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Abstract

Case summary A 6-year-old neutered male domestic shorthair cat presented with non-regenerative macrocytic anemia of 2 years' duration and minimally ambulatory paraparesis. Neurologic examination suggested an upper motor neuron paresis or T3–L3 myelopathy. The cat was positive for feline immunodeficiency virus (FIV), neutropenic, had polyclonal gammopathy and was euthanized following a hemolytic crisis. At autopsy, multifocal bilateral dark red masses were observed subpleurally around the costochondral junctions, extradurally and paraspinally in the spinal canal, and paravertebrally, on the lateral and ventral subpleural surfaces of the T4–11 vertebrae. Histologic examination of the masses revealed extramedullary hematopoietic tissue composed primarily of erythroid precursors and megakaryocytes, with occasional myeloid precursors and blood-filled sinuses. Bone marrow findings supported ineffective granulopoiesis, and decreased erythropoiesis and megakaryopoiesis, with probable myelodysplasia as the underlying cause of the hematologic abnormalities.

Relevance and novel information Thoracic, paraspinal and paravertebral extramedullary hematopoietis presenting as masses has not been described previously in cats with chronic anemia. This is a unique case of a thoracic–spinal–epidural extramedullary hematopoietic masses resulting in possible spinal cord compression and paraparesis in a cat.

Keywords: Chronic anemia; non-hepatosplenic extramedullary hematopoiesis; NHS-EMH; spinal cord compression; thoracic–spinal–epidural EMH

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Case description

A 6-year-old neutered male, mainly indoor, domestic shorthair cat presented to the Ross University School of Veterinary Medicine clinic in 2015 (day 83 after initial presentation for hair loss [day 0]; see Table 1) with a history of 5 days of dysuria. A presumptive diagnosis of feline idiopathic cystitis was made. At the same visit, the cat was diagnosed with severe non-regenerative macrocytic anemia and marked hyperproteinemia, and was started on pradofloxacin, doxycycline and prednisone because of concerns over its feline immunodeficiency virus (FIV)-positive status and potential for hemotrophycoplasmosis (based on the blood smear review).

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Table 1 Abnormal hematologic and biochemical data from a cat with chronic non-regenerative anemia

Analyte	Prior clinic visits			Presented with neurologic signs			RI*
	Day 0	Day 83	Day 106 [†]	Day 491 [†]	Day 508 ^{††}	Day 513 [†]	
PCV (%)	28	16	18	11	10	13	25–45
MCV (fl)	50	74	73	65	67	63	39–55
Reticulocytes ($\times 10^3/\mu\text{l}$)	NP	38.8	40.3	26.9	18.7	38.8	0–40.0
Neutrophils ($\times 10^3/\mu\text{l}$) [§]	5.1	5.5	3.5	2.8	1.2	2.8	2.5–12.5
Platelets ($\times 10^3/\mu\text{l}$)	45 [¶]	38 [¶]	127 [¶]	151 [¶]	62 [¶]	66	300–800
Morphology	Rouleaux	Macro-platelets	Agglutination, rouleaux, macroplatelets (19%)	Agglutination	Agglutination, ghost erythrocytes, suspicious for <i>M haemofelis</i>	Agglutination, macro-platelets (4%)	–
Total bilirubin (mg/dl)	0.4	NP	0.4	0.7	0.6	0.8	0.1–0.6
Total protein (g/dl)	8.3	9.7	NP	10.4	9.9	10.0	5.4–8.2
Globulins (g/dl)	5.8	6.3	NP	7.4	6.7	6.4	1.5–5.7
Albumin (g/dl)	2.5	3.4	NP	3	2.2	3.6	2.4–4.4

*RIs from Abaxis

[†]Saline agglutination test performed

[‡]Serum hemolysis (3+)

[§]All neutrophils were segmented. No band neutrophils were seen

[¶]Platelet clumping

RI = reference interval; PCV = packed cell volume; MCV = mean cell volume; NP = not performed; *M haemofelis* = *Mycoplasma haemofelis*

The cat did well until day 491, when it presented with minimally ambulatory paraparesis. Serum tested on this day was FIV-positive and feline leukemia virus (FeLV)-negative on the IDEXX SNAP FIV/FeLV Combo Test. A localized pain response was not elicited on manipulation of the spine in the T3–L3 region. Neurologic examination findings suggested an upper motor neuron lesion, likely in the thoracolumbar vertebrae area. It was concluded that the lesion was localized to the T3–L3 spinal cord segments. Other components of the neurologic examination were unremarkable. No history or signs of trauma were noted during the clinical examination. Radiographic findings of the thoracolumbar region of the spinal cord were unremarkable. MRI was not available.

Results of a complete blood count (CBC; Abaxis VetscanHM5) and serum biochemical profile (Abaxis Vetscan VS2) on day 508 indicated severe non-regenerative, macrocytic anemia with positive agglutination, mild hyperbilirubinemia and moderate hyperglobulinemia (Table 1). In subsequent analyses 2–3 weeks after presentation, neutropenia and many ghost erythrocytes were observed. Structures suspicious for *Mycoplasma haemofelis* were seen on occasional ghost erythrocytes (Figure 1a), but PCR analysis was not performed to confirm infection. Dysplastic nucleated erythrocytes (Figure 1b) on an increased background density suggestive of hyperproteinemia and hemoglobinemia (Figure 1c), as well as dysplastic platelets (Figure 1d), were seen on this occasion. Serum protein electrophoresis performed on days

83 and 513 indicated a broad peak in the late beta/gamma globulin region, which is obliterating the distinction between beta-2 and gamma globulin fractions. The sample was most consistent with a polyclonal gammopathy, suggesting immune stimulation, with an increase of 7.9% of beta globulin and 48.1% of the gamma globulin region. Saline agglutination tests done on 4/6 occasions were positive for agglutination (Table 1). Platelet clumping resulted in erroneous quantitative platelet counts, but platelet concentration appeared adequate in blood films, with macro-platelets occasionally observed (Table 1). However, on the final CBC from day 513, the platelet count was 66,000/ μl , with no platelet clumping noted.

The cat was sent home on day 513 and for the following 5 days treatment continued with already prescribed prednisone (1 mg/kg/day), for presumptive secondary immune-mediated hemolytic anemia, buprenorphine (0.015 mg/kg PO q8–12h), gabapentin (5 mg/kg PO q12h) for pain, amoxicillin/clavulanic acid (Clavamox 13.75 mg/kg PO q12h; Zoetis) for potential infection secondary to neutropenia, and famotidine (0.5 mg/kg PO q12h). Five days later, the owner described the cat as being unable to use the hindlimb, being in severe pain, unable to get in and out of its litter box, dragging itself around, vocalizing, etc. The cat had paraparesis with no overt pain on palpation on arrival at the time of euthanasia, although a few days prior, when seen on emergency, it was showing paraparesis with pain. Owing to the

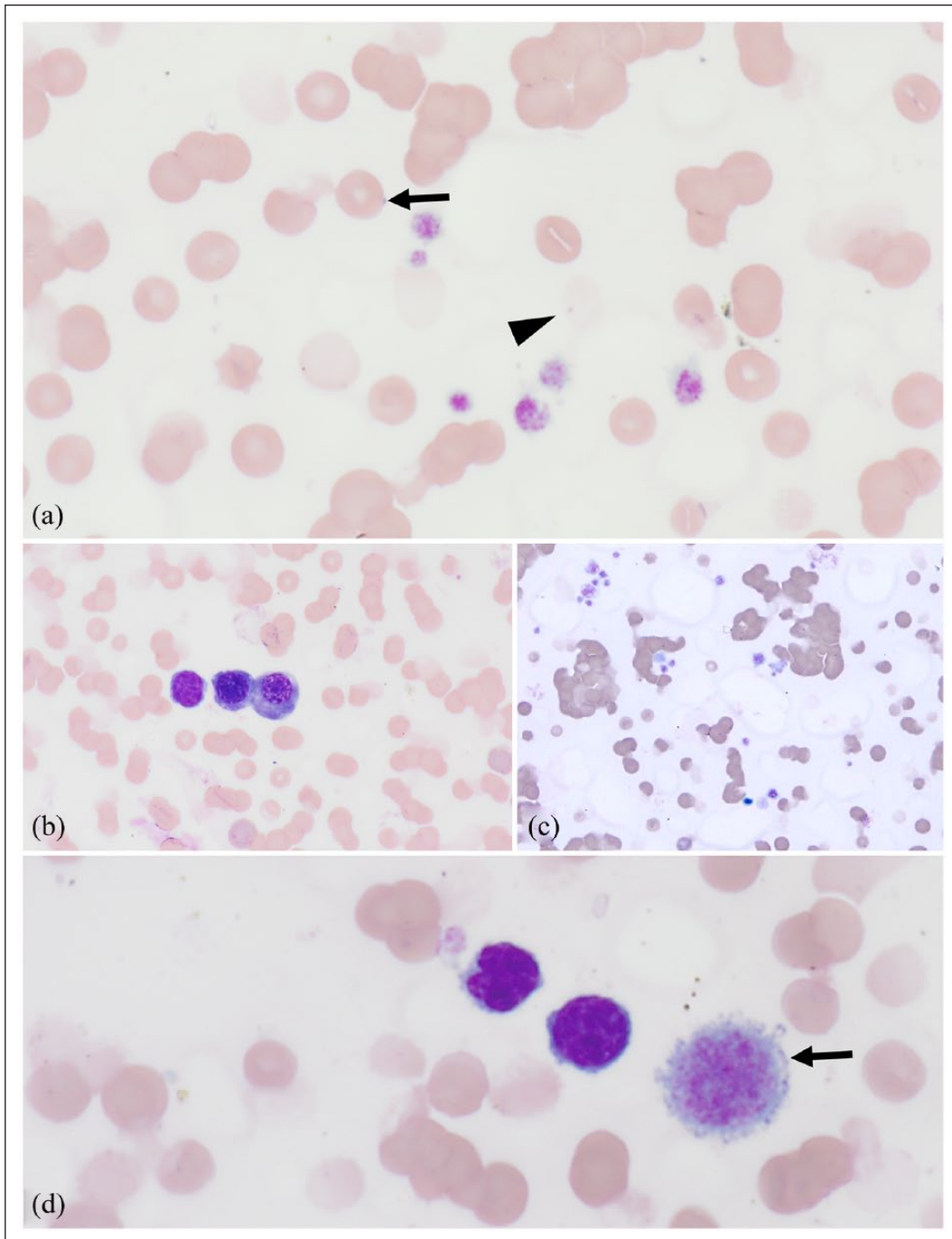


Figure 1 Blood film from the cat on day 508. (a) Many 'ghost' erythrocytes (arrowhead) are present. Structures suggestive of *Mycoplasma haemofelis* are seen on an erythrocyte (arrow) and on a ghost cell (arrowhead) (Wright's stain). (b) The nucleated cells consist of a lymphocyte on the left, and two nucleated erythrocytes (rubricyte) on the right. The nucleated erythrocyte on the far right appears dysplastic, with abundant cytoplasm (Wright's stain). (c) Marked agglutination. The increased background density is likely due to hyperproteinemia and hemoglobinemia (Wright's stain). (d) A giant dysplastic platelet (arrow) (Wright's stain)

ineffectiveness of treatment and the rapid deterioration of the cat, the owner elected humane euthanasia.

On post-mortem examination, the cat had pale mucous membranes. In the thoracic cavity, multiple smooth, dark-red, flat-to-slightly raised areas of tissue,

<1–3 cm wide, were seen bilaterally and subpleurally in the paracostal area of ribs 2–12 on the right and 2–11 on the left side, along the costochondral junctions, replacing intercostal muscle (Figure 2a). Similar dark red masses were seen in a paravertebral location on the lateral and

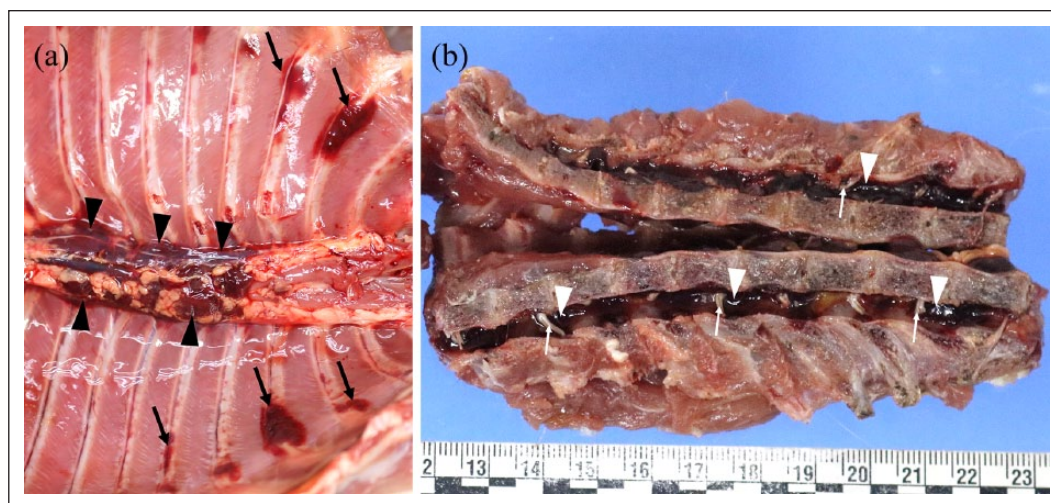


Figure 2 (a) The thoracic cavity contains multiple, dark-red, bilateral, subpleural paracostal masses (extramedullary hematopoietic [EMH] tissue) at the level of ribs 2–12 (arrows), as well as paraspinal/paravertebral EMH tissue (arrowheads). (b) Longitudinal section of the vertebral canal from T4 to T12 shows linear, focally extensive to circumferential extradural masses (arrowheads), sometimes around the spinal nerve roots (arrows)

ventral surfaces of thoracic vertebrae 4–11, with a linear distribution (Figure 2a). Dissection of the vertebral canal in the T4–12 region showed many paraspinal extradural masses that were linear focally extensive to circumferential, and often surrounded the spinal nerve roots (Figure 2b). Bone marrow from the femur and humerus was red. The liver was diffusely mildly enlarged, with a slightly raised yellow–red nodule, 1.5 cm in diameter, on the surface of the left medial lobe. The spleen was about three times the normal size (splenomegaly).

Microscopically, on hematoxylin and eosin stain, multifocal extensive extramedullary hematopoiesis (EMH) consisting mainly of erythroid precursors was found from the masses in the paravertebral area and within the spinal canal (extradural regions of the thoracic spinal cord) (Figure 3). On examination of the spinal cord and some spinal nerve roots at different levels, no histological evidence of compression was found. The masses near the costochondral junctions consisted of subpleural hematopoietic tissue, infiltrating and replacing the skeletal muscle was composed primarily of erythroid precursors and megakaryocytes, with occasional myeloid precursors and blood-filled sinuses (Figure 4a,b), consistent with EMH, and similar with the tissue in the paraspinal areas. Residual skeletal muscle fibers stranded in the center or at the periphery of the EMH lesion were multifocally vacuolated and degenerated. Evidence of EMH, consisting of megakaryocytes and erythroid precursors, was also seen in the alveolar capillaries of the lung, in the liver within hepatic sinusoids and red pulp of the spleen. The nodular area in the liver was well demarcated, non-encapsulated and hypercellular, representing EMH, similar histologically to the paravertebral and subpleural lesions, resulting in

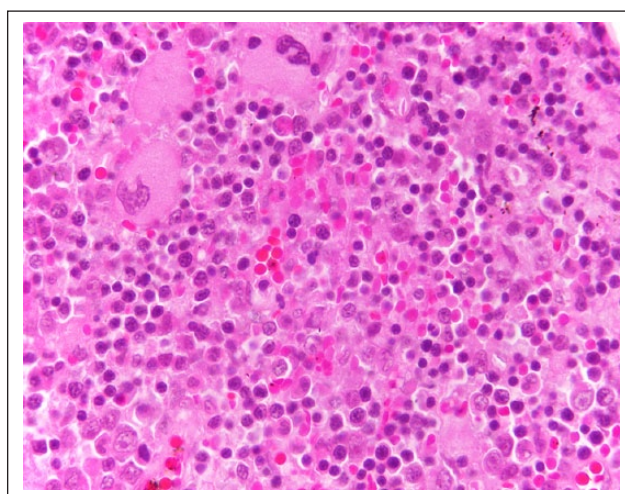


Figure 3 Extramedullary hematopoietic tissue from the epidural location (indicated by the arrowheads in the Figure 2b) with active hematopoiesis characterized mainly by erythroid precursors and megakaryocytes, with fewer myeloid precursors (hematoxylin and eosin)

compression atrophy of hepatocytes (supplementary Figure 1).

Bone marrow in sections of the ribs (Figure 4a,c) was hypercellular (estimated cellularity ~100%) but appeared notably different histologically than the EMH masses. A few small megakaryocytes with mature lobulated nuclei were noted. The estimated myeloid:erythroid ratio was approximately 4:1, with frequent early myeloid precursors, that comprised a mixture of myeloblasts and progranulocytes. Low numbers of myelocytes, metamyelocytes, and band and segmented neutrophils and eosinophils were observed. Erythroid precursors of all

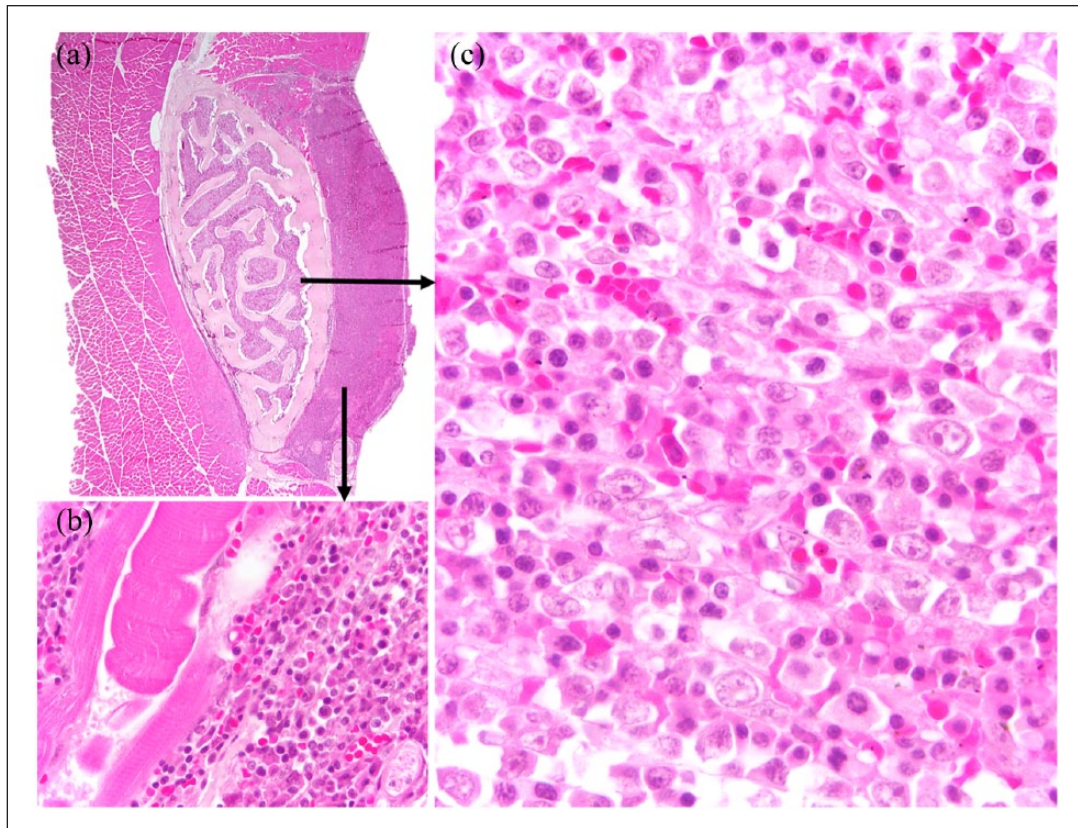


Figure 4 (a) Cross-section of rib, close to the costochondral junction: extramedullary hematopoietic (EMH) tissue infiltrating and replacing the skeletal muscle on the medial side subpleurally (right side of the image and detailed in [b] [arrow]). Bone marrow is hypercellular (detailed in [c] [arrow]). Hematoxylin and eosin (HE). (b) EMH tissue infiltrating and replacing the intercostal muscles consists primarily of erythroid precursors (similar to Figure 3). A vacuolated fragment of skeletal muscle fiber is also seen (HE). (c) Bone marrow from the rib is hypercellular and contains frequent early myeloid precursors (HE)

stages were present in low numbers, with primarily late-stage cells. The bone marrow interpretation was myeloid hyperplasia with a marked left-shift and erythroid and megakaryocytic hypoplasia. These findings, together with the cat's FIV positivity, persistent non-regenerative macrocytic anemia and neutropenia, were considered consistent with decreased erythrocyte and platelet production and ineffective granulopoiesis (probable myelodysplasia).

Discussion

We believe this is the first feline case of thoracic and paraspinal epidural non-hepatosplenic (NHS)-EMH masses. The cat was FIV positive with chronic macrocytic non-regenerative anemia and decreased bone marrow production with probable myelodysplasia and we suspect that the epidural EMH masses impinged on the caudal thoracic spinal cord. A neurologic clinical presentation resulting from EMH in a cat has not, to our knowledge, been reported previously. This is in contrast to what is known to occur in people, where spinal cord compression and neurologic signs due to NHS-EMH tissue is a rare but well-documented phenomenon.¹⁻¹⁰

The diagnostic approach to NHS-EMH in people includes a surgical biopsy from the masses (intrathoracic or paraspinal) in uncertain cases, which is an invasive risky procedure.¹¹ Previous reports in people with thoracic–spinal–epidural EMH have described similar hematopoietic cell types (erythroblast, megakaryocytes and myeloid cells) and features, as in this case.^{6,12} We were unable to obtain an ante-mortem bone marrow aspirate; however, post-mortem histologic findings supported myelodysplasia and decreased bone marrow production. Viral-induced myelodysplasia was considered most likely, but myelodysplasia due to other causes, myelodysplastic syndrome, pre-leukemia and acute myeloid neoplasia could not be ruled out. Acute myeloid leukemia was considered less likely because of maturation to progranulocytes and the lack of immature myeloid cells in blood or other tissues. Macrocytosis, megaloblastic rubricytes and macroplatelets suggested dysplasia affected these lineages as well, but a lack of a bone marrow aspirate precluded detailed precursor morphology. Myelodysplasia and decreased bone marrow production would explain the chronic macrocytic anemia, low platelet count and terminal neutropenia in this cat.

We ascribe the EMH in this cat to the chronic persistent anemia, exacerbated by hemolytic crisis, which may explain the erythroid predominance in the NHS-EMH foci. The anemia was likely the result of both decreased marrow erythropoiesis and hemolysis (suggested by the red blood cell agglutination, ghost erythrocytes, suspected *M haemofelis* infection and hyperbilirubinemia). *M haemofelis* is an epicellular parasite known to elicit an immune-mediated hemolytic anemia.¹³ FIV infection may have been responsible for the hyperglobulinemia, as previously described,^{14,15} as well as for the probable myelodysplasia.¹⁶ Previous reports have shown macrocytic hypochromic anemia in FIV-positive cats infected with *M haemofelis*,¹⁷ as well as in most cats with myelodysplastic syndromes.¹⁸ Macroplatelets were seen in three occasions in our case, and are reported to be a consistent finding in cats with myelodysplasia.¹⁹

EMH represents the development and formation of blood cells outside the medulla of the bone and is the result of underlying hematologic disease. Physiologic EMH, an essential process during fetal development in cats and dogs, takes place in hematopoietic organs such as liver and spleen prior to the maturation of bone.²⁰ These hematopoietic organs continue to provide favorable microenvironments for the induction of EMH in adult animals due to primary bone marrow failure associated with lympho- or myeloproliferative diseases, myelofibrosis or, more often, hematologic disorders that elicit an increased demand for mature blood elements, such as hemolytic anemia.^{13,21–25} In our case decreased production and ineffective granulopoiesis consistent with myelodysplasia was considered the major mechanism for most of the hematologic abnormalities and the trigger for the development of neutropenia.

Of the two previous reports linking an NHS-EMH lesion to a specific pathological condition in veterinary medicine (both in dogs), in one, EMH tissue was detected in the choroid plexus at the level of the fourth ventricle of five dogs presenting with neurologic signs/seizures.^{21,23} Only one of these five dogs had a moderate microcytic anemia, considered compatible with iron deficiency.²¹ In the other report, spinal cord compression occurred secondary to EMH in a dog, in which a mild thrombocytopenia was the only remarkable CBC finding.²⁶ NHS-EMH was also reported in two dogs in the mammary gland, associated with benign mixed mammary tumors.^{27,28} The current paradigm in veterinary medicine suggests that EMH lacks serious clinical or diagnostic implications, and is of no pathologic consequence to animals.²³ Contrary to this belief, and similar to what is seen in some cases in people,²⁹ we report a case of an FIV-positive cat with chronic non-regenerative anemia that developed hindlimb paresis attributed to an NHS-EMH lesion of the caudal thoracic spine.

NHS-EMH has been reported in many tissues, including lymph nodes, retroperitoneal tissue, the paravertebral area, adrenal gland, myocardium and, rarely, peripheral nerves, the cranial dura mater, and the spinal canal.^{3,29} In humans, one of the most common sites of NHS-EMH is the vertebral column of the thoracic region.²⁹ In a retrospective case series, 26% of 27 patients with an antemortem diagnosis of NHS-EMH had thoracic-paraspinal involvement.²⁹ Hematologic disorders such as chronic anemia were identified in the majority of these patients, with 63% of 27 patients developing site-specific symptoms related directly to the location of the NHS-EMH.²⁹ This pathogenesis is similar to our case, where a chronic anemia state resulted in NHS-EMH.

Another study showed up to 15% of EMH masses in people to have a paraspinal location causing a variety of neurologic symptoms as a consequence of spinal compression. Nevertheless, >80% of the human cases may remain asymptomatic, with the lesions being incidentally found using radiologic techniques.^{11,29} For neurologic signs to develop, EMH tissue must reach a large enough size to exert pressure on the spinal cord.⁵ The narrow diameter of the subarachnoid space and spinal canal in the area of the thoracic vertebrae predisposes the spinal cord to compression in this region such that even a small extradural mass may lead to neurologic dysfunction. This contrasts with other regions of the spinal cord, where masses must reach a larger size to exert sufficient pressure on the spinal cord to cause symptoms.¹¹ Neurologic signs in the cat in this case were likely due to extradural compression of thoracic spinal nerves by the paraspinal mass of EMH tissue, although in the histology samples of the spinal cord and spinal nerve roots examined we did not find evidence of spinal cord compression/degeneration.

Of the mechanisms proposed for the development of EMH in adjacent areas of the spinal cord and thoracic cavity, one hypothesis is that thoracic–spinal–epidural EMH results when hematopoietic tissue is extruded from the trabecular bone of the vertebral body, with circumferential involvement of the vertebrae. The hematopoietic tissue also may extend through the thin trabeculae at the proximal ends of the ribs, resulting in paracostal EMH in the thoracic cavity.^{5,6} Other theories suggest that remnants of embryonic hematopoietic cells within the epidural space are stimulated to proliferate as a result of anemia. Hematopoietic tissue is also proposed to develop from branches of intercostal veins,³⁰ or from embolic events.^{8,9} Regardless of etiology, the unique distribution of EMH lesions in this cat, extending from the paracostal region of the ribs, around the vertebrae, and forming an extradural mass, corresponded well to what has been described as thoracic–spinal–epidural EMH in people.

Limitations of our case include the lack of a bone marrow aspirate, lack of PCR confirmation of *M haemofelis*, lack of immunohistochemical characterization of bone marrow cells, lack of histological evidence of spinal cord compression in the examined tissues and lack of imaging (MRI/CT), a primary means of diagnosing paraspinal EMH in humans.^{5,6,11} We did, however, confirm histologically that the masses present epidurally, paravertebrally and subleurally consisted of hematopoietic tissue.

Conclusions


Thoracic–spinal–epidural EMH is a rare but important finding that should be considered in animals with severe hematologic or bone marrow abnormalities concurrent with neurologic signs of spinal cord compression.

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Supplementary material Supplementary Figure 1 illustrates EMH changes in the liver.

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