FOCAL POINT

- Horses with central nervous system lymphoma can present with a varying history and signalment and myriad clinical manifestations.

KEY FACTS

- Definitive diagnosis of central nervous system lymphoma in horses is difficult to achieve antemortem, p. 198.
- Cerebrospinal fluid analysis may reveal a lymphocytic pleocytosis or, less commonly, neoplastic lymphocytes, p. 198.
- Clinical signs are usually related to spinal cord compression from extradural or leptomeningeal neoplastic infiltration, p. 198.
- Although chemotherapeutic protocols are available for treating other forms of equine lymphoma, the severity and rapid progression of the neurologic disease usually preclude successful treatment, p. 200.

Lymphoma of the Central Nervous System in Horses

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ABSTRACT: Equine central nervous system (CNS) lymphoma can cause various clinical signs. Although diagnosis of CNS lymphoma is rarely achieved antemortem, a high degree of clinical suspicion may be reached by cerebrospinal fluid analysis. All reported cases describe spinal cord involvement, but other areas of the nervous system may be infiltrated with lymphoma as well. Prognosis for horses with CNS lymphoma is grave because clinical deterioration often occurs rapidly, and successful treatment has not been reported.

W
ith the exception of adenomatous hyperplasia of the pituitary gland, neoplasia involving the central nervous system (CNS) is considered uncommon in horses. Regardless, neoplasia should be included in the list of diagnostic differentials in some cases of equine neurologic disease. Of the various neoplasms that can affect the CNS, lymphoma is the most common. This article discusses four specific cases of lymphoma and provides a general overview of CNS lymphoma in horses.

CASE REPORTS

Case 1

A 1-year-old, 314-kg Standardbred filly presented with an acute onset of recumbency. The filly was at pasture with 17 other yearlings and appeared normal until the day before presentation when it was found down. After arising on one occasion, the horse appeared ataxic in all four limbs but then progressed to recumbency several hours later. The filly was current on all vaccinations except rabies. No other animals on the farm were affected. The horse had no known history of trauma.

On presentation, the filly was in lateral recumbency and severely lethargic but with encouragement could achieve and maintain a sternal position. A general physical examination was within normal limits, but neurologic examination revealed depressed mentation and left-sided facial nerve paralysis. Spinal reflexes
were difficult to assess, but the left patellar reflex was noted to be normal. A lesion involving the brain stem (medulla and nucleus of cranial nerve VII) was suspected, although a concurrent cervical lesion (C1-6) could not be excluded. Results of a complete blood count and chemistry panel revealed abnormalities consistent with mild inflammation, dehydration, anorexia, and muscle trauma from recumbency. Results of lumbosacral cerebrospinal fluid (CSF) analysis (Table I) and radiographs of the skull and cervical vertebrae were normal. Equine protozoal myelitis (EPM) Western blot on the CSF was positive. Treatment consisted of intravenous fluids, dimethyl sulfoxide, trimethoprim-sulfamethoxazole, pyrimethamine, ceftiofur, flunixin meglumine, and ocular triple antibiotic ointment. Two days after presentation, the filly’s neurologic condition deteriorated into seizures, unresponsiveness, and extensor rigidity in all four limbs; therefore, the horse was euthanized.

On pathologic examination, the CNS appeared grossly normal. A fluorescent antibody test for rabies on the left half of the brain was negative. Significant histopathologic abnormalities included moderate-to-severe perivascular multifocal lymphocytic cuffing in the right neocortex, cerebellum, and brain stem; the presence of occasional atypical lymphocytes within the parenchyma of the aforementioned areas; and occasional lymphocytic perivascular infiltrate within the hippocampus. These findings were consistent with diffuse neurologic lymphoma. The spinal cord was not studied.

Case 2
A 16-year-old, 489-kg Tennessee walking horse gelding presented with a 10-day history of hindlimb ataxia that progressed to recumbency. Treatment with trimethoprim-sulfamethoxazole was initiated on the farm after the onset of ataxia, and slight improvement was noted. At presentation, however, the gelding was permanently recumbent. The horse had been recently vaccinated for rhinopneumonitis, tetanus, influenza, eastern and western encephalitis, and rabies. The gelding was pastured with other horses, all of which were normal. The horse had no history of trauma.

On presentation, the gelding was in lateral recumbency and struggling violently to stand without success. Results of a physical examination, after sedation, were within normal limits. Neurologic examination showed normal mentation, normal cranial nerve function, and quadriparesis. Tail and anal tones were normal. Spinal reflexes were not assessed. A cervical spinal cord lesion was highly suspected. Results of a complete blood count and serum chemistry panel revealed changes consistent with moderate inflammation and evidence of muscle trauma from recumbency. Lumbosacral CSF sample analysis (Table I) showed features of nonsuppurative inflammation; there was an increase in both the protein and nucleated cell count, with 93% of the cells being atypical lymphocytes. Based on the finding of lymphocytosis (relative and absolute) and the presence of abnormal lymphocytes, lymphoma involving the CNS was strongly considered. EPM Western blot testing on the CSF was deemed suspect. Treatment consisted of intravenous fluids, dimethyl sulfoxide, and dexamethasone, but the horse was euthanized 10 hours after admission because of its grave prognosis.

### TABLE I

Cerebrospinal Fluid Results in Three Horses with Nervous System Lymphoma²³

<table>
<thead>
<tr>
<th>Clinical Finding</th>
<th>Normal</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Color</td>
<td>Colorless</td>
<td>Colorless</td>
<td>Light yellow</td>
<td>Light yellow</td>
</tr>
<tr>
<td>Turbidity</td>
<td>Clear</td>
<td>Clear</td>
<td>Slightly cloudy</td>
<td>Slightly cloudy</td>
</tr>
<tr>
<td>Nucleated cells (leukocytes/µl)</td>
<td>0–6</td>
<td>6</td>
<td>1200</td>
<td>393</td>
</tr>
<tr>
<td>Total erythrocytes (cells/µl)</td>
<td>0–2000</td>
<td>5</td>
<td>300</td>
<td>2500</td>
</tr>
<tr>
<td>Protein (mg/dl)</td>
<td>5–100</td>
<td>67</td>
<td>119</td>
<td>167</td>
</tr>
<tr>
<td>Cytologic findings</td>
<td>Predominant cell types are small lymphocytes and macrophages</td>
<td>Normal</td>
<td>93% lymphocytes, 7% macrophages; lymphoid cells intermediate in size with moderate amounts of pale-blue cytoplasm; pleomorphic nuclei with condensed chromatin and no visible nuclei</td>
<td>90% small lymphocytes, 8% reactive lymphocytes, 2% macrophages; normal morphology</td>
</tr>
</tbody>
</table>

²²Cerebrospinal fluid analysis
²³Neurologic condition
²⁴Nucleated cell count
Gross necropsy findings were normal, but diffuse histopathologic lesions involving the spinal cord were present. Neoplastic lymphocytes were found within the spinal cord leptomeninges and parenchyma, including the central canal, starting at the cervical intumescence and continuing caudally into the lumbosacral intumescence. There were neoplastic cell infiltrates in the spinal roots of the cervical intumescence and the lumbosacral intumescence contained focal submeningeal neoplastic nodules that compressed the adjacent lateral funiculi (white matter). Immunoperoxidase staining of the neoplastic lymphocytes showed the lymphoma to be of T-cell origin.

Case 3

A 16-year-old, 624-kg Clydesdale stallion presented with a 4-week history of a grade 5/5 (non-weight-bearing) lameness of the right forelimb. A 10-day treatment course with phenylbutazone did not alleviate the condition. The stallion had been stabled alone on a farm and was current on all vaccines. The animal had no history of trauma.

On presentation, the stallion was bright and alert but could not bear weight on the right forelimb and had a deviation of the muzzle toward the left side. Physical examination revealed fever (39.4°C), tachycardia (heart rate, 76 beats/min), and tachypnea (respiratory rate, 60 breaths/min). The right forelimb could be partially advanced. There was partial carpal and fetlock extension, but the limb would collapse when weight was borne on it. The horse showed no reluctance to use the limb and no discomfort on limb manipulation. The right scapular, triceps, and cranial antebrachial muscles were atrophied, and the right forelimb was dropped at the elbow. These findings were consistent with incomplete brachial plexus paralysis. The deviated muzzle was not accompanied by an eyelid or ear abnormality, suggesting involvement of the buccal branches of the right facial nerve. The remainder of the neurologic examination was normal. Nerve blocks performed proximal to the fetlock did not improve the condition of the right forelimb. Radiography of the shoulder, elbow, and fetlock, in addition to ultrasonography of the right axilla, did not reveal any abnormalities. A serum titer for EPM was positive. No further diagnostics were performed. The stallion was released with a splint on the right front limb, and the client was instructed to continue phenylbutazone therapy. One week after discharge, the stallion was found in his stall profusely sweating and appearing uncomfortable. The referring veterinarian did not identify any reason for the presumed colic but did note that the horse appeared blind because of an absent menace response bilaterally. Over the next several hours, the horse became obtunded and was subsequently euthanized.

Pertinent findings on gross necropsy were gastric ulcers (glandular and nonglandular stomach), enlargement of the right axillary and cubital lymph nodes, and firm enlargement of the proximal radial nerve and ventral branch of the 8th cervical spinal nerve (Figure 1A). The latter enlargement continued proximally through the dorsal and ventral roots to the surface of the spinal cord. All these enlargements were caused by accumulation of infiltrating lymphocytes within the epineurium and throughout the endoneurium of each fascicle (Figures 1B and 1C). Many spinal nerves contained lymphoid infiltrates but to a lesser degree than did the
right 8th cervical spinal nerve. The right facial buccal branches were similarly infiltrated with lymphocytes. In the brain stem, there were scattered clusters of blood vessels surrounded by many layers of lymphocytes.

Case 4

A 22-year-old, 520-kg Arabian gelding was presented with recumbency of several hours’ duration. The horse had a 4-week history of stumbling and lameness in the right forelimb. Radiographs and nerve blocks of the right forelimb several weeks before presentation had failed to reveal the cause of the lameness. Signs progressed slowly to include cervical pain, reluctance to bend the neck, hindlimb ataxia, and, finally, recumbency. Previous treatments included trimethoprim-sulfamethoxazole, pyrimethamine, vitamin E, and antiinflammatory drugs. The horse was current on all vaccinations; no other horses on the farm were affected. The gelding had no history of trauma.

On presentation, the gelding was bright and alert but in lateral recumbency. With encouragement, the horse could achieve and maintain sternal recumbency. Results of a physical examination were within normal limits. Neurologic examination revealed normal mentation, cranial nerves, muscle, tail and anal tone, but quadriparesis was present and the horse was unable to rise. Spinal reflexes were difficult to assess. Because of the severity of the quadriparesis and an inability to bear weight on the limbs, the horse was not maintained in the sling. Results of a complete blood count and serum chemistry profile revealed only an increase in muscle enzymes presumed to be secondary to recumbency. Lumbosacral CSF analysis (Table I) revealed nonsuppurative inflammation, characterized by a lymphocytic pleocytosis and an increased protein. Although the lymphocyte morphology was normal, lymphoma was still suspected. Results of EPM Western blot testing on the CSF were positive. Radiographs of the cervical vertebrae were normal. Treatment included intravenous fluids, dimethyl sulfoxide, flunixin meglumine, trimethoprim-sulfamethoxazole, pyrimethamine, and thiamin. Over the next 2 days, the gelding became progressively worse. When the horse was no longer able to lift its head and neck, the owners elected euthanasia.

On gross necropsy, an extradural mass was noted along the right dorsolateral portion of the spinal cord that extended out of the intervertebral foramen at T1-2, along the ventral root. The mass compressed the adjacent spinal cord, and a subdural hematoma was located dorsally. On histologic examination, the mass was composed of neoplastic lymphocytes. Neoplastic lymphocytes infiltrated the spinal cord white matter of T-1 and were found perivascularly in the spinal roots of sections taken from C-7, T-8, and L-3.

HISTORY AND SIGNALMENT

Horses with lymphoma affecting the CNS may be of any age (from 20 months to 20 years), with a median age of approximately 10 years.4–11 The history of horses with CNS lymphoma can vary widely, and the clinical signs depend on the location and growth rate of the neoplasm. Some horses have chronic gait abnormalities, as described in case 4, and exhibit lameness, paresis, or ataxia.4–11 The condition may stabilize until a sudden exacerbation of signs occurs. In one report, a 17-year-old mixed-breed gelding with lymphoma presented for evaluation of Horner’s syndrome, which had remained static for 70 days, after which the horse suddenly developed ataxia.6 Acute onset of ataxia with rapid deterioration has also been reported.6,5,7,9 This was described in case 1, in which the horse had a sudden onset of quadriparesis and recumbency.

PHYSICAL AND NEUROLOGIC EXAMINATION FINDINGS

There are no specific physical examination findings in horses with CNS lymphoma. Because these cases may be part of the multicentric form of lymphoma, clinical examination abnormalities may reflect involvement of other body systems. For example, peripheral lymphadenopathy,7,8 subcutaneous masses,7,9 emaciation,6 asymmetric muscle atrophy,9–11 colic,4 anorexia,4 and lethargy4,8–10 may be evident. Two horses have been reported to have respiratory distress related to masses in the upper or lower respiratory tract before a neurologic component to their illness became apparent.6,8

Because lymphoma has been reported in many areas throughout the CNS, neurologic deficits will depend on the lesion’s location. Spinal cord involvement with subsequent ataxia, paresis, urinary and fecal incontinence, poor anal and tail tone, and muscle atrophy are most common.4–12 Involvement of the brain or brain stem has been associated with the development of Horner’s syndrome,6,10 facial nerve paralysis (case 3),7,9 sensory trigeminal deficits,9 and seizures.11

Lymphoma is often diffuse or multifocal in nature; therefore, a thorough neurologic examination will often reveal several neuroanatomic abnormalities, such as described in case 3. As with most neoplastic conditions, the clinical signs associated with CNS lymphoma are progressive.

DIAGNOSTIC DIFFERENTIALS

The diagnostic differentials will vary, depending on
the localization of the lesion as well as the history, signalment, and duration of clinical signs. Inflammatory, infectious (bacterial, viral, fungal, parasitic), metabolic, traumatic, neoplastic, degenerative, toxic, and idiopathic conditions could be included on a list of diagnostic differentials for horses with CNS lymphoma.

Performing diagnostic tests—in addition to addressing the history, signalment, and clinical signs—can aid in determining or strongly suspecting CNS lymphoma. However, a definitive diagnosis may be difficult to achieve antemortem because of diagnostic limitations related to the CNS. In addition, the diagnosis may be clouded by tests with a moderate specificity (such as in cases 1 and 4) in which an EPM Western blot on the CSF was positive but EPM was not present at postmortem examination. The reason for the false-positive EPM titer was likely related to either altered blood–brain barrier permeability or blood contamination during CSF collection. In those cases, the use of other clinical and diagnostic findings, such as a lymphocytic pleocytosis on the CSF cytology (cases 2 and 4), could assist in ruling out certain differentials.

**DIAGNOSTIC TESTING**

Results of blood work in animals with CNS lymphoma are often unremarkable. Although horses with multicentric or alimentary lymphoma are often anemic, anemia was present in only one of five cases of CNS lymphoma. Leukograms may show evidence of inflammation (e.g., leukocytosis, neutrophilia, monocytosis), as was present in cases 1 and 2; and this presumably results from a nonspecific response to neoplasia. Lymphopenia, possibly caused by a systemic stress response or depression of lymphocyte proliferation, could be present. Frank leukemia in cases of lymphoma is rare and has not been reported in association with CNS involvement. A serum biochemistry profile may show various abnormalities secondary to conditions such as dehydration (azotemia, hyperproteinemia), muscle trauma (increased creatine kinase and aspartate transferase activity), chronic inflammation (hyperglobulinemia), or anorexia (hyperbilirubinemia). Hypercalcemia associated with pseudohyperparathyroidism is an uncommon finding in lymphoma cases and has not been reported in animals with neurologic disease. Finally, selective IgM deficiency, which is a nonspecific finding in lymphoma, has not been investigated in animals with neurologic involvement.

Cerebrospinal fluid analysis may be helpful in diagnosing CNS lymphoma. Total nucleated cell counts may be elevated, although a lymphocytic pleocytosis is not a consistent finding. One horse in the described case studies had normal CSF cytology, whereas
the other two had increases in total protein and a lymphocytic pleocytosis (Table I). An elevated lymphocyte count in the CSF may also be present as a result of spinal cord compression (by other causes), infectious agents (e.g., bacteria, viruses, fungi, parasites), or presumed immune-mediated conditions (e.g., polynuereitis equi). Finding neoplastic lymphocytes in the CSF would be diagnostic for lymphoma, as seen in two cases reported by Williams and colleagues and case 2. Non-specific CSF abnormalities may include neutrophilic inflammation, an increased total protein level (cases 2 and 4), or xanthochromia (cases 2 and 4).

Further diagnostic testing in animals in which a lesion can be localized may be beneficial. Although routine radiographs have not proven to be diagnostic in cases of CNS lymphoma, a myelogram may reveal abnormalities if spinal cord compression is present. One report describes a myelographic study that showed a probable compressive mass lesion at T17-18, which was confirmed as lymphoma on postmortem examination. Ultrasonography can be used to further investigate peripheral neuropathies, although a negative ultrasonographic examination does not rule out lymphoma, such as in case 3. To date, there are no reports using computed tomography or magnetic resonance imaging to diagnose CNS lymphoma in horses, but these methods could potentially provide significant information.

PATHOLOGIC FINDINGS

Central nervous system lymphoma most commonly involves the spinal cord, as all reported cases demonstrated the presence of lesions in this area. Typically, the neoplastic lymphocytes are found within the vertebral canal, either in the epidural space or within the leptomeninges, which usually leads to spinal cord compression.

In a few cases, clinical signs of spinal cord disease were also related to invasion of the parenchyma with neoplastic cells. If lesions are more local within the vertebral canal, there appears to be a predilection for the thoracic or thoracolumbar area. In this aspect, equine disease is similar to bovine CNS lymphoma, which usually presents with hindlimb paresis and ataxia or paralysis, related to extradural lumbar spinal cord compression. Lympoma may also infiltrate peripheral nerves with associated clinical signs (case 3). The brain, brain stem, or cerebellum may also be affected, as was reported in over half of the cases. The predilection of lymphoma for extradural structures could explain the uncommon finding of neoplastic lymphocytes within the CSF. In two reported cases, as well as case 2, the abnormal lymphocytes seen on CSF analysis may reflect parenchymal or meningeval involvement or actual sampling of neoplastic tissue during CSF collection.

In the majority of cases reported, lymphoma was found in other body systems or within lymph nodes, supporting the concept that CNS involvement is part of the multicentric form of lymphoma. There is only one report of primary CNS lymphoma that diffusely affected the meninges. Although three of the cases (cases 1, 2, and 4) appeared only to have neoplastic tissue in the CNS, histopathology was not performed on all peripheral lymph nodes or other grossly normal organs; therefore, other neoplastic locations may have been overlooked.

Immunophenotyping of equine lymphoma has been reported infrequently. We have characterized a T-cell lymphoma, via immunoperoxidase staining, affecting the spinal cord in case 2. Further defining the functional, biochemical, and immunologic features of equine lymphoma may assist with the prognosis and treatment of this disease in horses.

TREATMENT

Treatment of equine CNS lymphoma has not been reported, although there are protocols described for treating other forms of equine lymphoma. Chemothertapeutic agents (e.g., cytosine arabinoside, cyclophosphamide), which can penetrate the blood–brain barrier, along with immunosuppressive doses of glucocorticoids, could be used. However, because of the usual rapid progression and severity of signs with neurologic lymphoma, it would seem unlikely that chemotherapy would significantly change the course of the disease. Although other treatments (e.g., irradiation) are used in humans with CNS lymphoma, impracticality may preclude its use in horses.

REFERENCES


About the Authors
When this article was written, Drs. Adolf, Perkins, Ainsworth, and de Lahunta were affiliated with the Department of Clinical Sciences, Cornell University Hospital for Animals, Ithaca, New York. Dr. Adolf is currently associated with Ledgewood Equine Medical Center in Ontario, New York. Drs. Perkins, Ainsworth, and de Lahunta are Diplomates of the American College of Veterinary Internal Medicine.

ARTICLE #6 CE TEST

Choose only the one best answer to each of the following questions; then mark your answers on the test form inserted in Compendium.

1. The most common neoplasm in the equine CNS is
   a. lymphoma.
   b. melanoma.
   c. hemangiosarcoma.
   d. pituitary adenomatous hyperplasia.

2. In regard to equine CSF, which of the following nucleated cell counts and cytologic analyses is considered normal?
   a. 0 to 25 leukocytes/µL; predominant cell type is neutrophil.
   b. 0 to 6 leukocytes/µL; predominant cell types are small lymphocytes and macrophages.
   c. 0 to 25 leukocytes/µL; predominant cell types are small lymphocytes and macrophages.
   d. 0 to 6 leukocytes/µL; predominant cell type is neutrophil.

3. The median age of horses presenting with CNS lymphoma is ____ years.
   a. 10
   b. 5
   c. 15
   d. 25

4. The most common physical examination abnormality in horses with CNS lymphoma is
   a. emaciation.
   b. peripheral lymphadenopathy.
   c. respiratory distress.
   d. none of the above

5. The most common neurologic abnormality found in horses with CNS lymphoma is
   a. seizures.
   b. cranial nerve deficits.
   c. ataxia and paresis or paralysis.
   d. Horner’s syndrome.
6. _________ has not been reported in horses with CNS lymphoma.
   a. Hypercalcemia  c. Lymphopenia
   b. Anemia  d. Increased creatine kinase

7. An elevated lymphocyte count in the CSF has been observed in all of the following conditions except
   a. viral encephalitis (e.g., rabies).
   b. polynuritis equi.
   c. spinal cord trauma.
   d. CNS lymphoma.

8. Nonspecific CSF abnormalities found in horses with CNS lymphoma include all of the following except
   a. xanthochromia.
   b. increased creatine kinase.
   c. increased total protein.
   d. suppurative inflammation.

9. In cases of CNS lymphoma, there appears to be a predilection for the ____________ areas of the spinal cord.
   a. cervical or cervicothoracic
   b. thoracic or thoracolumbar
   c. cervical or sacral
   d. lumbar or lumbosacral

10. In equine CNS lymphoma, ataxia is most commonly caused by
    a. epidural or meningeal lymphocytic infiltration with spinal cord compression.
    b. lymphocytic infiltration of the spinal cord with parenchymal damage.
    c. inflammation within the subarachnoid space.
    d. lymphocytic infiltration of the brain stem with parenchymal damage.