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CASE REPORT
Unusual histiocytic disease in a Somali cat

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An 8-year-old Somali cat presented with a 9-month history of inappetence, vomiting and weight loss. The disease progressed to involve neurological signs associated with a mass lesion at the level of the first lumbar vertebra. Histopathology identified the condition as malignant histiocytosis affecting the lungs, stomach, mesenteric lymph nodes, liver, spleen, brain and spinal cord. However, the presentation of this case differs from previously reported cases of malignant histiocytosis, and may therefore represent a variant form of histiocytic disease.

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An 8-year-old female neutered Somali cat was referred to the University of Edinburgh Hospital for Small Animals, for investigation of vomiting and weight loss of 9 months duration. The cat lived indoors, but had regular access outside. She was regularly wormed and routinely vaccinated against feline panleucopenia virus, feline herpesvirus, feline calicivirus and feline leukaemia virus (FeLV). Her previous medical history consisted of seasonal dermatitis, and occasional fight wounds.

Investigations prior to referral included routine haematology and serum biochemistry, the results of which were unremarkable. In-house tests for FeLV antigen and feline immunodeficiency virus antibody had been negative. A lateral thoracic radiograph taken 8 months before presentation was reported to show a patchy, mixed lung pattern. An exploratory coeliotomy had been performed. No gross abnormalities were reported, and biopsies were obtained from the stomach, mesenteric lymph nodes and jejunum. Histopathology of the gastric biopsy reported the presence of nodular to coalescing infiltrates, which consisted of histiocytes with neutrophils and variable numbers of lymphocytes and plasma cells and abundant fibrosis. No multinucleated giant cells or infectious agents were detected (acid-fast and periodic acid Schiff staining were performed). The lymph node histopathology was similar to that of the gastric biopsy, and the small intestinal histopathology suggested mild to moderate lymphocytic enteritis.

Treatments prescribed before referral consisted of antibiotics (clavulanic acid potentiated amoxicillin, 17 mg/kg q 12 h; metronidazole, 13 mg/kg q 12 h), dietary modification (Hill's i/d) and various courses of corticosteroids, namely prednisolone (1.7 mg/kg q 12 h), dexamethasone (0.3 mg/kg q 48 h; Dexadresson; Intervet) and methylprednisolone acetate (4 mg/kg once, 3 weeks before presentation; Depo-medrone V; Pharmacia). Initially, there had been some improvement (increased appetite and decreased frequency of vomiting) following the introduction of the prednisolone. However, the owner had been unable to administer the metronidazole due to

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difficulty in medicating the cat, and this also accounted for the change to injectable steroids.

At the time of referral, vomiting was occurring 2–3 times per week, although the signs had waxed and waned over the previous 8 months. The nature of the vomit had changed from bilious fluid to undigested food. Defecation had not been observed, but blood had occasionally been noticed at the cat's anus. There had been a mild increase in thirst over this time period, and slow, insidious weight loss.

On physical examination, the cat was considered to be thin, weighing only 2.96 kg (body condition score 3/9). On abdominal palpation, there was suspicion of a mid-abdominal mass, but physical examination was otherwise unremarkable except that the cat tended to sit with her right hind limb extended cranially.

Routine haematology and serum biochemistry were repeated, but again were found to be unremarkable. No abnormalities were detected on urinalysis, including culture. Faecal culture was negative, as was analysis for enteric parasites, *Cryptosporidia*, *Giardia* and *Coccidia* species. Serum levels of cobalamin, feline pancreatic lipase and trypsin-like immunoreactivity were all within the reference ranges. Serum folate level was slightly reduced (7.1 μg/l; reference range: 9.7–21.6 μg/l), consistent with small intestinal disease. Thoracic radiography revealed a generalised bronchointerstitial pattern, but abdominal radiography was unremarkable. Abdominal ultrasonography revealed prominent mesenteric lymph nodes, with one large lymph node (0.8 × 1.7 cm) exhibiting heterogeneous echogenicity. The submucosal layer of the stomach showed generalised thickening.

Endoscopy of the gastrointestinal tract was performed. The oesophagus was unremarkable. The mucosa of the stomach appeared rather irregular and friable. The small intestine was grossly normal, but the colonic mucosa bled very easily. Multiple pinch biopsies were taken from the stomach, small intestine and colon. Low to moderate numbers of *Helicobacter*-like organisms were identified in the gastric pits, but no organisms were cultured from a gastric biopsy. The histopathology of the small and large intestine was considered normal.

A presumptive diagnosis of deep-seated inflammatory bowel disease was made, and the cat was discharged on prednisolone (1.7 mg/kg q 48 h), along with an exclusion diet of chicken only. In addition, when the biopsy results revealed the presence of *Helicobacter*-like organisms, a 10-day course of metronidazole (14 mg/kg q 24 h) and spiramycin (26 mg/kg q 24 h; Stomorgyl; Merial Animal Health) was prescribed. This formulation was chosen to try to facilitate medication of an uncooperative cat.

The cat was re-presented 24 days after the initial referral. Although the gastrointestinal signs had improved, the right hind lameness had progressed. Decreased muscle tone and strength were noticed, along with decreased conscious proprioception of the right hind limb.

Serum was submitted for a coronavirus profile, including albumin:globulin ratio (0.89), coronavirus antibody titre (0) and α_1 acid glycoprotein (100 μg/ml; reference range <500 μg/ml), the results of which indicated that the cat was very unlikely to have feline infectious peritonitis.

The cat was anaesthetised for further investigations. Plain radiographs of the spinal column were obtained, before collection of a cerebrospinal fluid sample and performance of a myelogram. The cerebrospinal fluid was unremarkable. The myelogram demonstrated an intra-medullary lesion at the level of the first lumbar vertebra (see Fig 1). Neoplasia was considered a significant differential diagnosis, therefore, the owner elected for euthanasia with consent given for a post-mortem examination to be performed.

The results of the gross and histopathological examinations are reported in Table 1, and led to a pathological diagnosis of malignant histiocytosis.

Histiocytes are tissue macrophages derived from the CD34+ committed stem cell precursor (Moore and Affolter 2005). Histiocytic disorders in dogs may be broadly divided into cutaneous and non-cutaneous diseases. The cutaneous disorders include cutaneous histiocytoma, multiple histiocytomas, metastatic histiocytoma and Langerhans cell histiocytoma (Moore and Affolter 2005). The non-cutaneous diseases include histiocytic sarcoma, disseminated histiocytic sarcoma, systemic histiocytosis and malignant histiocytosis. A review of these histiocytic diseases has been given by Moore and Affolter (2005).

The histiocytes in this case were identified by staining with vimentin, which confirmed mesenchymal origin (Smoliga et al 2005), and Mac 387, which is a human histiocyte–monocyte marker (Smoliga et al 2005), although the ideal marker for feline histiocytes is yet to be established. More recently, immunophenotyping has been used to differentiate lymphocytes which express CD3 or CD79a from histiocytes, which do not,

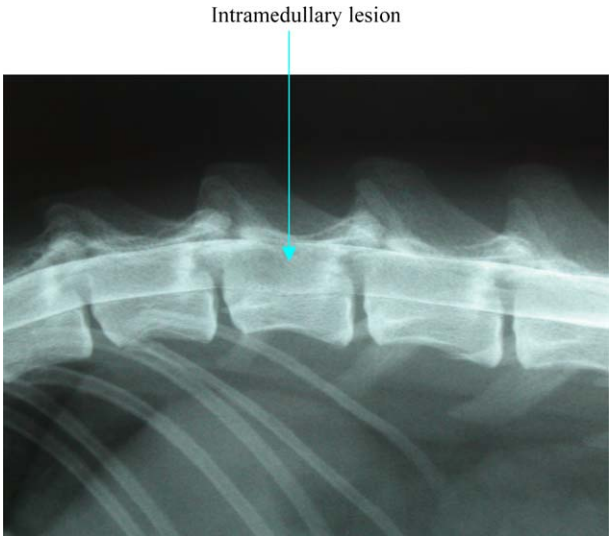

Fig 1. Myelogram of lumbar spine illustrating intra-medullary lesion at the level of the first lumbar vertebra.

and further classification of the histiocytic lineage may be achieved with immunophenotyping for CD1, CD11b, CD11c, CD11d, CD18, CD90, MHCII and E-cadherin (Moore and Affolter 2005).

In this case, the diagnosis of malignant histiocytosis was based on the finding of populations of atypical and pleomorphic histiocytes, their presence within multiple organs, and their dissemination to organs that do not normally contain large numbers of histiocytes (see Table 1 and Fig 2).

Malignant histiocytosis is a rare disorder, most commonly affecting Bernese Mountain Dogs. The disease is typified by systemic proliferation and invasion of tissues by morphologically atypical histiocytes, which occurs simultaneously within multiple sites. This is typically a very aggressive disease, with affected animals showing a rapid clinical course. Infiltrates are commonly identified within the lymph nodes, spleen and liver early in the course of the disease, and the bone marrow later in the course of the disease (Moore and Rosin 1986). Reports of malignant histiocytosis in the cat amount to only seven cases (Court et al 1993, Freeman et al 1995, Walton et al 1997, Fritz et al 1999, Kraje et al 2001). The ages of the affected cats ranged from 1 to 13 years, with weight loss, inappetence and lethargy being common presenting signs. The course of the disease was rapid, with euthanasia being performed between 2 and 7 weeks after onset of clinical signs. In the cases reported previously, anaemia, splenomegaly and icterus were consistent findings, with thrombocytopenia, hypoproteinaemia and hyperglycaemia being seen frequently. In the three cases where clotting times (prothrombin time and activated partial thromboplastin time) were performed, they were found to be prolonged (Kraje et al 2001).

The case reported here is unusual for a number of reasons. The chronicity of the clinical signs is very different from the previously reported cases. In addition, no haematological or biochemical abnormalities were detected. Clotting times were not performed, but there was no suggestion of a bleeding disorder. The bone marrow was not examined histologically, but the absence of haematological abnormalities suggests that it is unlikely to have been involved. Pulmonary infiltration was previously reported in one cat (Kraje et al 2001), but this is seen much more commonly in dogs (Moore and Rosin 1986). Spinal cord involvement has recently been reported in one cat, but was attributed to extension of a histiocytic sarcoma, rather than malignant histiocytosis (Smoliga et al 2005).

Histiocytic diseases other than malignant histiocytosis were considered in the differential diagnoses of this case. Systemic histiocytosis is unlikely, as skin lesions are a consistent finding in this condition (Moore 1984). In disseminated histiocytic sarcoma, a primary histiocytic sarcoma becomes widely distributed throughout the body. Although histiocytic sarcomas often arise on the limbs, they may occur in cryptic sites such as lung, spleen or bone marrow, which

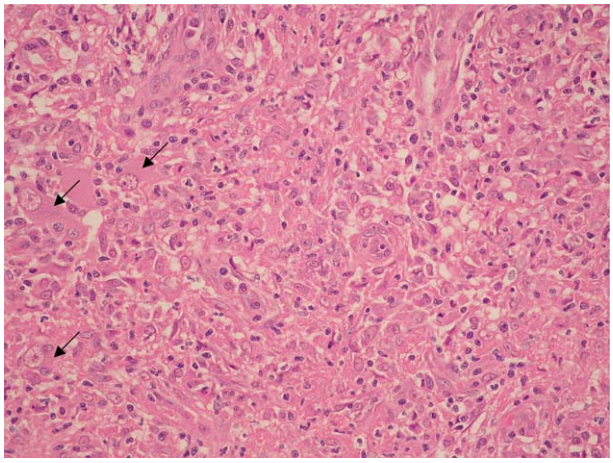

Fig 2. Pleomorphic histiocytes in the thalamus. Haematoxylin and eosin stain; ×400 magnification. Large, pleomorphic histiocytes within the thalamus are indicated by arrows.

Table 1. Significant pathological findings

Organ	Gross post-mortem findings	Histopathological findings	Additional comments
Lungs	Diffusely congested, with a cream, mottled appearance. Several raised, white, irregular, nodules (5–10 mm), which felt gritty when cut, and were diffusely scattered throughout the lung parenchyma.	Multifocal to coalescing non-encapsulated masses comprising a mixture of histiocytic cells, neutrophils, and a few plasma cells and small lymphocytes. These cell aggregates were mainly scattered throughout the pulmonary interstitium, but they were also present within the lumen of bronchi and bronchioles (admixed with desquamated lining epithelial cells and eosinophilic proteinaceous material) and occasionally within the lumen of blood vessels. The histiocytes were large, polygonal with large oval vesicular nuclei with single prominent nucleoli and abundant eosinophilic cytoplasm. Mitoses were not observed. There was mild anisokaryosis of the histiocytes.	Negative staining with Gram's, Grocott's and Ziehl Neelsen stains. Immunostaining with GFAP[*]: negative, S-100[†]: negative, Vimentin: positive, Mac 387: positive
Liver	Uniformly congested, containing small (5 mm), irregular white foci. The diaphragmatic surface had a 7 mm firm, creamy nodule involving the hepatic parenchyma.	Multiple, randomly distributed, irregularly shaped foci were scattered throughout the hepatic parenchyma. These aggregates were composed mainly of large histiocytic cells and neutrophils, with fewer numbers of plasma cells. Apoptotic bodies were scattered throughout the parenchyma. Haemosiderin was abundant in the cytoplasm of hepatocytes, within sinusoidal Kupffer cells, and occasionally in the centre of inflammatory foci within the cytoplasm of the histiocytes.	
Spleen	Markedly enlarged and congested.	Depleted white pulp, with prominent germinal centres, containing occasional small foci of atypical histiocytes. The red pulp was markedly acellular with the few cells consisting mainly of erythrocytes and scattered foci of histiocytes in the sinusoids. These cells were histologically similar to those seen in the lungs and liver.	

Table 1. (*Continued*)

Organ	Gross post-mortem findings	Histopathological findings	Additional comments
Lymph nodes	The ileocaecal lymph node was prominent, and the mesentery contained a solitary enlarged (10 × 5 mm) lymph node.	The mesenteric lymph node contained a prominent cortical area with lymphoid follicles with distinct germinal centres. The follicles contained a mixed cell population of predominantly small mature lymphocytes, fewer plasma cells and macrophages, and numerous tingible body macrophages.	
Spinal cord	An irregular area of grey discoloration of 5 × 5 mm at the level of the first lumbar vertebra.	Multiple foci comprising a mixture of histiocytes, abundant small lymphocytes and occasional plasma cells and lymphocytes, randomly distributed throughout grey and white matter. Histiocytic cells were predominant and occasionally had a spindleoid appearance, forming streams and whorls. There was marked evidence of Wallerian degeneration, and widespread neuronal chromatolysis.	
Brain	A large, well-circumscribed, non-encapsulated cellular mass was identified in the area of the lateral geniculate body and periaqueductal grey matter of the midbrain. This extended to above the third ventricle in the thalamus and the temporal cortex.	Cellular masses consisted of whorls and bundles of histiocytes, and occasional neutrophils, plasma cells and clusters of small lymphocytes. Aggregates of lymphocytes were present at the periphery of the two masses present in the thalamus and temporal cortex.	Immunostaining with GFAP*: negative, S-100†: negative, Vimentin: positive, Mac 387: positive

*GFAP = glial fibrillary acidic protein (to rule out glial cell tumour).
†S-100 = polyclonal rabbit S-100 protein (to rule out amelanotic melanoma).

may delay their recognition. Unfortunately, once the condition is well advanced, differentiation from malignant histiocytosis can be extremely difficult (Moore and Affolter 2005). While metastatic spread of a histiocytic sarcoma could explain the more insidious onset in this current case, the location of the primary lesion would remain in doubt. A reactive histiocytic disease was considered less likely due to the lack of identification of a causal agent, and the variety of organ systems involved. However, reactive histiocytic disease is poorly documented in the cat.

In conclusion, the spectrum of histiocytic disease is complex, and differentiation of these conditions is complicated by their rarity, particularly in the cat. Improved understanding of this spectrum of disease in this species requires further reports to aid recognition, and the development of immunophenotyping to assist with classification. This may in turn lead to identification of more effective treatments.

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