Case Report

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Neurolymphomatosis caused by T-cell lymphosarcoma in a cat: imaging description and treatment review

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Abstract

Case summary A 16-year-old domestic shorthair cat was evaluated for acute-onset right pelvic limb monoparesis localized to the sciatic nerve. MRI revealed a homogeneously contrast-enhancing, well-demarcated mass effacing the right sciatic nerve from its intravertebral origin to the end of the viewable field (mid-femur). Abdominal ultrasound revealed thickened small intestinal loops and enlarged mesenteric lymph nodes. Cytology of the small intestine was suggestive of lymphosarcoma. T-cell lymphosarcoma of the sciatic nerve and small intestines was confirmed with incisional biopsy. Treatment consisted of systemic chemotherapy with vincristine followed by the Wisconsin–Madison feline lymphosarcoma protocol, but despite treatment the patient neurologically worsened and was euthanized after 54 days.

Relevance and novel information We present herein one of the first descriptions of neurolymphomatosis in the domestic cat that included post-intravenous contrast MRI. Treatment options based on recommendations for people with neurolymphomatosis include systemic chemotherapy, intrathecal chemotherapy and/or localized radiation chemotherapy. The authors recommend that all cats be screened for concurrent non-neuronal areas of lymphosarcoma before undergoing treatment for neurolymphomatosis, regardless of clinical signs.

Keywords: Lymphosarcoma; sciatic nerve; infiltrative; neurolymphomatosis; T cell; mononeuropathy; neuropathy

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Introduction

Neurolymphomatosis (NL) is an uncommon condition seen across multiple species (including people, domestic dogs and cats, and bovine and avian species), characterized by infiltration of nerve(s) with neoplastic lymphocytes.[1–21] Though the condition has only recently been recognized as NL in the veterinary literature, reports of neoplastic lymphocytic nerve invasion have been documented in animals.[2–9,15–19]

The patterns of NL recognized in people, in decreasing occurrence, include painful polyneuropathy, cranial neuropathy, non-painful polyneuropathy and mononeuropathy, with sciatic neuropathy as the most common mononeuropathy.[13] MRI of NL shows enlarged nerves, which enhance with gadolinium administration.[13] Clinical signs of NL are appreciated prior to a diagnosis of non-Hodgkin lymphoma in 28% of affected people. Primary

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and secondary forms of non-Hodgkin lymphoma are recognized as manifestations of NL in humans.[14]

This report represents one of the first high-field MRI – including post-intravenous contrast administration imaging – description of NL in the domestic cat.

Case description

A 16-year-old spayed female domestic shorthair cat was evaluated for a 9 day history of progressive right pelvic limb lameness. The patient was receiving medication for well-controlled hyperthyroidism (methimazole 2.5 mg PO q24h). A complete blood count, serum biochemistry and total thyroxine level performed by the primary veterinarian prior to referral were within normal reference intervals. Retroviral screening (feline leukemia virus [FeLV] and feline immunodeficiency virus [FIV]) was negative.

Physical examination abnormalities included a grade 2/6 left parasternal systolic murmur and a thin body condition (grade 2/5). Neurologic examination revealed normal cranial nerves, segmental reflexes and postural reactions (hopping and proprioception) on all limbs but the right pelvic limb. Postural reactions and sciatic nerve reflexes (cranial tibial, gastrocnemius and withdrawal reflexes) were diminished in the right pelvic limb, but the patellar reflex (femoral nerve) remained intact. The patient had difficulty ambulating on the right pelvic limb and was only able to advance it with flexion of the hip (femoral nerve). In periods of weight bearing, the right hock would rest in hyperflexion, resulting in a plantigrade stance. Mild pain was elicited when palpating along the lumbar spine. Anal tone was intact, as was urinary and bowel control. Combined neurologic findings indicated localization to the right sciatic nerve root branches or the sciatic nerve proper.

Initial diagnostics included Doppler analysis of both femoral and pedal arteries (to confirm positive blood flow and to evaluate blood pressures) and electrocardiography; both were within the normal ranges. Thoracic radiographs revealed no nodular pulmonary metastatic neoplasia. An echocardiogram revealed mild hypertrophy of the left ventricular free wall.

Non-contrast and contrast-enhanced multiplanar MRI of the caudal lumbar spine and pelvis was performed under general anesthesia using a 3 Tesla magnet (Signa Excite HDx Magnet; General Electric) and a spine coil (PA CTL Spine Coil; USA Instruments). The patient was administered gadolinium (0.1 mmol/kg, 0.048 mmol/lb; total dose 0.5 ml [Omniscan; GE Healthcare]) IV for contrast imaging.

Dorsal planar sequences demonstrated a large mass (6.4–9 mm wide) invading the right sciatic nerve. In comparison, the left sciatic nerve measured only 2.9–3.7 mm in width at equivalent locations. The mass appeared isointense to the spinal cord on T1-weighted images and hyperintense to the surrounding soft tissue and fat on short tau inversion recovery images. The mass was homogeneously, avidly and uniformly enhanced by contrast administration. Multiplanar imaging localization identified the mass as stemming from the right lateral aspect of the conus medullaris, originating at the L6–7 vertebral space and traveling caudally within the vertebral canal. It exited through both the L7–S1 and S1–2 foramen, where it converged medially to the iliac wing and ventral to the sacrum. The mass continued dorsally over the iliac wing at the greater ischiatic notch and ventrocaudally, caudal to the acetabulum to travel distally following the femur (Figure 1). Comparisons with the unaffected left sciatic nerve revealed the mass to be infiltrative of and following the same route as the sciatic nerve. Ultrasonography-guided aspiration of the mass was unsuccessful in yielding a diagnosis.

Abdominal ultrasound was performed to investigate for primary sources of neoplasia and/or other metastatic disease. The mesentery was hyperechoic, and the mesenteric lymph nodes were markedly hypoechoic and enlarged. Diffuse jejunal and ileal muscularis layer thickening was seen, with one loop of small bowel demonstrating a loss of normal wall layering and severe thickening (up to 5 mm), allowing for fine-needle aspiration. Cytology was suggestive of lymphoma.

After consideration of all findings, surgical exploration and biopsies were recommended. Incisional biopsies of the small intestines, liver, pancreas, mesenteric lymph nodes and right sciatic nerve were obtained. Histopathologic abnormalities seen included neoplastic lymphocytic infiltration of the mesenteric lymph nodes, walls of all segments of small intestine and the right sciatic nerve. The cells infiltrating the right sciatic nerve were medium-sized round cells with scant cytoplasm, oval-to-round nuclei with 1–2 prominent nucleoli and coarsely stippled chromatin. The mitotic rate is three mitotic figures per 10 high-powered fields (Figure 2). Immunohistochemistry revealed diffuse positive staining of the neoplastic lymphocytes by CD3 and absence with CD79, confirming the presence of T-cell lymphosarcoma.

Owing to the multicentric nature of our patient's disease, systemic chemotherapy was chosen as the treatment modality. Vincristine (0.5 mg/m^2 IV once; Hospira) was followed with the Wisconsin–Madison Feline Lymphoma Chemotherapy Protocol.[22] The patient progressed to paraplegia 54 days post-treatment and was humanely euthanized.

Discussion

Differential diagnoses for acute-onset paraparesis or pelvic limb monoparesis in cats include thromboembolic disease, demyelinating disease (diabetes mellitus or peripheral neuropathies), spinal or vertebral neoplasia

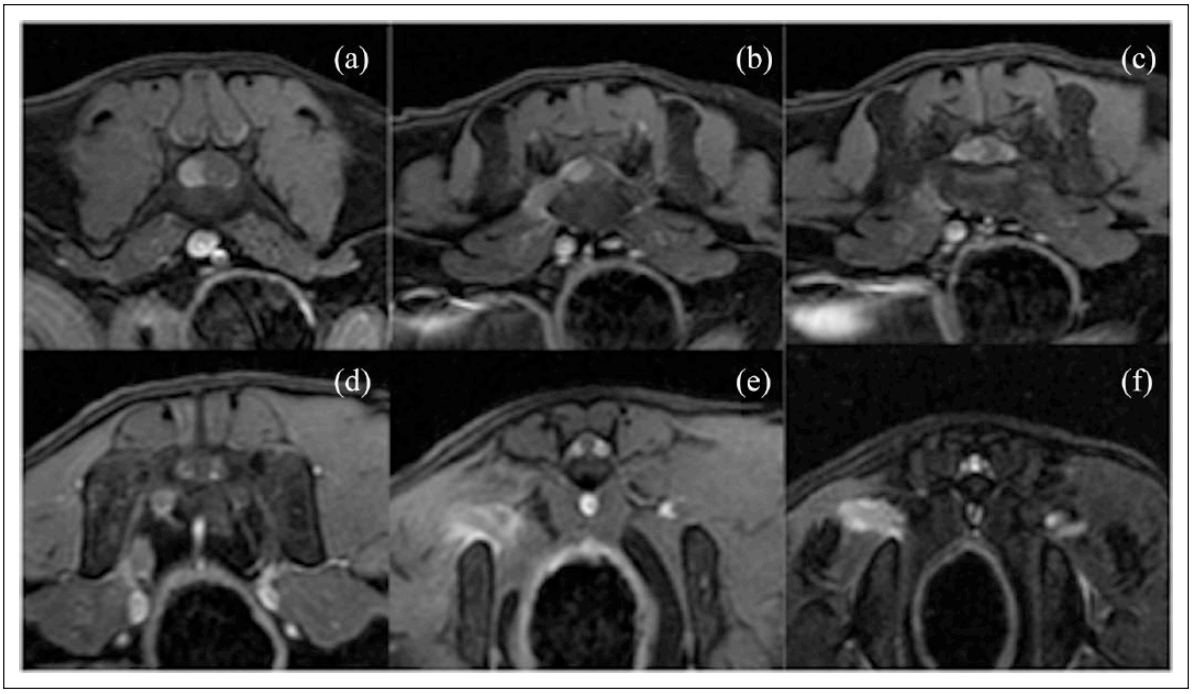

Figure 1 Sequential transverse MRI ([a–e] T1 Fat Saturated (FS) + Contrast and [f] T2 FS) starting at (a) caudal L6, (b) L7–S1 foramen, (c) S1, (d) S1–2 foramen and (e,f) caudal ilial wing, demonstrating (a–e) strong contrast enhancement of the mass and (f) T2 hyperintensity. The mass occupied approximately 40% of the width of the spinal canal at the (b) L7–S1 junction, causing moderate compressive myelopathy and leftward deviation of the spinal cord and cauda equina. (a) The walls of loops of small bowel included in the imaging field were subjectively noted to be thickened

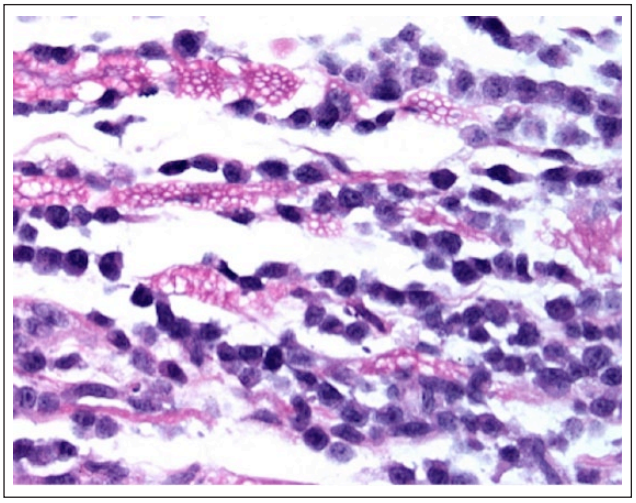

Figure 2 Haematoxylin and eosin staining (× 40) of the right sciatic nerve, longitudinal section. Neoplastic lymphocytes are seen dissecting along the perineurium, widely separating nerve fibers. In some foci, neoplastic lymphocytes tracked along demyelinated axons

(eg, lymphosarcomas [LSAs], meningiomas, osteosarcomas, glial cell tumors), infectious myelitis (toxoplasmosis, mycoses, FeLV/ FIV, feline infectious peritonitis), and, less commonly, fibrocartilaginous embolisms, intervertebral disc protrusions or herniations, and trauma.[23–26] NL is a less frequently discussed differential diagnosis, the biology of which is important to understand in order to diagnose and treat affected patients successfully. Reported sites of neoplastic lymphocytic invasion of nerves include the brachial plexus, sciatic and femoral nerves, cranial nerves (including the trigeminal nerve), sympathetic nerves, vagus nerve and other spinal nerves.[4–11,15,16,19] Our findings of T2 hyperintensity and T1 hypointensity with strong contrast enhancement agree with reports of NL in people and previously reported central nervous system (CNS) LSA in cats.[13–16,19,27,28]

In people, cerebrospinal fluid (CSF) abnormalities include elevated proteins (61%) and elevated total cell counts (44%); cytologic findings include malignant lymphocytic cells in spinal fluid (40%) or cells with suspicious cytologic changes (13%).[14] CSF collection was not performed in the patient of this report but may have enabled diagnosis in a manner less invasive than surgical biopsies.

Though LSA is the most common secondary tumor of peripheral nerves in cats, treatment of NL is rarely discussed in veterinary literature.[5] This can be partially explained when the previous case reports of NL in domestic animals are examined further; the previous reports dealt with post-mortem evaluations and, as such, treatment protocols were not evaluated. Treatment guidelines can therefore be tentatively constructed from

treatment protocols in people, those in canine neural lymphoma and protocols for solitary LSA in cats.

Treatment for NL in people is aimed at a systemic treatment owing to the likelihood that NL is an accompaniment of non-Hodgkin lymphoma. Common chemotherapeutic treatments include methotrexate, cytarabine, rituximab or various combinations thereof.[12–14] Intrathecal chemotherapy and localized radiation therapy have also been employed.[13,14] There are reports of excellent local control in patients with mononeuropathies who had chemotherapy in combination with radiation therapy.[13] Overall survival time in people is 10 months, with a 12 month survival of 46% and a 36 month survival of 24%.[14] People with primary NL tend to live longer than those with secondary NL.[14]

Canine NL is reported as uncommonly as in cats, with only four case reports published.[1–3,18] The longest survival time of 53 days was described after treatment with a combination of systemic chemotherapy with lomustine and radiation therapy in a dog with T-cell neurolymphoma of the radial nerve.[18] Treatment protocols described for generalized canine CNS lymphoma are surgical decompression, systemic chemotherapy and radiation therapy. Chemotherapy appeared to benefit dogs most compared with other modalities; however, the dog with the longest survival time (1939 days) received all three treatment modalities. Evaluation of lymphoma should include flow cytometry, immunohistochemistry and clinical staging, as these assessments lead to a better understanding of the appropriate treatment modalities for the different types of lymphoma.[17]

As feline NL and its treatment are rarely reported, treatment guidelines have been constructed from those described for a solitary feline LSA. In one recent case report of two cats with NL of spinal nerves, both reported positive for CD20, treatment with the Wisconsin–Madison protocol and palliative prednisolone had survival times of 100 days and 231 days, respectively.[19] In cats, solitary LSA (retrobulbar, mediastinal, mandibular, maxillary and subcutaneous) treated with radiation therapy with or without steroids and chemotherapy had mean complete remission time of 861 days in 80% of patients (n = 8/10).[29] The longest survival time was found after treatment with a combination of systemic chemotherapy (vincristine, cyclophosphamide, methotrexate, doxorubicin, prednisone, L-asparaginase and cytosine arabinoside) and radiation (3–4 doses of 4–8 Gy/treatment).[30] Median survival time in this group was 125 days (range 40–210 days). In another group of cases with spinal epidural LSA, complete remission was achieved with chemotherapy alone for 98 days in 3/10 animals; partial remission was noted in an additional 3/10 animals for 42 days. Surgical decompression in one cat extended complete remission to 434 days.[31] It should be noted that in a third study with similar populations, 3/4 cats were euthanized within 5 months of diagnosis after treatment with local spinal radiation followed by systemic chemotherapy due to systemic relapse.[32]

Even without the presence of gastrointestinal signs, the patient of this report was diagnosed with an intestinal LSA; this would indicate this patient's NL was of secondary origin. Had no extraneural involvement been found (primary NL), treatment would have consisted of local radiation therapy with chemotherapy ± radical surgery. Perhaps local radiation therapy in addition to systemic chemotherapy would have slowed disease progression, leading to a longer survival period in this patient.

Conclusions

NL should be considered as a differential diagnosis for any cat presenting with a mono- or polyneuropathy. It is important to recognize this disease not only as a differential for neuropathies in cats and dogs, but also as a differential for animals with known lymphosarcoma and neuropathies, which might otherwise be overlooked as a paraneoplastic neuropathy or neuropathy secondary to chemotherapy administration.[33,34]

This is the first published contrast-enhanced MRI description of a peripheral nerve affected with NL in a cat. Prior to treatment, these cats should be screened for further areas of LSA involvement, even in the face of no outward clinical signs, with imaging of the thorax and abdomen, as well as CSF analysis. Treatment depends on the areas affected, but should include systemic and/or intrathecal chemotherapy and localized radiation therapy to maximize survival times.

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