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Diagnostic Exercise
From The Latin Comparative Pathology Group*

Equine herpesvirus myeloencephalopathy

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Clinical History:

A euthanized, 14-year-old, Warmblood gelding that had participated in an equine show was presented for necropsy and diagnostic workup to the San Bernardino laboratory of the California Animal Health and Food Safety Laboratory System. The animal had a 4-day history of mildly swollen limbs and hyperthermia, and developed neurologic signs shortly before euthanasia.

Necropsy and Microscopic Findings:

The urinary bladder had multifocal to coalescing hemorrhages in the mucosa and approximately 5 ml of turbid urine with sandy sludge (Fig. 1A). The entire spinal cord was removed and cross-sectioned serially after fixation in 10% neutral-buffered formalin during 48h. Multifocally, in multiple sections of the cervical, thoracic, and lumbar segments, there were uni- or bilateral and asymmetrical, wedge-shaped areas of gray discoloration and hemorrhage (Fig. 1B-1D). In addition, there were extensive hemorrhages around the nerve roots of the cauda equina.

Follow-up Questions:

- *Five differential diagnoses for the gross lesions in the spinal cord (Fig. 1B-1D)*
- *Microscopic description for the lesions in the spinal cord (Fig. 2A-2D)*
- *Most likely cause based on clinical history and gross and microscopic findings.*

**The Diagnostic Exercises are an initiative of the Latin Comparative Pathology Group (LCPG), the Latin American subdivision of The Davis-Thompson Foundation and published in cooperation with the Brazilian Journal of Veterinary Pathology. These exercises are contributed by members and non-members from any country of residence. Consider submitting an exercise! A final document containing this material with answers and a brief discussion will be posted on the CL Davis website: https://davisthompsonfoundation.org/diagnostic-exercise/*

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Gross and Microscopic Findings:

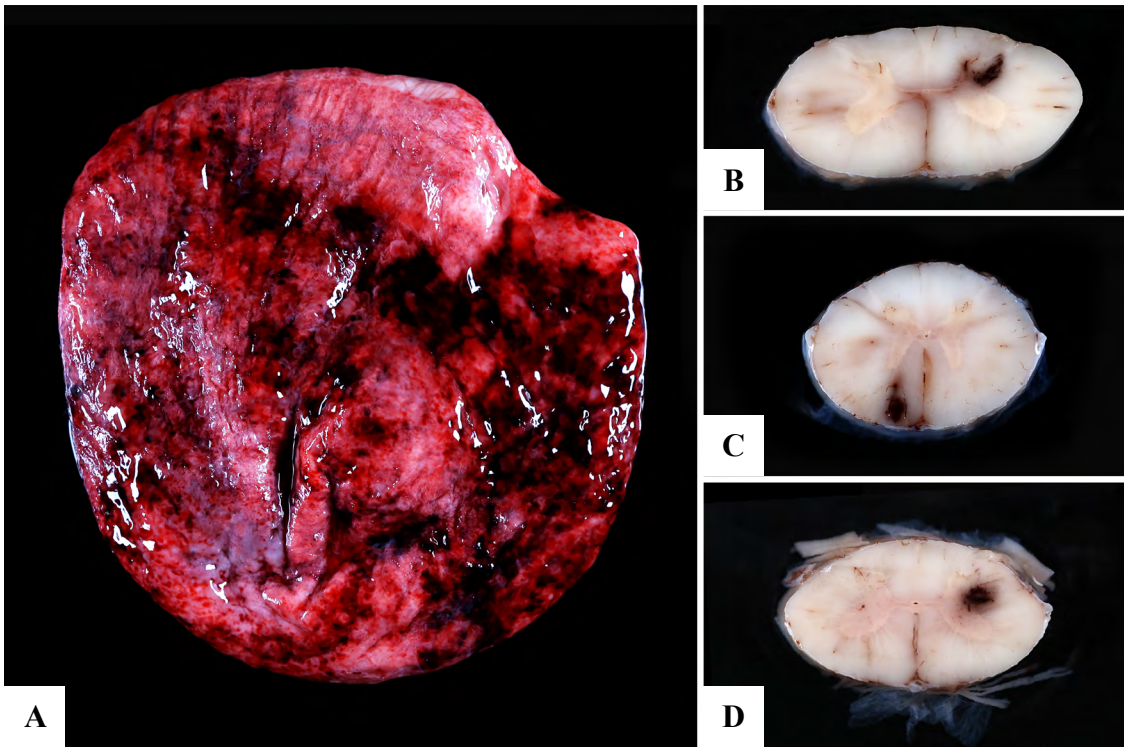

Figure 1. A. Urinary bladder. **B-D.** Transverse sections of formalin-fixed spinal cord: **B.** Cervical spinal cord. **C.** Thoracic spinal cord. **D.** Lumbar spinal cord.

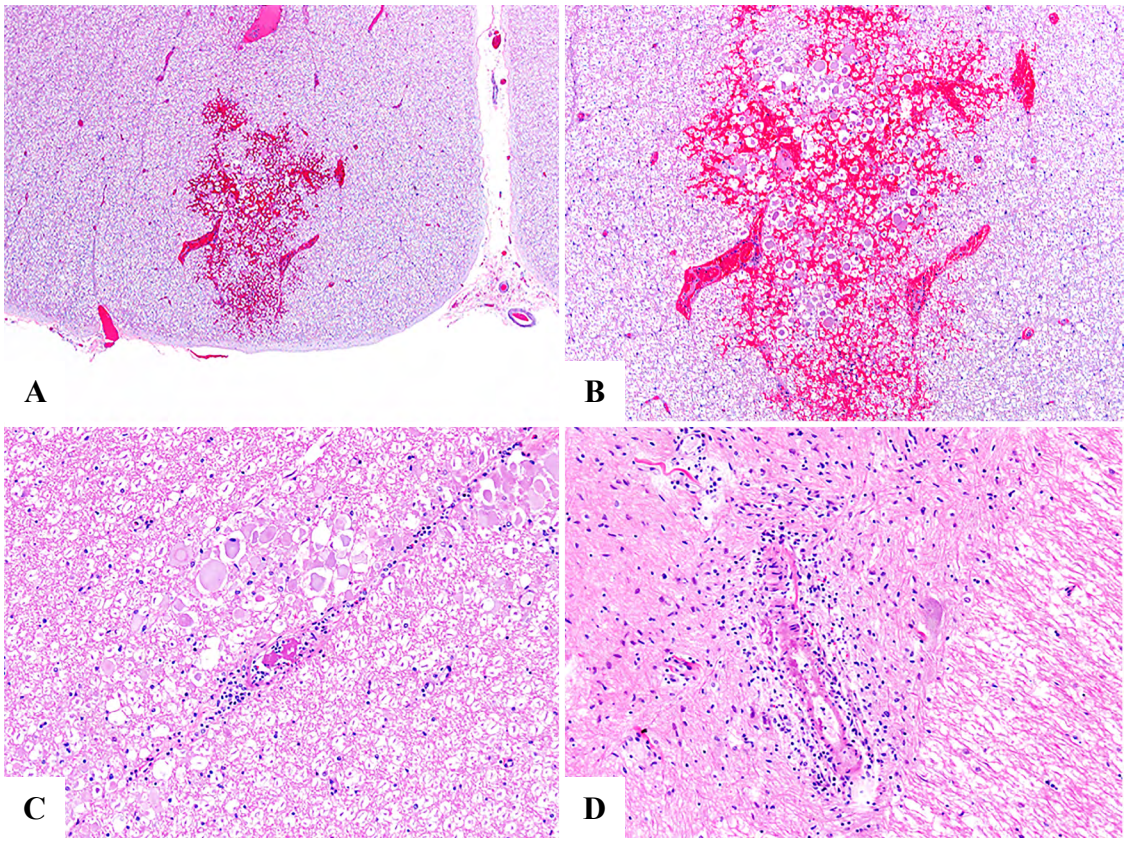

Figure 2. Spinal cord. Hematoxylin and eosin.

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- ***Five differential diagnoses for the gross lesions in the spinal cord (Fig. 1B-1D)***

  (i) Equine herpesvirus myeloencephalopathy (equine herpesvirus-1), (ii) West Nile virus (flavirirus), (iii) rabies (lyssavirus), (iv) equine protozoal myeloencephalitis (*Sarcocystis neurona*, *Neospora hughesi*), (v) alphaviral equine encephalomyelitis (Eastern, Western, and Venezuelan equine encephalomyelitis viruses [alphavirus]), (vi) post anesthetic (hemorrhagic) myelopathy, (vii) fibrocartilaginous embolic myelopathy.

- ***Microscopic description for the lesions in the spinal cord (Fig. 2A-2D)***

  There is a unilateral, focally extensive area of hemorrhage and necrosis in the ventral funiculus of the white matter (Fig. 2A & 2B). Myelin sheaths are dilated and frequently contain swollen, hypereosinophilic axons (spheroids; Fig. 2B & 2C). Blood vessels are surrounded by small lymphocytes that also infiltrate the wall, which is hypereosinophilic (vasculitis, fibrinoid necrosis; Fig. 2C & 2D), and a vascular lumen contains a fibrin thrombus (Fig. 2C).

- ***Most likely cause based on clinical history and gross and microscopic findings.***

  Equine herpesvirus 1 – The history of participation in an equine show and a fever spike with neurologic signs shortly after, coupled with necrohemorrhagic myelitis with vasculitis and thrombosis, and hemorrhages in the urinary bladder, is very suggestive of equine herpesvirus myeloencephalopathy.

Discussion:

This is a case of equine herpesvirus myeloencephalopathy (EHM) caused by equine herpesvirus-1 (EHV-1) from a recent outbreak that occurred in California. EHV-1 qPCR without the neuropathogenic marker was positive in nasal and lung swabs and in a pool of brain and spinal cord tissue. Rabies fluorescent antibody assay was negative in brainstem and cerebellum. West Nile virus RT-qPCR was negative in a pool of brain and spinal cord tissue. *Escherichia coli* and *Streptococcus equinus* were isolated from the urinary bladder, which histologically had extensive submucosal hemorrhages.

EHV-1 is an alphaherpesvirus that causes abortions, neonatal death, respiratory disease, or neurologic manifestations (commonly referred to as EHM) in horses and other species [6,9]. EHV-1 is considered endemic in several horse populations, with mild upper respiratory tract disease, transient pyrexia, and latency in immunocompetent animals, which may later experience disease reactivation in periods of immunosuppression [9]. Transmission occurs primarily via inhalation, and epithelial cells of the upper respiratory tract are initially infected [6]. Respiratory disease is usually transient and self-limiting. Some foals may become infected very early in life, even immediately before parturition, resulting in neonatal disease with disseminated infection, including pneumonia and hepatic necrosis [9]. Viremia occurs via leukocyte trafficking and there is subsequent infection of endothelial cells with secondary vasculitis and thrombosis in several locations [2,7]. If endometrial vessels of the pregnant uterus are targeted, abortions occur, whereas if vessels of the spinal cord and brain are affected, animals develop EHM. There are several genetic variants, some of them more prone to cause EHM (neuropathogenic variant) and others most often associated with abortions (non-neuropathogenic variant), that can be differentiated by PCR targeting a specific single point mutation in the open reading frame 30 [4,5]. Nevertheless, all disease manifestations (respiratory, abortions, neurologic) can be observed independently of the variant [8]; this present case is an example of the latter, since a non-neuropathogenic variant caused EHM.

A fever spike usually precedes the clinical onset of EHM [9]. Clinical signs may include lethargy, mild to severe ataxia, weakness of the hind limbs to tetraplegia, edema of the distal limbs, urinary incontinence or urinary retention, prostration, and death [6,9]. Gross lesions can be subtle or even absent, and mainly consist of asymmetric foci of malacia and hemorrhage in the brain and spinal cord, especially in the white matter of the spinal cord [1]. Histologically, a thrombo-occlusive, nonsuppurative to necrotizing vasculitis associated with areas of hemorrhage and neuropil necrosis with axonal swelling, is seen [1].

Cases of EHV-1 are frequently reported around the world and EHM is considered an emerging disease in the USA. An outbreak of EHM occurred in 2021 in Valencia, Spain, with related cases in several other European countries and Qatar, which fostered worldwide awareness about this disease [3,10]. In the USA, there have been no cases directly related to this European outbreak to our knowledge, but cases of EHM are reported every year to the Equine Disease Communication Center (https://equinediseasecc.org/alerts). In California, EHM is a regulatory condition per the California Department of Food and Agriculture and a high profile diagnosis, which often entails quarantine decisions and requirements for exports and shows for the submitting client. Cases are detected regularly, either individually or as in outbreaks. The most recent outbreak began on February 2022 and affected multiple counties of southern and northern California.

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