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Diagnostic Exercise
From the Latin Comparative Pathology Group and the Davis-Thompson Foundation

Necrotizing meningoencephalitis in a calf

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Clinical history:

A 6-month-old male Red Angus calf from São Vicente do Sul, Rio Grande do Sul (Brazil) died after an 8-day history of anorexia, dullness, blindness, aimless walking, and circling. The calf was part of a herd of 300 calves that had been weaned and placed on an oat pasture 20 days before the onset of clinical signs. Two additional calves had similar clinical signs and died during the same period.

Autopsy findings:

Gross findings were restricted to the brain (Figs. 1, 2). There was widespread hyperemia of leptomeningeal vessels. The frontal telencephalic cortex was partially collapsed and distinctly depressed, with flattening of gyri, narrowing of sulci (edema), and dark red areas of hemorrhage.

Follow up Questions

- *Most likely differential diagnoses*
- *Morphologic diagnosis*
- *Cause*
- *Diagnostic confirmation*

**The Diagnostic Exercises are an initiative of the Latin Comparative Pathology Group (LCPG), the Latin American subdivision of The Davis-Thompson Foundation (DTF). 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 DTF website: https://davisthompsonfoundation.org/diagnostic-exercise/*

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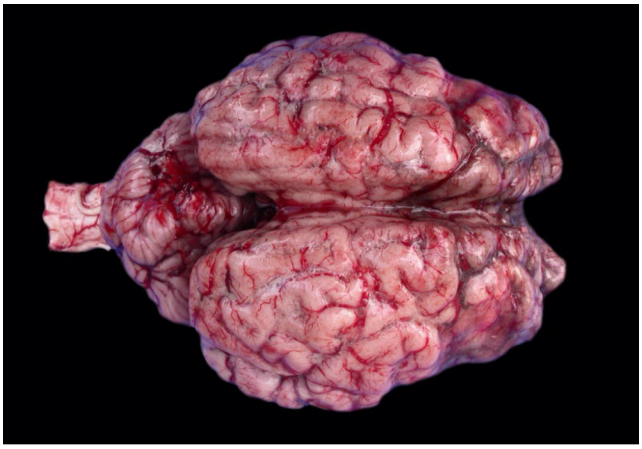

Figure 1. Brain, calf. The frontal telencephalic cortex is depressed, with flattening of gyri, narrowing of sulci (edema), and dark red areas of hemorrhage. Leptomeningeal vessels are hyperemic.

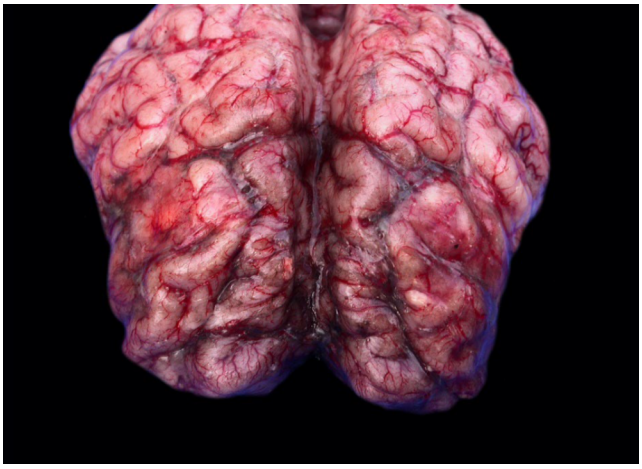

Figure 2. Brain, calf. There is a sharp demarcation between the partially collapsed frontal telencephalic cortex and the unaffected telencephalon.

ANSWERS

Histologic findings: The frontal telencephalic cortex was partially collapsed due to widespread neuronal necrosis, inflammation, edema, and hemorrhage. Necrotic neurons had shrunken and hypereosinophilic cytoplasm with pyknotic nuclei (Fig. 3). There was rare neuronophagia. The surrounding gray matter was often disrupted and infiltrated by numerous foamy macrophages with areas of astrogliosis (Fig. 4). Rare intranuclear viral inclusions were present in neurons and astrocytes (Fig. 5). Perivascular spaces throughout the adjacent gray matter and leptomeninges were surrounded by a moderate to large number of lymphocytes and plasma cells.

Most likely differential diagnoses: Herpesviral meningoencephalitis, cerebrocortical malacia.

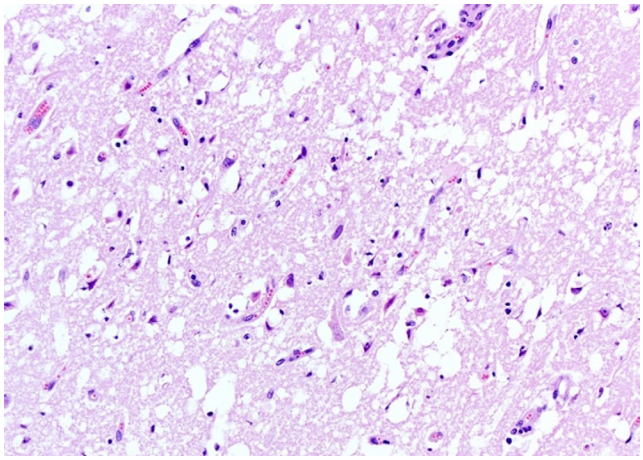

Figure 3. Brain, calf. Cortical neurons with hypereosinophilic, shrunken cytoplasm and pyknotic nuclei (necrosis).

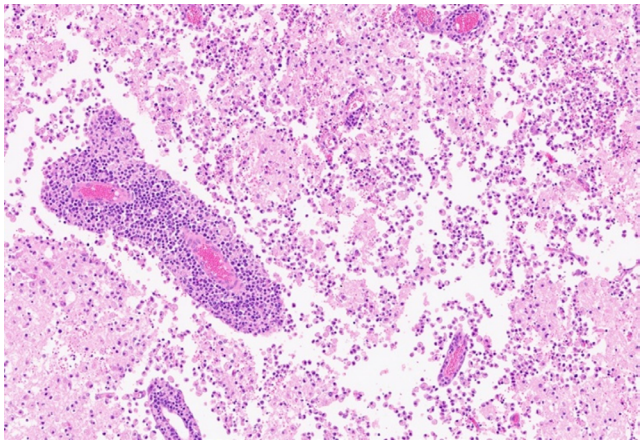

Figure 4. Brain, calf. The gray matter is disrupted by numerous foamy macrophages and perivascular lymphocytes and plasma cells.

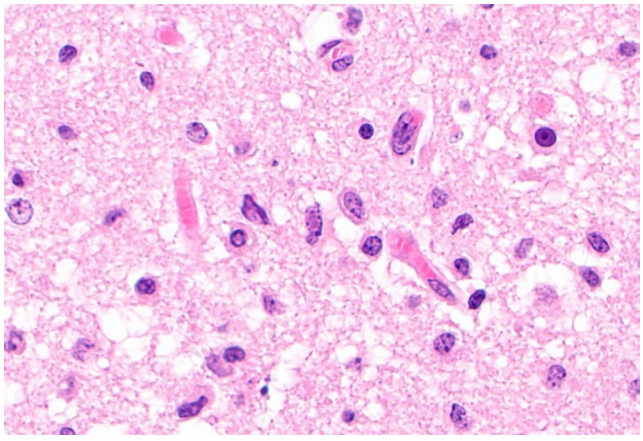

Figure 5. Brain, calf. An intranuclear eosinophilic viral inclusion within an astrocyte (center).

Cause: Bovine herpesvirus-1 (BoHV-1) or -5.

Diagnostic confirmation: Pathologic findings and viral inclusions are strong indicators for the diagnosis of herpesviral meningoencephalitis in endemic areas, but diagnostic confirmation should be achieved with fluorescent antibody test, immunohistochemistry, and/or PCR for BoHV.

Comments: BoHV-1 and 5 are DNA viruses of the family *Herpesviridae*, subfamily *Alphaherpesvirinae*, genus *Varicellovirus* (4). BoHV-1 is associated mainly with respiratory disease (bovine infectious rhinotracheitis), reproductive disease (abortion, vulvovaginitis, and balanoposthitis), systemic infections in newborn calves, and neurologic disease (4). BoHV-5 is associated primarily with neurologic disease that is clinically and pathologically identical to that caused by BoHV-1 (2).

Necrotizing meningoencephalitis by BoHV-1 and BoHV-5 occurs mainly in South America and Australia (1,2,3,4). Clinical disease typically affects calves and less commonly adult cattle submitted to stressing situations such as such as weaning, changes in feeding, transport, crowding, and introduction of individuals from other herds (1,2,3). Affected calves in our outbreak had been weaned and transported to a pasture 20 days before the onset of the clinical signs.

Infection occurs after direct or indirect contact among susceptible individuals, typically via respiratory route (3). After primary replication in the oral, nasal, oropharyngeal, and ocular mucosa, viral particles reach local nerve endings and are transported to sensory ganglia, in which they replicate and establish latency (3). Viral transport to the brain occurs via retrograde transport along the olfactory and less often facial and trigeminal nerves and may result in replication with neurological disease or subclinical infection (2,3). Massive viral replication in the brain following the olfactory route takes place in the rostral portions of the telencephalic cortex (2). This neuroanatomic distribution of lesions is typical of bovine herpesviral meningoencephalitis and should promptly raise suspicion of BoHV-1 or -5 infection in endemic areas (3). Subclinical disease results in recovered and latently infected individuals, which will become a source of infection to other susceptible cattle in case of virus reactivation from latency (3).

Clinical signs may vary but typically reflect the respiratory and ocular infection and the frontal telencephalic lesions observed in most affected animals (1,2). The main clinical signs include anorexia, nasal and ocular discharge, dullness, blindness, circling, head pressing, nystagmus, opisthotonos, tremors, incoordination, seizures, and recumbency. The clinical course typically lasts from 1 to 15 days (1,2,3). Neurologic disease almost invariably leads to death.

As observed in our case, autopsy findings are restricted to the brain in most cases, although some animals can have evidence of rhinitis and/or conjunctivitis (3). The most striking lesions in the brain consist of reddening and softening of the frontal telencephalon, with flattening of gyri and narrowing of sulci (edema). The temporal and parietal lobes, as well as the basal nuclei and thalamus can be occasionally affected. Overtime, the gray matter within affected areas undergoes necrosis and swelling, and subsequently collapse, as evidenced by our case. On cut surface, the cerebral cortex may appear as dark brown and granular due to hemorrhage and necrosis. There is usually leptomeningeal hyperemia throughout, with occasional cerebellar herniation through foramen magnum (1,2,3).

Histologically, lesions consist of extensive necrotizing meningoencephalitis that affects primarily the telencephalic gray matter. Early lesions include cortical neuronal necrosis that is often accompanied by neuroparenchymal and leptomeningeal perivascular accumulations of lymphocytes and plasma cells. As the clinical course evolves, there may be neuronophagia, astrogliosis, and microgliosis, with different degrees of neuroparenchymal hemorrhage and edema. After a few days, the lesions will be dominated by scattered and subsequently dense infiltration of foamy macrophages that replace necrotic areas and surrounding perivascular spaces (1,2,3). Eosinophilic intranuclear viral inclusions can be observed in neurons and astrocytes but may be rare and should not be relied upon for the diagnosis (2,3).

The diagnosis can be supported by the epidemiology, clinical signs, and pathologic changes (3). BoHV-1 and BoHV-5 are closely related genetically and antigenically, and while diagnostic confirmation of herpesviral meningoencephalitis can be achieved by fluorescent antibody test, immunohistochemistry, and PCR, the differentiation between both viruses by these routine diagnostic tests is not possible (1,2,3). The detection of a specific region of the viral glycoprotein C is necessary and available for the discrimination between BoHV-1 and BoHV-5 (2,4).

While the gross changes in cases of polioencephalomalacia could be similar to those associated with bovine herpesviral meningoencephalitis, the presence of dense inflammatory infiltrates and viral inclusions should be more consistent with BoHV-1 or -5 infection (5).

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