acid phosphatase/esterase reactive macrophages) had an endo- and perimysial distribution. Peroxidase reactive eosinophils were not

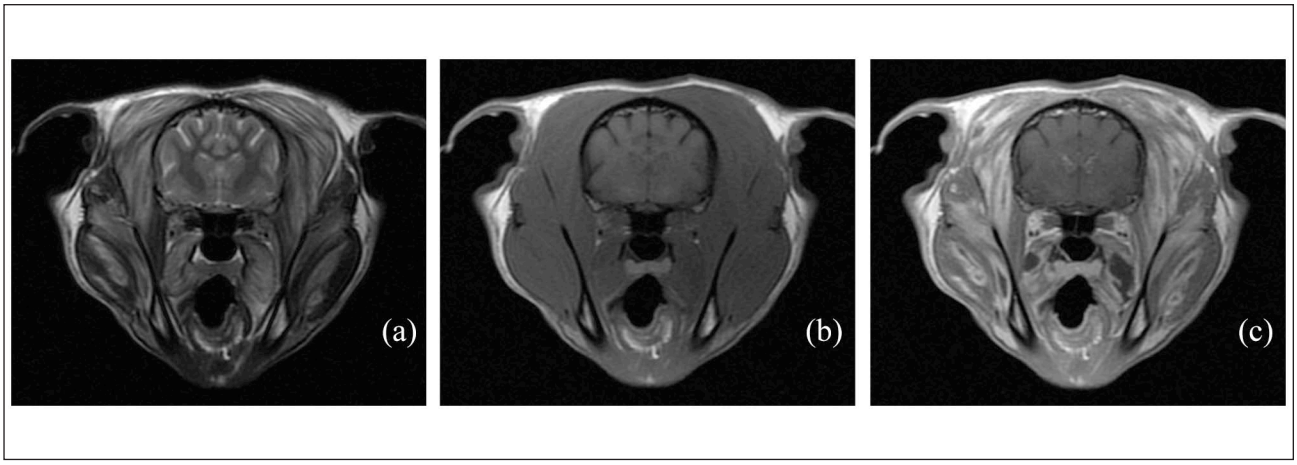

Figure 2 Transverse T2-weighted [T2W] (a), and T1-weighted precontrast (b) and postcontrast (c) MRI of the cat's head showing increased volume of the masticatory muscles, with ill-defined patchy hyperintense areas on the T2W image corresponding to areas of contrast enhancement and areas of non-enhancement, consistent with necrotic regions or fluid

identified. Scattered necrotic fibres were undergoing phagocytosis. Moderate perimysial fibrosis was observed. No fibre loss, organisms or cytoarchitectural abnormalities were identified. A multifocal inflammatory myopathy (myositis) with mild perimysial fibrosis and no obvious myofibre loss was diagnosed (Figure 3).

Consequently, the diagnosis of immune-mediated MM was established. The cat was started on an immunosuppressive dose of prednisolone (30 mg; 4.4 mg/kg q24h [Prednidale; Dechra]). The dose was decreased every 6 weeks with the aim of discontinuing administration 36 weeks after the initiation of treatment. Repeating the measurement of serum CK activity and serological titres for type IIM myofibres prior to decreasing the dose of prednisolone was recommended on each occasion. However, owing to the cat's non-compliant behaviour, this was not achieved. Frequent email and telephone communications were maintained with the cat's owner and photographs of the cat's face were regularly checked.

Three months after starting treatment (prior to decreasing the prednisolone dose from 2 mg/kg q24h to 1 mg/kg q24h), the serum CK activity and type IIM myofibre titres were 387 IU/l and negative at <1:100, respectively. Ten months after initial presentation, while receiving prednisolone at 1.5 mg (0.2 mg/kg) q48h for 6 weeks, the cat showed mild lethargy and an episode of unprovoked aggression to a family member. No changes in facial expression were noticed. At this point, the serum CK activity was within the RI and type IIM myofibre titres were positive at 1:500. Repeating muscle biopsies was recommended by the authors but declined by the owner. The prednisolone dose was therefore increased to 15 mg (2.1 mg/kg) q24h. Type IIM myofibre titres returned to within the RI (<1:100) and the prednisolone dose was halved after 2 months. Titres remained negative 6 weeks later inciting a further decrease in prednisolone dose to 5 mg (0.7 mg/kg) q24h. Following unremarkable blood tests 2 months after the prednisolone dose reduction, a further decrease in dose to 2.5 mg (0.35 mg/kg) q24h was implemented. Five months later,

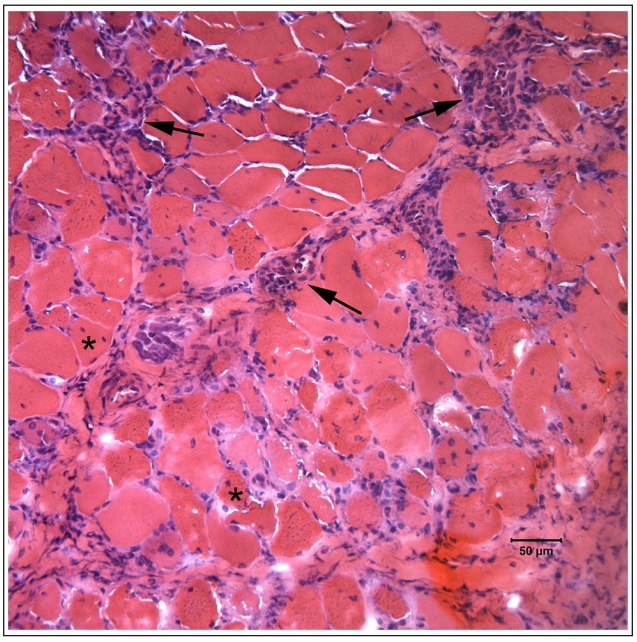

Figure 3 Haematoxylin and eosin-stained cryosections of the temporalis muscle biopsy from the affected cat showing variability in myofibre size, several myofibres with internal nuclei (asterisks) and multifocal and scattered mononuclear cell infiltrations having an endomysial and perimysial distribution (arrows). Fibrosis was not obvious. Bar = 50 µm

despite the cat appearing clinically normal, type IIM myofibre titres became positive at 1:500. Until this time, no significant side effects of prednisolone had been observed. The prednisolone dose was increased to 5 mg (0.7 mg/kg) q24h and ciclosporin (Atopica oral solution; Elanco) was started at 4 mg/kg q12h and continued to date. Three months later, negative type IIM myofibre titre tests were achieved. Ensuing polyphagia and weight loss prompted the performance of blood analyses, and the cat was diagnosed with diabetes mellitus. Appropriate treatment was started by the primary care veterinary surgeon; the prednisolone dose was halved (2.5 mg; 0.35 mg/kg q24h) and gradually discontinued. Immunosuppressive treatment was continued with ciclosporin alone (for 60 days at the time of writing). No reoccurrence of neurological clinical signs has been reported to date, with a follow-up of 27 months after initial diagnosis.

Discussion

MM has been extensively described in dogs and other carnivores.[1–15] To our knowledge, this case represents the second report of MM in a cat.[14] The first reported case was a 1-year-old neutered male mixed-breed cat that presented with a 2-month history of an inability to fully open the mouth and reduced ability to hold food.[14] Severe bilateral, symmetrical masticatory muscle atrophy associated with severe reduction of the vertical mandibular range of motion (VROM) was noticed upon clinical examination. Advanced imaging (CT) of the head was declined by the cat's owner but was performed post mortem. Clinical findings, together with complete histopathological analysis of temporal and masseter muscle specimens, were suggestive of a severe and end-stage inflammatory myopathy with extensive fibrosis.

In companion animals, both acute and chronic forms of MM have been reported. In the early stages of the disease, as described in the present case report, the most common clinical sign is swelling of the masticatory muscles and secondary pain, and inability or reluctance to open the mouth.[10,11,16] If untreated, the disease progresses to severe atrophy and fibrosis of the masticatory muscles, which may produce significant reduction of the VROM of the temporomandibular joints and mechanical inability to open the mouth.[3,14] The median age of onset of MM in dogs is 3 years.[17] The cat in this case report and in the previously published one were both young (1 and 4 years old, respectively).[14]

Similar to human inflammatory myopathies,[18] the diagnosis of MM in small animals is based on the combination of clinical, laboratory, serological, MRI and histopathological criteria.[19] Haematological and biochemical changes such as anaemia, eosinophilia, hyperglobulinaemia, increased CK activity and other enzymes in serum and proteinuria have been reported and may vary depending on the stage of the disease and the severity and extent of the muscle damage.[17]

The single most important test to reach a diagnosis of MM, in the absence of infectious diseases, is histopathological analysis of affected muscles.[6,19] In the present report, complete histopathological analysis of the left temporal muscle showed features suggestive of the acute form of the disease, which have previously been described in dogs.[17] Histopathological examination does not only provide diagnostic information, but also information on potential response to medical treatment and long-term prognosis.[3] However, muscle biopsy is an invasive procedure with limited value in monitoring the progression of the disease.[19] Muscular lesions, particularly when focal, can be overlooked on individual biopsy samples. Furthermore, muscle biopsy has been reported as less sensitive than MRI at identifying inflammatory myopathies (66% vs 89%, respectively).[20,21]

In dogs, the presence of serum antibodies against the type IIM myofibres is a very sensitive (85–90%) and specific (100%) non-invasive test.[22] However, false-negative results may occur in patients treated with immunosuppressants or in end-stage MM.[1] A canine ELISA assay has been found to be a reliable indicator for feline IIM cross-reacting antibodies,[14] but to date there is no feline-specific assay and no validation of the canine ELISA system RIs for the detection of MM in cats. Measuring serum antibodies against the type IIM myofibres gives important diagnostic information and anecdotally may be used to monitor for clinical or subclinical relapses, guiding the tapering of immunosuppressive medications. As previously reported,[14] type IIM myofibres serum antibody levels were used as a confirmatory diagnostic test and appeared elevated at the time of initial presentation and at the time of clinical relapse in light of subtle and non-specific clinical signs. However, antibody titres may be therapeutically lowered and may just reflect the immunosuppressive treatment and not the stage of the disease.

The importance of MRI in the early diagnosis and characterisation of myositis should not be underestimated.[6,9,19] It is a relatively non-invasive test that provides important information regarding extent and intensity of changes within affected muscles and has been shown to be more sensitive in detecting inflammatory myopathies, in correlation with disease progression, compared with serum CK activity.[6,19–21,23–27] Furthermore, MRI allows identification of the surgical biopsy site(s) and optimise the likelihood of achieving diagnostic histological results.[6,19,20,23,24,27,28]

The use of MRI, particularly STIR sequences, has been considered an effective and accurate diagnostic tool for early diagnosis of canine MM.[9] In the present case report, MRI provided accurate information about lesion

characteristics, location and extent, and it guided the diagnostic path. To our knowledge, MRI findings in feline MM have not been reported previously. Advanced imaging may also represent a useful modality to monitor the evolution of muscle changes in the course of medical therapy; however, a general anaesthetic is required.

EMG is a sensitive, but not specific, test. Electrical muscle abnormalities may be overlooked, particularly in focal diseases, and the recorded abnormal spontaneous electrical activity is usually non-specific.[27] Compared with MRI, EMG is more invasive, can cause focal iatrogenic myositis and is characterised by a lower specificity.[20,23,24,27,28] Because the cat in the present report could not be fully examined due to its uncooperative behaviour, in order to rule out a multifocal or diffuse myopathy, EMG was performed in the masticatory, truncal and appendicular muscles. Surprisingly, no abnormal electrical activity was recorded in the masticatory muscles despite extensive muscle changes on MRI and histological examination. Myofibre loss and fibrosis were not obvious in the biopsy sections, making the absence of muscle fibres an unlikely cause of the lack of EMG changes. Technical and operator-related problems were considered as possible reasons for the EMG results. However, normal insertional activity in each muscle tested and the absence of abnormalities in previous and subsequent EMG studies performed with the same machine and cables, in the same environment by the same, as well as different, operators, made this an unlikely limitation. Considering the histopathological changes, laboratory findings and appearance of the masticatory muscle on MRI, the normal EMG was atypical and unexpected. No plausible explanation can be surmised to support the latter and more research is needed to evaluate the sensitivity of this diagnostic procedure in feline patients affected by MM.

Treatment of MM generally consists of immunosuppressive doses of corticosteroids. Doses are gradually decreased over 4–6 months, reaching the lowest dose that controls the clinical signs.[29] Medical treatment can be lifelong, discontinued or combined with other immuno suppressive drugs.[17] In the present report, subtle signs of possible relapse were immediately identified by the owner and confirmed with serological testing leading to swift adjustment of immunosuppressive therapy with no relapse of clinical signs seen 13 months after the last clinical relapse and favourable outcome 27 months after the initial diagnosis.

Conclusions

To our knowledge, this is the first case report to describe the MRI appearance, treatment response and follow-up of MM in a cat. Combining clinical, serological, MRI and histopathological findings and ruling out infectious aetiologies of feline myositis can help to achieve a diagnosis of MM in cats.

Conflict of interest The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical approval The work described in this manuscript involved the use of non-experimental (owned or unowned) animals. Established internationally recognised high standards ('best practice') of veterinary clinical care for the individual patient were always followed and/or this work involved the use of cadavers. Ethical approval from a committee was therefore not specifically required for publication in *JFMS Open Reports*. Although not required, where ethical approval was still obtained it is stated in the manuscript.

Informed consent Informed consent (verbal or written) was obtained from the owner or legal custodian of all animal(s) described in this work (experimental or non-experimental animals, including cadavers) for all procedure(s) undertaken (prospective or retrospective studies). For any animals or people individually identifiable within this publication, informed consent (verbal or written) for their use in the publication was obtained from the people involved.

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