T-Cell Spinal Lymphoma in a 3-Year-Old Mixed Breed Dog

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Introduction

This case review follows an interesting case of how paraparesis in a 3-year-old dog should not be assumed to be Intervertebral Disc Disease (IVDD). It also explores the considerations and difficulties encountered when trying to save the life of a patient that is severely clinical with T-cell spinal lymphoma.

History and Presentation

On January 8, 2018, a 3-year-old female spayed mixed breed dog was presented to Veterinary Specialty Center (VSC) through the Neurology Department for a 10-month history of progressive paraparesis, ataxia, and muscle atropy of the pelvic limbs. Clinical signs had progressed to weakly ambulatory paraparesis with moderate proprioceptive ataxia on the day of presentation. Her owners first noticed problems in March of the previous year when she became ataxic and subsequently, reluctant to jump into their car. Supportive care from her primary veterinarian significantly improved her clinical signs; notably, she responded well to treatment with prednisone. In late November, she became significantly worse after boarding and being allowed to play with other dogs. Given the previous response to steroids, another course was prescribed by her primary veterinarian, however, no clinical improvement was noted. Consequently, she was referred to VSC Neurology Department to pursue workup, including MRI, of suspected IVDD.

Besides worsening ataxia and paraparesis, Pepper showed no other signs of illness. On physical exam, lymph nodes were noted to be enlarged, with the right submandibular lymph node being particularly prominent, measuring 3cm x 3cm. A grade II/VI heart murmur was ausculted, which had never been noted before. The rest of her physical exam, excluding her neurologic exam, was within normal limits. All of the patient's cranial nerves functioned

normally. She exhibited pain on palpation at the thoracolumbar junction, as well as throughout her lumbar spine. Her pelvic limbs exhibited severe disuse muscle atrophy and lacked conscious proprioception (CP), although CPs remained normal in the thoracic limbs. Spinal reflexes were normal in all limbs. She was given a neuroanatomic localization of T3-L3 myelopathy. With these findings in mind along with the signalment of the patient, IVDD remained the top differential diagnosis. Infectious/inflammatory causes followed, and neoplastic causes of her condition were also included.

Diagnostic Approach

Our patient was pre-booked for an MRI because her owner understood that would be critical to ascertaining a diagnosis of her pet's progressive neurologic signs. Bloodwork, including a complete blood count (CBC) and neurochemistry were also performed. Results of the CBC were unremarkable; however, results of the neurochemistry showed a marked increase in ALT (809 U/L, reference range: 10 - 90 U/L) and ALP (617 U/L, reference range: 11 – 140 U/L). MRI showed unexpected findings: there were T2 and STIR hyperintense lesions that were also contrast enhancing located in multiple vertebral bodies throughout the lower thoracic and lumbar spine, as well as the wings of the ilium bilaterally. There were also T2 hyperintense, contrast enhancing extradural masses causing severe compression of the spinal cord at the levels of L3 and L6-7. The extradural masses explained the severe signs of paresis and ataxia, and neoplasia, particularly a round cell tumor given the patient signalment and enlarged lymph nodes noted during physical examination, replaced IVDD as the top differential diagnosis.

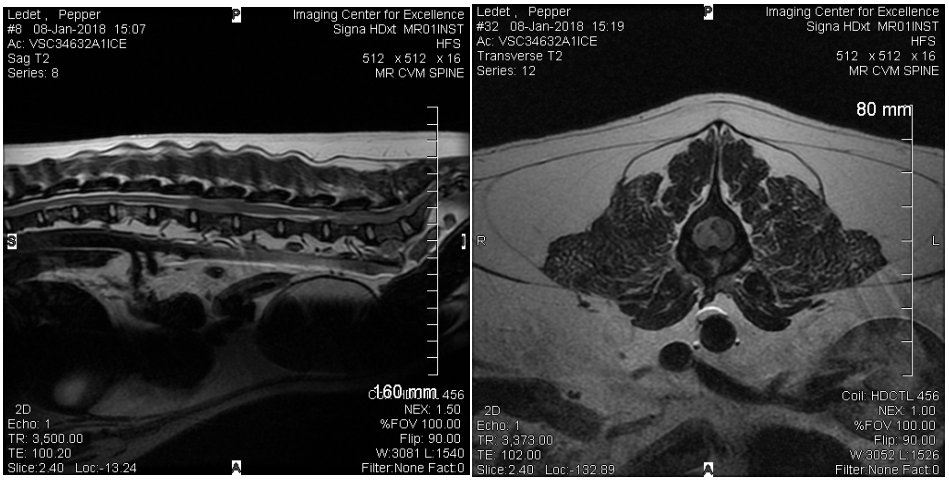

Figure 1: Sagittal view on left and transverse view on right at the level of L3 vertebra showing T2 hyperintense extradural mass compressing spinal cord

Case Outcome

The patient was hospitalized overnight on pain medication including Gabapentin and Tylenol-4. Based on the MRI findings, which were suggestive of neoplasia and hence, the suspicion of peritumoral edema being present, prednisone at 1 mg/kg/d was added to her treatment protocol. The patient remained unchanged at her 8 PM treatments that night, but had progressed to paraplegia with blunted nociception by the morning. The patient's owner was updated with the decline in neurologic status and offered 3 options. The first option would include a full workup of the suspected neoplasia which would include aspiration of the lymph nodes, abdominal ultrasound with fine needle aspirates of the liver and spleen, and debulking surgery. Surgery would not be intended to be curative, although the surgeon would attempt to remove as much of the tumors as possible without causing further damage to the surrounding spinal cord (Shores 240). The intent of surgery would be to debulk and resect as much of the gross disease as possible, therby decompressing the spinal cord in hopes of improving the patients clinical status. That morning, deep pain remained present, but because she had progressed so quickly from paraparesis to paraplegia with blunted nociception overnight, it was reasonable to assume that she could quickly progress to deep pain negative. For the highest chance of return to function after loss of deep pain, surgery should be performed to relieve the

compression within 24 hours. Thus, time was of the essence in this case. As an alternative to surgery, the option of radiation remained a possibility - although radiation would best be performed after finding a definitive diagnosis which had not yet been obtained (Shores 242).

The second was discharge with prednisone and pain medications, with the understanding that the patient would likely worsen over time and that her quality of life should be evaluated daily. This option would also need to include at home bladder management, as loss of motor in the pelvic limbs also comes with loss of the ability to voluntarily urinate. The third and final option presented was humane euthanasia.

Given the rapidity of progression of clinical signs over 24 hours, prognosis for return to function, as well as quality of life concerns, our patient's owner elected for humane euthanasia. Her body was submitted and a necropsy was performed the same day.

Diagnostics Revisited

The following comments on gross necropsy, histopathology, and special staining were obtained from the necropsy report prepared by Dr. Timothy Morgan, D.V.M., Ph.D., Dipl. A.C.V.P. On gross necropsy, the spinal column was dissected and there were no signs of vertebral body pathology noted, despite the lesions that appeared on the MRI. On examination of the spinal column, a white, lobulated, soft, pliable, 3cm x 1cm extradural mass was noted on the right side between L4-L5, and on excavation of the spinal cord, roughly half of the mass remained attached to the vertebral wall, and the other remained attached to the spinal cord. An additional white, lobulated, soft, pliable, 1.5cm x 1cm extradural mass was noted on the left spinal column between L2-L3, and was able to be visualized once the spinal cord was removed. On histopathology, the extra-dural mass was found to be composed of a monotonous population of round cells with scant eosinophilic cytoplasm and small, round nuclei with densely stippled

chromatin and multiple small nucleoli. Mitotic figures are up to 7 or more per high power field with occasional bizarre mitotic figures. Rare eosinophils are present within the mass. The adjacent ventral white matter contained mildly increased numbers of dilated axon sheaths and occasional digestion chambers.

Enlarged lymph nodes were readily apparent due to their large size. They were firm, bulged on cut surface, and lacked cortical and medullary distinction. Histopathology showed that the lymph nodes were infiltrated, expanded, and effaced by the same monotonous population of round cells that was seen in the extradural masses.

The liver was grossly enlarged and pale with scalloped edges. Histopathology showed it was not metastasis of the neoplasia as expected, rather a chronic and severe steroid hepatopathy from nearly a year of prednisone usage.

The heart appeared grossly pale. Unfortunately, the heart was inadvertently discarded at pathology rounds, and histopathology was unable to be performed. Given the appearance, the pathologist suspected that lymphoma had spread to the heart as well, although this was unable to be confirmed. There were no significant findings in the spleen, kidneys, or bone marrow.

Special staining of the neoplastic cells was strongly positive for CD3, negative for CD79, and negative for multiple myeloma oncogene 1 (MUM1), which is diagnostic of T-cell lymphoma. For reference, CD79 is a marker for B cell lymphoma, and MUM1 is a marker for plasma cells, which would be indicative of multiple myeloma.

Pathophysiology and Discussion

Lymphoma is one of the most common malignancies in the canine. It can be categorized by immunophenotype and stage based on location and presence of clinical signs. Immunophenotyping splits lymphoma into 2 major categories: B cell and T cell lymphomas. B

cell lymphoma is more common, with T cell lymphoma only accounting for 17 – 28% of canine lymphoma (Moore 2016). It is important for prognosis to immunophenotype because T cell lymphoma carries a much more guarded prognosis, due to a lower rate of response and decreased time in remission when compared to B cell lymphomas (Moore 2016). It is also useful to stage lymphoma, because the higher the stage, the worse the prognosis. Staging can be further categorized based on the presence or absence of clinical signs, and unsurprisingly, patients showing clinical signs when diagnosed have decreased survival times (Moore 2016). It is unknown why T-cell lymphoma occurs, and the true reason is likely multifactorial. Certain breeds appear to be predisposed – such as huskies, sharpeis, and boxers (Modiano 2005). Interestingly, the patient in this case review was believed to be a boxer mix. T-cell lymphoma has been found to have a higher prevelance in dogs less than 3 years of age (Modiano 2005). The patient in this case report was 3 years of age.

Management and Treatment Options

The remainder of this case report will investigate the course forward for this patient had her owner elected to pursue aggressive therapy. As previously mentioned, staging would have been essential in determining the path ahead. Had lymph node aspirates been obtained, examined, and then specially stained with CD3, CD79, and MUM1 early in the workup, a definitive diagnosis would have been achieved and the best targeted therapy could begin for the patient. With this knowledge, the immediate path forward begs the question: debulking surgery or radiation therapy? Both of these options would depend on the logistics of availability of neurosurgeons or the radiation oncologist to move forward with therapy the day that the patient's clinical signs worsened. For nearly all extradural spinal tumors, debulking surgery is the treatment of choice and should be pursued as soon as possible, as decreased duration of clinical

signs is associated with increased likelihood for a positive response (Shores 240). Lymphoma may be the one exception to the rule. Lymphoma is exquisitely sensitive to radiation therapy (Shores 240). If surgery was not an option due to owner concerns, logistics in the hospital that day, or health status of the patient, radiation therapy would be a good alternative. The unfortunate truth is that even a radiation oncologist cannot be certain how these specific masses in this dog would respond to radiation therapy. There may not have been a rapid enough decrease in tumor size to allow motor function to return in the pelvic limbs, in addition to mitigating progression to deep pain negative status. Furthermore, if the patient had become deep pain negative, her prognosis for return to function would have immediately diminished. And, if she remained deep pain negative for greater than 24 hours, she would have had a poor prognosis for a functional recovery. Therefore, radiation therapy could be attempted first, however it would have been imperative for the owner to understand that if deep pain negative status preceeded a reduction in tumor size, and subsequent improvement in clinical signs, there would need to be an immediate decompressive surgery. Due to the location of these particular masses, a multi-level hemilaminectomy would need to be performed to gain access. Given the invasiveness of these masses, it was unlikely that all gross disease would be removed. This knowledge, coupled with the data that most T cell lymphomas will metastasize to other locations in the body (Moore 2016) along with the finding of the T cell lymphoma in the lymph nodes necessitates the need for follow up with chemotherapy.

The most commonly used chemotherapy protocol for lymphoma, CHOP, which utilizes cyclophosphamide, doxorubicin, vincristine and prednisolone, has fallen out of favor as the treatment of choice for T cell lymphoma due to poor response to doxorubricin. Remission and survival times are so much worse for T cell lymphoma than B cell lymphoma with this protocol

that other combination chemo protocols are being investigated. Two alternatives have been proposed: LOPP and MOPP. MOPP, a combination chemo protocol that utilizes mechlorethamine, vincristine, prednisone, procarbazine was studied and published (Brodsky 2009). This study found that this protocol might result in longer progression free survival and overall survival time (OST) when compared to historic studies using the CHOP protocol. A 2017 study of a chemotherapy protocol called LOPP, which includes the drugs lomustine (CCNU), vincristine, procarbazine and prednisolone, showed increased overall response rates, increased disease free interval, and increased median survival time when compared to CHOP. When compared to MOPP, it showed significantly less toxicity (Brown 2017). Another important point to consider when comparing the protocols is the availability and ease of use of the drugs in both protocols. Mechlorethamine, a component of the MOPP protocol is less available and has stricter handling requirements for its preparation. Because our patient would have received chemotherapy at Mississippi State University College of Veterinary Medicine, and this institution does not have the proper equipment for preparations of mechlorethamine, we would have recommended using the LOPP protocol.

Unfortunately, there is no data available specifically on survival time of dogs with T cell spinal lymphoma based on varied treatment protocols. Additionally, there is no gold standard for treatment of T cell spinal lymphoma. Because of the poor prognosis associated with T cell lymphoma and the high cost of treatment, many owners elect for humane euthanasia. This owner had a particularly difficult decision to make; treatment needed to be aggressive, expedient, and would be a huge financial undertaking. Even if money and logistics were not a concern, there was still not a good prognosis for long term survival. Ultimately, euthanasia was considered the

most humane option. Although uncommon in young dogs, it is critical to keep neoplastic causes of paraparesis on your differential list.

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