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Central Nervous System Hemangiosarcoma in a Horse

S.M. Ladd, M.V. Crisman, R. Duncan, J. Rossmeisl, and F.S. Almy

An 18-year-old 600-kg Percheron cross gelding presented with neurologic signs of 24-hour duration. The gelding had no history of illness.

Initial physical examination showed abnormalities that included a small corneal ulcer in the left eye and periocular skin abrasions on the right side. The gelding had depressed mentation and right head turn. The horse circled to the right, had a tendency to lean and fall to the right, and was ataxic in all limbs. Cranial nerve dysfunction included bilateral facial paralysis, spontaneous horizontal nystagmus (fast phase to the left), diminished tongue tone (without appreciable atrophy), right nasofacial hypalgesia, and pharyngeal dysphagia. General proprioceptive deficits were present in the right thoracic and pelvic limbs, while extensor tone was present in the left thoracic and pelvic limb muscles.

Neurologic examination findings were consistent with a diffuse brainstem lesion, mainly on the right side and extending from the rostral to the caudal medulla. A right telencephalic or diencephalic lesion could not be ruled out to explain the head turn and circling to the right. Based on the presence of a diffuse or multifocal lesion and neuroanatomic lesion localization, the primary differential diagnosis included infectious causes of meningoencephalitis (equine protozoal meningoencephalomyelitis [EPM], atypical presentation of equine herpes virus I, rabies, or West Nile virus), trauma, and neoplasia with associated mass effect. Although the clinical signs were acute in onset, trauma was not likely, given the multifocal nature and region of the brain involved. Neoplasia was considered possible due to brainstem involvement; however, acute onset is unlikely with brain tumors. Neoplasia remained on the list of possible causes, as some of the clinical signs may have been missed before presentation or if hemorrhage was associated with the tumor. The left facial nerve paralysis was attributed to trauma that occurred during transportation, as the referring veterinarian reported that the horse did not have evidence of the left corneal ulceration immediately before referral.

Other than a mild lymphopenia (1,863 $\times$ $10^3/\mu L$; reference interval: 2,190–5,900 $\times$ $10^3/\mu L$), hematologic variables were within reference range.

Abnormalities in the serum chemistry included a high serum creatinine (1.9 mg/dL; reference interval, 0.7–1.5 mg/dL) and hyperbilirubinemia (2.1 mg/dL; reference interval, 0.7–1.7 mg/dL) due primarily to an increased direct bilirubin (0.5 mg/dL; reference interval, 0.0–0.4 mg/dL). Serum bile acid concentration was below reference range. The changes in the serum chemistry values were attributed to mild dehydration and anorexia. Other serum chemistry values were within reference intervals. Urinalysis did not reveal any abnormalities.

There were no radiographic abnormalities in the basioccipital and stylohyoid bones, guttural pouches, or the first and second cervical vertebra. Because of the horse's instability, size, and inability to safely ambulate, additional cervical radiographs were not obtained, and the guttural pouches were not evaluated endoscopically.

Lumbosacral cerebrospinal fluid (CSF) aspirate was light pink and clear. Fluid analysis showed a high RBC (7,400 cells/μL; reference interval, 0.0/μL) and a total nucleated cell count of 2 nucleated cells/μL (reference interval, $\leq$5 μL). Both CSF glucose and total protein concentrations were within reference intervals. Nucleated cells consisted of nondegenerate neutrophils, small lymphocytes, and a few large monocytoid cells; there was no erythrophagia nor hemosiderin apparent on cytologic examination. It was unclear if the increased number of neutrophils was the result of blood contamination of the sample or acute hemorrhage. However, the atypical light pink color was considered most consistent with intrathecal hemorrhage.

Western blot analysis of the serum and CSF were positive for antibodies to *Sarcocystis neurona.* The CSF antibody index supported blood contamination of the lumbosacral sample. A serum neutralization titer for EHV-1 was 1 : 64; the immunofluorescence titer to EHV-1 was 1 : 2,560. These titers were consistent with recent vaccination or early disease rather than active infection. The IgM capture ELISA for West Nile Virus was negative at 1 : 400.

Therapy instituted at initial examination included flunixin meglumine[a] (1.1 mg/kg IV q12h), DMSO[b] (1 g/kg, 10% solution, IV q24h), ponazuril[c] (5 mg/kg PO q24h), and intravenous fluid therapy (75 mL/kg/d, lactated Ringer's solution[d]). Because the horse continued to deteriorate over the next 24 hours, dexamethasone[e] (0.05 mg/kg IV q24h) was administered. The horse was recumbent on day 6 of hospitalization, not responding to therapy, and was euthanized.

An atlanto-occipital CSF aspirate obtained immediately after euthanasia was moderately xanthochromic. The clear yellow CSF had an increased RBC count (1,063/μL; reference interval, 0.0/μL), total nucleated cell count (10/μL; reference interval, $\leq$5/μL), and total protein concentration (1,737 mg/dL; reference interval, 60–115 mg/dL). Cytolog-

From the Departments of Large Animal Clinical Sciences (Ladd, Crisman), Biomedical Sciences and Pathobiology (Duncan, Almy), and Small Animal Clinical Sciences (Rossmeisl), Virginia Maryland Regional College of Veterinary Medicine, Blacksburg, VA.

Reprint requests: S.M. Ladd, VMRCVM Department of Large Animal Clinical Sciences, Duckpond Drive, Phase II, Blacksburg, VA 24061; e-mail: smladd@vt.edu.

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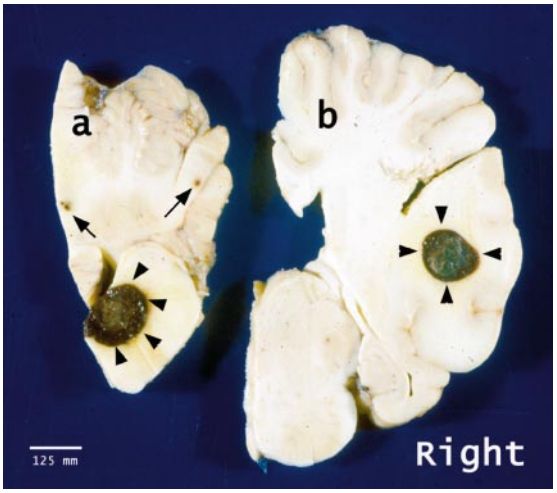

Fig 1. Transverse right hemisections of equine brain at the level of the lateral recess of the medulla oblongata **(a)** and temporal lobe of the cerebrum **(b)**. Arrowheads indicate grossly hemorrhagic mass lesions infiltrating the right medial aspect of the medulla oblongata **(a)** and in the right temporal lobe of the cerebrum **(b)**. Multiple pinpoint areas of hemorrhage are also present in the cerebellar white matter (arrows).

ic examination showed slight lymphocytic pleocytosis. A few large monocytoid cells of normal morphology were observed, but there was no evidence for erythrophagia or hemosiderin.

Abnormalities noted during gross postmortem examination included multifocal, variably sized (pinpoint to 2 cm in diameter), pink to gray nodules diffusely scattered throughout the lungs and myocardium. There was a 12-cm focus of confluent, coalescing nodules in the right middle lung lobe similar in appearance to those previously described. A similar nodule was present in the right middle gluteal musculature. There were multiple discrete macroscopic dark reddish-gray focal lesions within the brain; the largest of these were within the neuropil of the right temporal lobe of the cerebrum (1.1 cm in diameter) and in the right cerebellopontomedullary area (1.9 cm × 1.3 cm × 1.5 cm). The neuropil surrounding these foci were discolored yellow and were interpreted as locally extensive edema. There were several other pinpoint red foci, including 2 depicted in the right caudal cerebellar peducle and cerebellar white matter (Fig 1).

Microscopically, a pleomorphic population of spindloid cells extensively effaced pulmonary parenchymal architecture in multiple locations. There were anisokaryosis, anisocytosis, karyomegaly, and high nuclear to cytoplasmic ratios present. Nuclei were ovoid, with coarsely granular chromatin and large nucleoli. Mitotic figures were numerous and often bizarre. The neoplastic cells frequently formed blood-filled channels. There were occasional foci of necrosis and suppurative inflammation. Other findings included multifocal suppurative tracheobronchial lymphadenitis and multifocal infiltration and architectural replacement of the myocardium by neoplastic cells similar to those described in the lung.

The masses within the brain noted during gross examination were composed of hemorrhage interspersed with

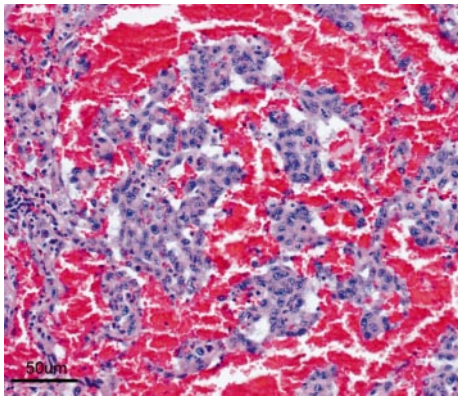

Fig 2. Hematoxylin and eosin stain of the cerebral mass: areas of hemorrhage and foci of spindloid cells lining blood-filled channels. Note the high nuclear to cytoplasmic ratio, large nucleoli, granular chromatin, and anisokaryosis and anisocytosis.

neoplastic spindloid cells that formed irregular vascular spaces identical to those noted in the lung and myocardium. The largest of these masses were located in the right temporal lobe of the cerebrum (Fig 2) and the medial portions of the right pontomedullary area, beginning at the level of the caudal cerebellar peduncle and extending caudally to the level of the olivary nucleus. In each instance, the foci were expansile and compressed adjacent edematous neuropil. Multiple microscopic foci were also present in the right temporal and parietal cerebral cortices and adjacent subcortical white matter tracts, as well as in the right caudal cerebellar peduncle and in the area of the right ventrolateral medulla. There was erythrophagocytosis and hemosiderosis noted in some fields. The focus noted grossly in the right middle gluteal muscle was not examined microscopically.

Factor VIII immunohistochemical analysis was performed on the tumor by a streptavidin-biotin-peroxidase method and rabbit anti-human polyclonal factor VIII antibody.[f] Tissue samples from one of the brain masses in this horse stained positive for factor VIII.

Based on the gross postmortem examination, histopathologic findings, and immunohistochemistry, a diagnosis of hemangiosarcoma with pulmonary, myocardial, and multifocal brain involvement was made. Equine hemangiosarcoma is a rare malignant neoplasm of the vascular endothelial cells that most often affects middle-aged horses but can be seen in horses of all ages, including foals.[1–6] Hemangiosarcoma can be focal, locally invasive, cutaneous, or disseminated[7]; common primary sites in the horse include the lung, right heart, and spleen. In a study of 35 cases, metastases were found in the respiratory tract (77%), musculoskeletal system (46%), and spleen (43%), as well as in the heart, gastrointestinal tract, skin, and rarely, by postmortem examination, in the central nervous system (CNS).[5,7–9] A literature review (1970–1997) of 25 cases of nonpituitary CNS tumors reported 2 hemangiosarcomas. Neither of the involved horses demonstrated neurologic signs.[7,8,10]

Common presenting complaints for equine hemangiosarcoma include signs attributable to hemorrhage.[7] Antemortem diagnosis of hemangiosarcoma in horses is difficult without direct visualization and biopsy. None of the pre-

viously reported clinical signs associated with hemangiosarcoma were present in this horse. The rapid course and progressive nature of the disease as well as the lack of response to standard therapy for infectious or inflammatory CNS disease indicated a possible neoplastic condition.

The frank blood in the CSF of this horse, coupled with the positive serum titer for EPM, indicate that the weak positive CSF Western blot analysis results were likely from blood in the CSF rather than from intrathecal production of antibodies to *S neurona.* The likely source of blood in the CSF was hemorrhage associated with the CNS hemangiosarcoma rather than blood contamination at the time of sampling. Furthermore, the postmortem CSF analysis supported intrathecal hemorrhage as the cause.

The multifocal asymmetric intracranial neurologic deficits exhibited by the horse described in this case are consistent with the neoplastic masses identified within the right cerebrum and pontomedullary regions. The mental depression observed may have resulted from neoplastic infiltration of the pontomedullary portions of the ascending reticular activating system (ARAS). The ARAS occupies a central location in the brainstem, is part of the reticular formation, and functions in the maintenance of consciousness via the polysynaptic transmission of afferent multimodality sensory stimuli through diencephalic reticular centers to the cerebral cortex.[11] The right cerebral tumor and its associated edema were postulated to be a possible cause of the right head turn and may also have contributed to the depressed mentation in this horse.

With the exception of the left facial nerve paralysis, which was suspected to be the result of trauma sustained in transport, the remainder of the neurologic deficits present in this horse can be explained by the extensive nature of the hemangiosarcoma and the associated hemorrhage and edema involving the right pontomedullary region. Microscopically, the neoplasm effaced the dorsolateral aspect of the medulla adjacent to the fourth ventricle and subsequently incorporated the right vestibular and hypoglossal nuclei, accounting for the signs of central vestibular dysfunction (nystagmus, circling, falling, contralateral appendicular extensor muscular hypertonicity, and ipsilateral proprioceptive deficits). Glossal muscular weakness without atrophy was attributed to involvement of the hypoglossal nuclei, but may have been a nonspecific indicator of either upper motor neuron or lower motor neuron dysfunction. The right nasofacial hypalgesia, right facial nerve paralysis, and pharyngeal dysphagia likely resulted from compression of, or hemorrhage into, the nucleus of the spinal tract of the trigemminal nerve, facial motor nucleus, and nucleus ambiguous, respectively. Although no alterations in mentation were observed in this horse before presentation, behavioral changes (subtle and dramatic) are important indicators of potential intracranial disease.[11]

Immunohistochemistry has been useful in differentiating hemangiosarcoma from other carcinomas and lymphangiosarcomas in several species. Factor VIII–related antigen, an endothelial cell marker, has been used successfully in multiple species to identify endothelial-cell origin cutaneous tumors as well as ocular angiosarcoma.[12–15] In this case, factor VIII analysis confirmed the gross and histopathologic diagnosis of CNS hemangiosarcoma.

Although hemangiosarcoma more commonly affects other body systems,[5] it may involve the CNS, resulting in devastating, progressive clinical disease. This case illustrates that neoplasia of the CNS, albeit uncommon, should be considered as a differential diagnosis in horses that present for clinical signs attributable to intracranial CNS lesions.

Footnotes

[a] Flunixin meglumine (Banamine®), Phoenix Scientific Inc, St. Joseph, MO
[b] DMSO, Ft. Dodge, Fort Dodge, IA
[c] Ponazuril (Marquis®), Bayer Healthcare LLC, Shawnee Mission, KS
[d] Dexamethasone, Vedco, St. Joseph, MO
[e] Lactated Ringer's solution, Abbott, Abbott Park, IL
[f] Rabbit anti-human polyclonal factor VIII antibody, DAKO, The Netherlands

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