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Authors

Massie, Anna M

Skorupski, Katherine

Vernau, William

et al.

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CASE REPORT

Large T-cell extradural lymphoma with concurrent marked cerebrospinal fluid eosinophilia in a dog

Anna M. Massie[1] | Katherine Skorupski[2] | William Vernau[3] | Ehren McLarty[2] | Rachel V. Brady[4] | Karen M. Vernau[2]

[1]Department of Clinical Sciences and Advanced Medicine, University of Pennsylvania School of Veterinary Medicine, Philadelphia, Pennsylvania, USA

[2]Department of Surgical and Radiological Sciences, University of California School of Veterinary Medicine, Davis, California, USA

[3]Department of Pathology, Microbiology and Immunology, University of California School of Veterinary Medicine, Davis, California, USA

[4]Cell and Molecular Biology Graduate Program, Colorado State University, Fort Collins, Colorado, USA

Correspondence
Karen M. Vernau, One Garrod Drive, Davis, CA 95616, USA.
Email: kmvernau@ucdavis.edu

Abstract

A 3-year-old male pit bull terrier was presented for a 4-day history of progressive tetraparesis and cervical pain. Magnetic resonance imaging confirmed an extradural mass within the left lateral vertebral canal extending from caudal C5 to mid-T2. Lumbar cerebrospinal fluid (CSF) demonstrated marked (90%) eosinophilic inflammation. A C6-7 dorsal laminectomy and C7-T2 left hemilaminectomy were done, with gross disease remaining. Histopathology revealed a large T cell lymphoma with marked eosinophilic infiltration. The dog underwent CHOP-based chemotherapy with resolution of clinical signs, with a similar course of therapy performed at recurrence 37 months after initial presentation. The dog was euthanized 39 months after presentation for multiorgan failure secondary to neutropenic sepsis and aspiration pneumonia. This represents a positive long-term response to multimodal treatment of extradural T-cell lymphoma within the vertebral canal associated with a marked CSF eosinophilia.

KEYWORDS
ataxia, CHOP, decompression, neoplasia

1 | INTRODUCTION

Lymphoma is the most common extradural soft tissue spinal tumor in dogs[1] and most frequently presents as a component of multicentric or systemic disease.[2] Primary CNS lymphomas are rare (2.7%) but occur in low numbers and with poor long-term outcome.[2,3]

2 | CASE DESCRIPTION

A 3-year-old, 28 kg, male pit bull terrier was referred to the University of California-Davis for 4-day history of progressive difficulty walking, becoming acutely stiff followed by trembling in the pelvic limbs. At original presentation, complete blood count (CBC) and chemistry panel were normal, and an unknown antibiotic and analgesic were prescribed. Three days later, the dog had progressive difficulty walking in the thoracic limbs and was cowering and yelping. An unknown dose of corticosteroids PO was prescribed, and the dog progressed to being painful on neck palpation. The dog had no clinical signs preceding presentation, was up to date on vaccinations, and had no travel history or known tick exposure.

Upon presentation, vital signs were within normal limits. On neurological examination, the dog was tetraparetic, weakly ambulatory with the thoracic limbs more severely paretic than pelvic. Proprioceptive positioning was delayed in the thoracic limbs, absent in the pelvic limbs. All segmental reflexes were normal, with an incomplete flexor reflex in the thoracic limbs. There was no palpable spinal

Abbreviations: CSF, cerebrospinal fluid; CBC, complete blood count; UW-25, 25-week University of Wisconsin-Madison.

pain, though intermittent fine head tremors were assessed as a manifestation of pain. When resting, he maintained a "downward dog" posture. A C6-T2 myelopathy was diagnosed. Urinalysis and thoracic radiographs were normal. Abdominal ultrasound showed a diffusely enlarged, homogeneous, mildly mottled spleen that was considered likely because of passive congestion and not cytologically sampled. Vertebral column radiographs showed enlargement of the caudal cervical articular processes.

MRI of the cervical vertebral column showed an extradural mass within the left lateral vertebral canal extending from caudal C5 to mid-T2 (Figure 1). The mass was mildly hyperintense on T2W sequences, isointense to muscle on T1W sequences, and diffusely contrast-enhancing. From mid-C6 to mid-T1, the mass caused marked left lateral compression of the spinal cord with complete loss of the subarachnoid and epidural space. The left C8 nerve root was enlarged and contrast enhancing. Diffuse meningeal enhancement was noted from C1-T3 (Figure 2). Lumbar cerebrospinal fluid (CSF) analysis showed mildly increased erythrocytes (397 rbcs/uL, RI 0/uL), markedly increased nucleated cell count of 643 cells/uL (RI < 4 cells/uL), 90% of which were eosinophils, along with rare erythrophagia and occasional hemosiderin containing macrophages. The CSF was interpreted as marked eosinophilic inflammation with hemorrhage with no identifiable etiology (Figure 3A).

A C6-7 dorsal laminectomy and C7-T2 left hemilaminectomy was performed. The spinal cord was markedly compressed on the left lateral aspect by an indistinctly demarcated white, friable, soft tissue adherent to the spinal cord ventrally and extending into the T1 nerve roots. The C8 nerve root was not observed. The mass was debulked with visible decompression of the spinal cord but could not be safely removed in its entirety ventrally because of spinal cord adhesions. Samples were submitted for bacterial culture and sensitivity, cytology, and histopathology. The dog was administered enrofloxacin (10 mg/kg IV q24h), ampicillin and sulbactam (50 mg/kg IV q8h), metronidazole (7.5 mg/kg IV q8h), pantoprazole (1 mg/kg IV q8h), and dexamethasone SP (0.1 mg/kg IV q24h).

Cytology of the mass showed marked mixed, predominantly eosinophilic, inflammation with reactive fibroplasia and a population of large immature appearing lymphocytes (Figure 3B). Some of the large lymphocytes had cytoplasmic fine pink granules. The presence of marked concurrent inflammation precluded definitive cytological diagnosis. Compounded L-asparaginase (Diamondback Drugs, Scottsdale, Arizona) was administered (10 000 IU SQ) 24 hours post-operatively; antibiotics and pantoprazole were discontinued. The dog improved neurologically and was discharged 4 days post-operatively, strongly ambulatory tetraparetic, receiving prednisone (0.5 mg/kg PO q12h) and gabapentin (10 mg/kg PO q8h).

Histopathology revealed a densely cellular unencapsulated mass composed of sheets of round cells that had large ovoid nuclei with finely granular chromatin and a single nucleolus. Cells had variably distinct cell borders and scant eosinophilic to amphophilic cytoplasm. Anisocytosis and anisokaryosis were moderate. The mass was infiltrated by large numbers of eosinophils that variably obscured the round cells interpreted as T-cells based on CD3 immunoreactivity. Neoplastic cells were immunonegative on CD20 immunohistochemistry. Molecular clonality PCR identified a clonal T-cell receptor gamma (TRG) gene rearrangement, confirming T cell lymphoma given the morphologic findings. Bacterial culture was negative.

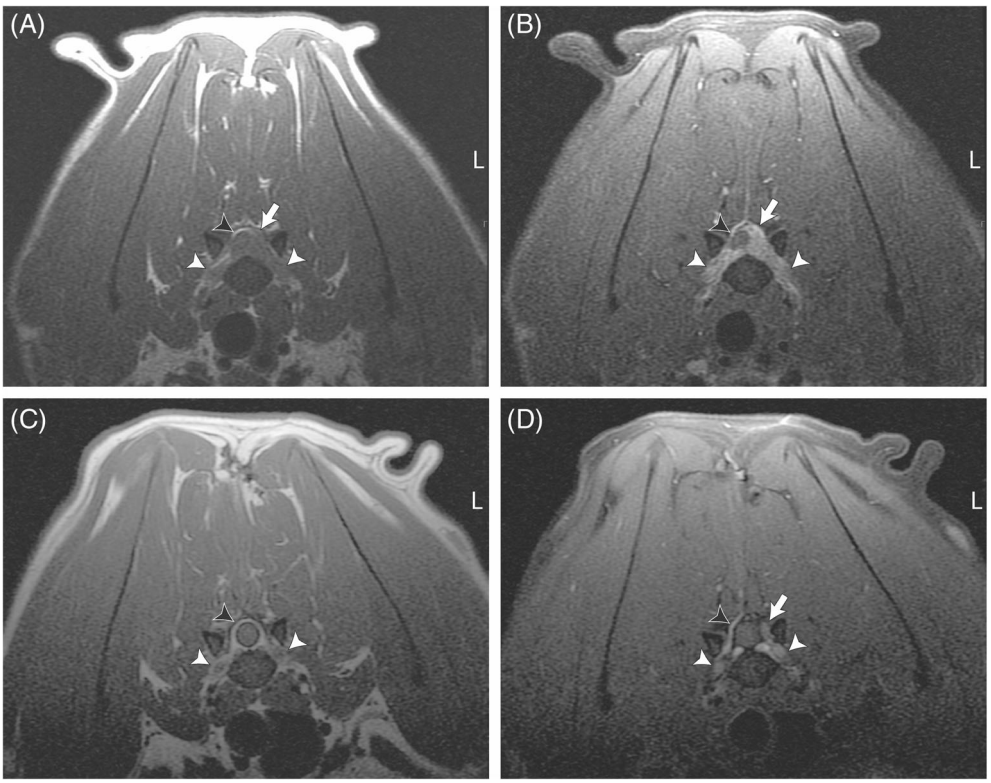

FIGURE 1 Pre-contrast (A and C) and post-contrast (B and D) T1-weighted transverse MRI images of the vertebral column at the level of the C8 nerve roots before (A and B) and after (C and D) surgery. Before surgery there is an extensive, contrast-enhancing extradural mass (white arrow) in the left vertebral canal with contrast enhancement of the C8 nerve roots (white arrowheads) and enlargement of the left C8 nerve root. The spinal cord (black arrowhead) is compressed and displaced toward the right. Six months after surgery there is a smaller amount of contrast-enhancing tissue in the left vertebral canal (white arrow), the left C8 nerve root is reduced in size, and the spinal cord is not displaced or compressed.

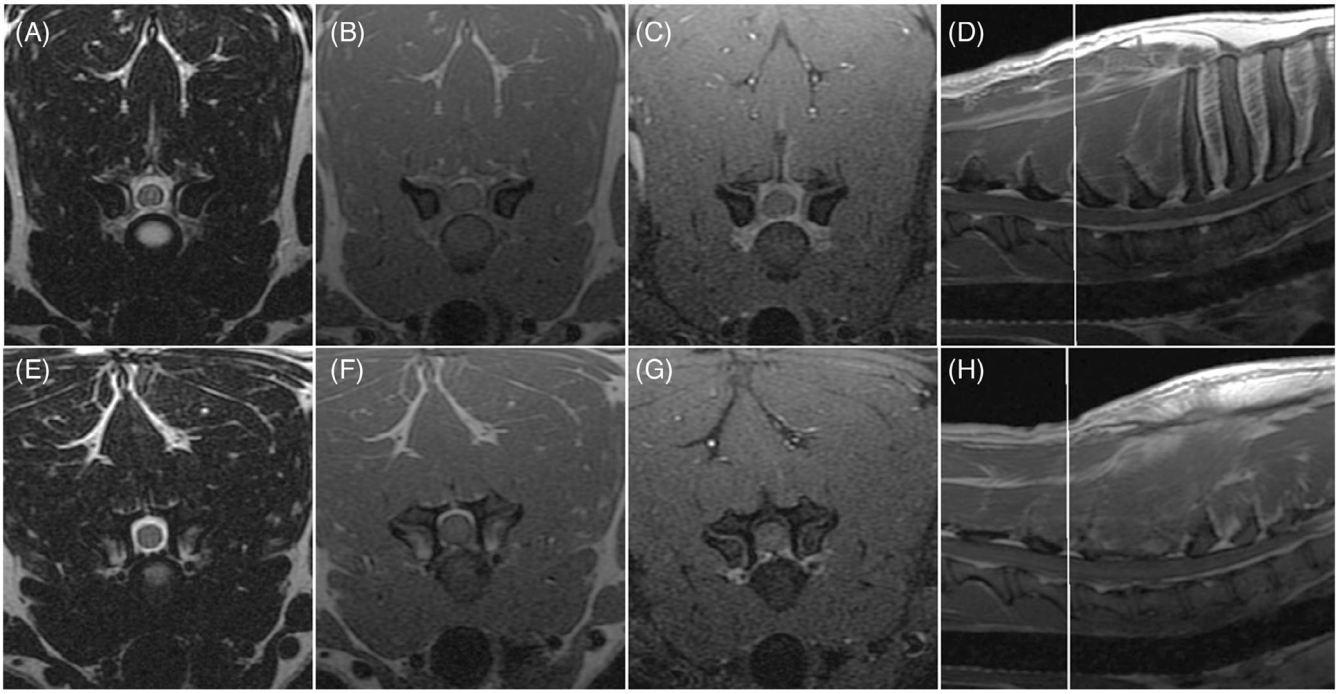

FIGURE 2 Images A to D demonstrate diffuse meningeal enhancement on initial presentation which is not seen in the 6-month follow-up scan (images E-H). From left to right images include T2W, T1W, and T1W post-contrast fat-saturated transverse and T1W post-contrast sagittal.

The dog was presented 2 days after discharge ambulatory with mild tetraparesis. A complete blood count showed a stress leukogram and slight basophilia (117 basophils/uL, RI 0-50). Serum chemistry panel revealed mild hypochloremia (105 mmol/L; 108-116) and increased ALT (218 IU/L; 21-72), AST (56 IU/L; 20-49), ALP (194 IU/L; 14-91), and GGT (11 IU/L; 0-5). Peripheral eosinophil concentration was within normal limits. A modified version of the 25-week University of Wisconsin-Madison (UW-25) chemotherapy protocol was initiated with substitution of cytosine arabinoside for cyclophosphamide in all 4 cycles. Cytosine arabinoside was started at 500 mg/m^2 in a 6-hour infusion and dose escalated in later cycles to 600 mg/m^2. Adjunctive radiation therapy was discussed declined. Prednisone was decreased to 0.36 mg/kg PO q12h.

Two weeks post-operatively, the dog was ambulatory with mild tetraparesis. Prednisone was decreased to once daily and gradually tapered until discontinuation after 4 months. All neurologic deficits resolved 4 weeks post-operatively. The scheduled chemotherapy protocol was continued to completion.

Six months after surgery, the dog started having episodes of muscle fasciculations. Neurologic examination revealed delayed proprioceptive positioning in the pelvic limbs and decreased nonpainful range of motion of the neck. Deficits were localized to T3-L3, though C6-T2 myelopathy could not be ruled out. Thoracic radiographs were normal. Abdominal ultrasound revealed mild asymmetry of the medial iliac lymph nodes with an enlarged right internal iliac lymph node (5.8 mm) and unchanged splenomegaly. The lymph nodes were deemed not accessible for cytologic sampling, and the owners declined splenic aspirate. CBC and serum chemistry revealed mild eosinophilia 1932/µL (RI 0-1500/µL).

A recheck MRI was performed 6.5 months post-operatively. No abnormalities were noted on neurological examination. On MRI, there was a small amount of T2W hyperintense, homogenously contrast-enhancing extradural material in the left dorsal aspect of the vertebral canal at C7-T1 as well as extending slightly down the left C7-T1 intervertebral foramen (Figure 3). This resulted in mild left dorsal flattening of the spinal cord without displacement of the spinal cord or loss of the signal from CSF/epidural fat. The previous meningeal enhancement was resolved. Lumbar CSF showed slight mixed inflammation with an eosinophilic component. The owner declined additional chemotherapy, and recommended recheck examinations were not pursued.

Fifteen months later (22 months after initial presentation) the dog was presented after a 1-month history of progressive stiffness and difficulty ambulating. He was bright and alert with diffuse temporal muscle atrophy. He was nonvisual OD with a lack of direct pupillary light reflex. The dog was non-ambulatory with marked paraparesis and normal segmental reflexes in all limbs. Proprioceptive positioning was absent in the pelvic limbs, normal in the thoracic limbs. There was no pain on spinal palpation. Localization was multifocal CNS disease including the right optic nerve and a T3-L3 myelopathy.

CBC showed mild anemia (HCT 37.3%; RI 40-55), neutrophilia with left shift (neutrophils 25 583/uL; 3000-10 500, bands 2516/uL; rare, metamyelocytes 419/uL; 0), and eosinophilia (6291/uL; 0-1500). Repeat thoracic radiographs, abdominal ultrasound, MRI, and CSF tap were declined for financial reasons, and the owners elected to restart chemotherapy for presumed lymphoma relapse. Asparaginase (10 000 IU SQ) and cytosine arabinoside (600 mg/m^2 over 5 hours) were administered, and prednisone (0.75 mg/kg PO q24h) was

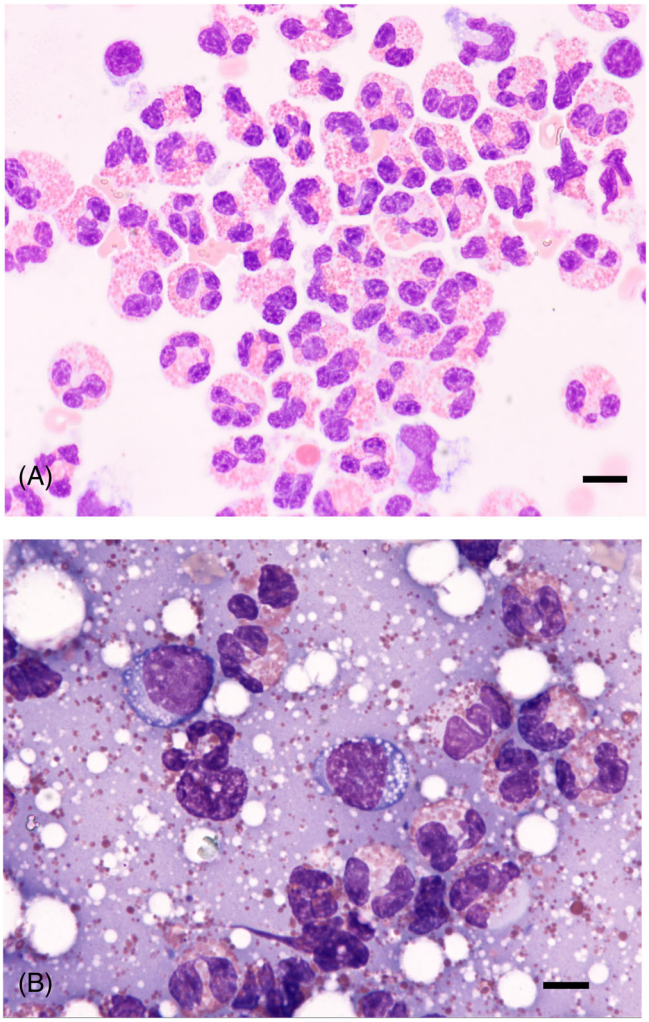

FIGURE 3 (A) Cerebrospinal fluid from a 3-year-old male intact pit bull terrier that has a markedly increased nucleated cell count of 643 cells/uL (RI < 4 cells/ul), 90% of which are eosinophils. (B) Impression smear of a large, compressive extradural spinal cord mass in the same dog. Cells are predominantly eosinophils, along with numerous free eosinophil granules throughout the background. Scattered throughout are also large, immature appearing, neoplastic lymphocytes (2 in this image) that have moderate volumes of deep blue, variably vacuolated cytoplasm, and sometimes fine pink cytoplasmic granules. Wright-Giemsa stain, scale bars = 10 µm.

prescribed. Treatment was continued with the modified UW-25 chemotherapy protocol. The dog improved with the ability to ambulatory with moderate ataxia. He remained nonvisual OD. Chemotherapy was discontinued 26 months after initial presentation, 19 weeks after suspected relapse, at the completion of the prescribed chemotherapy protocol with static clinical signs.

Sixteen weeks later, the dog presented for evaluation of a swollen right eye. Neurologic exam findings remained unchanged. Ophthalmologic exam revealed right-sided severe conjunctival hyperemia and chemosis, diffuse cellular infiltration of the cornea, marked corneal edema, and optic nerve atrophy. Findings were consistent with ocular lymphoma; sampling was declined. A third round of the modified UW-25 protocol was considered but because of financial constraints a single-agent protocol was instead elected. CCNU (lomustine, 65 mg/m^2), prednisone (topical and oral), and Denamarin (Nutramaxx Laboratories) were prescribed. Conjunctival and corneal changes resolved. CCNU was discontinued after 3 doses 3 weeks apart because of progressive increase in serum activity of liver enzymes.

Thirty-seven months after initial presentation, the dog's ataxia again worsened and chemotherapy was re-initiated with an alternating protocol of CCNU (65 mg/m^2) and DTIC (dacarbazine, 1000 mg/m^2). The dog's neurologic signs improved mildly but he experienced episodes of severe neutropenia (VCOG-CTCAE grade 4) and thrombocytopenia requiring hospitalization after the first dose of DTIC and the second dose of CCNU. Bone marrow dysfunction from chronic chemotherapy and/or infiltrating lymphoma was suspected. Bone marrow aspirate was not performed. Thirty-nine months after initial presentation, the dog was euthanized because of multiorgan failure secondary to neutropenic sepsis and aspiration pneumonia. Necropsy was declined.

3 | DISCUSSION

This report documents positive long-term treatment response in a dog with cervicothoracic extradural T-cell lymphoma and marked CSF eosinophilia. The neoplastic lymphocytes were not present in the CSF. 68% of dogs with CNS lymphoma were diagnosed by CSF assessment, including 71% of T-cell lymphoma cases.[2] In contrast, CSF eosinophilia secondary to lymphoma is rarely reported, with CSF eosinophilia occurring most often with idiopathic, parasitic, or fungal etiologies.[4-8] Eosinophilia or regional eosinophilic infiltration is associated with lymphoma in dogs.[9-13] Intestinal T-cell lymphoma can be associated with regional eosinophilic infiltration[10] and hypereosinophilia.[11] Eosinophilia occurs with splenic and multicentric B-cell lymphoma.[12,13]

Paraneoplastic hypereosinophilia of peripheral blood and CSF is reported in 1 dog with spinal extradural T-cell lymphoma.[9] Like the dog presented here, this was a young (3-year-old) large breed dog with rapidly progressive tetraparesis. This dog had mild eosinophilic CSF pleocytosis. In contrast, the lumbar CSF sample collected from the dog reported here had marked pleocytosis that included 90% eosinophils but without peripheral eosinophilia. Peripheral eosinophilia was, however, present in multiple follow-up visits and often associated with relapsing clinical signs. Though the previously reported dog initially clinically improved following surgery and chemotherapy, acute neurologic deterioration occurred 18 days later and the dog was euthanized. In our case, the dog surviving 39 months after initial diagnosis. Whether development of peripheral eosinophilia was evidence of further progression of primary disease or development of multifocal disease is unknown. In humans, eosinophilic CSF secondary to lymphoma is infrequently reported with T-cell lymphomas,[14-23] and is a rare but treatable complication of Hodgkin lymphoma.[24] This phenomenon is considered to most likely be secondary to cytokine release by the neoplastic lymphocytes.[23,25-27] Peripheral eosinophilia is used as a diagnostic or therapeutic marker in a variety of other neoplastic conditions.[28,29]

This dog's lymphoma is presumed to represent primary CNS lymphoma because of the primary abnormalities at time of diagnosis. Secondary CNS lymphoma is diagnosed when CNS involvement occurs concurrently with disseminated disease. Primary CNS lymphoma is rare in dogs, and most often with B cell.[2,30] The extent of staging in this case was considered thorough (full blood work, thoracic radiographs, and abdominal ultrasound), none of which showed evidence of disseminated disease. While splenomegaly can represent infiltrative disease, passive congestion was considered more likely.

Lymphoma of granular lymphocyte type is uncommon in dogs, and most reports describe involvement of the abdominal viscera.[31-33] It is typically a high-grade lymphoma with a short clinical course.[31] Other anatomic locations reported include peripheral lymph nodes, mediastinum, effusions of the pericardium and pleura, bladder, and skin.[34-38] In 1 other case with suspected CNS involvement, LGL lymphoma was diagnosed via aspirates of the spleen and abdominal lymph node, with MRI indicating severe meningeal infiltrates; the neurologic status improved rapidly upon initiation of chemotherapy, and a survival of 195 days was reached.[39] On review of the other case reports and small case series of LGL lymphoma in dogs, neurologic involvement is not reported. Although complete staging was not done, the long survival time in the dog described here is most consistent with a primary spinal extradural lymphoma of granular lymphocyte type.

Because of the extant veterinary literature regarding eosinophilic CSF and MRI findings consistent with potential empyema, an infectious process was the highest differential at the time of surgery. Reports on the MRI appearance of spinal lymphoma in dogs are scarce and highly variable.[9] The extradural lesions noted on MRI in this case were mildly hyperintense on T2-weighted images, iso-intense to muscle on T1-weight images, and diffusely contrast enhancing. This is consistent with reports in the veterinary literature.[40-42] Other reports, however, demonstrate hyperintensity on T1-weighted images,[9,43,44] emphasizing the importance of tissue sampling for diagnosis.

Surgical debulking of the mass was done but gross disease remained where adhesion required manipulation of the spinal cord and nerve root. Radiation therapy was therefore discussed with the owners but declined.

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CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

The following antimicrobials were used off-label. Enrofloxacin 10 mg/kg IV q24h, ampicillin and sulbactam 50 mg/kg IV q8h, metronidazole 7.5 mg/kg IV q8h.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Consent for treatment was provided by the owner.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

ORCID

Anna M. Massie https://orcid.org/0000-0002-0598-4200

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