Joint Pathology Center
Veterinary Pathology Services

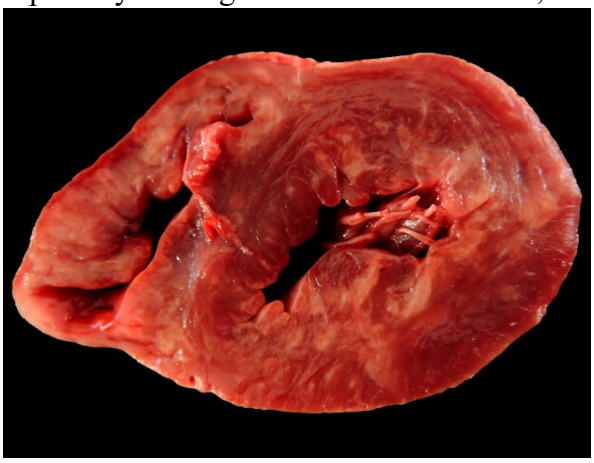
WEDNESDAY SLIDE CONFERENCE 2024-2025

Conference #24 — 23 April 2025

CASE I:

Signalment:
120-day-old, male, commercial swine (*Sus scrofa domesticus)*

History:
Two growing-finishing farms in the Midwest region of Brazil experienced outbreaks of sudden death among pigs aged between 120 and 130 days. The mortality rate ranged between 9% and 10% in the affected batches. Upon clinical examination, some pigs exhibited nonspecific signs such as trembling, dyspnea, and squealing sounds shortly before death. Pigs from multiple pens of both sexes, especially the largest animals in the batch, were affected. The antimicrobial and antipyretic treatment used did not yield any response. Additionally, large numbers of black rats (*Rattus rattus*) were observed inhabiting the facilities during farm visits. The rodent control measures implemented on the farm were ineffective.

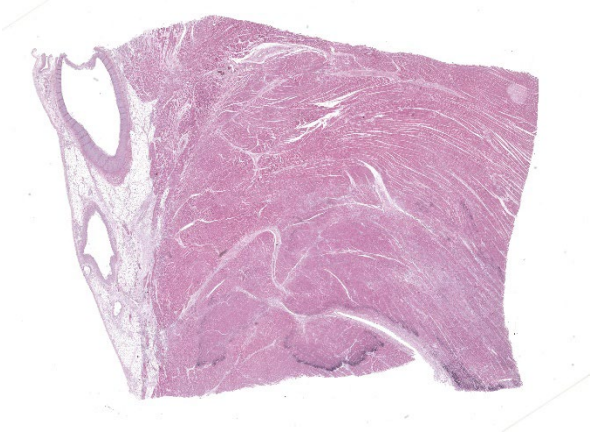


Heart, pig: On the cut surface of the myocardium, there were areas of pale tan discoloration ranging from 0.5-1 cm in diameter, sometimes coalescing, and more pronounced in the right and left ventricles. (Photo courtesy of Faculdade de Veterinária, Universidade Federal do Rio Grande do Sul, Setor de Patologia Veterinária, http://www.ufrgs.br/patologia).

Gross Pathology:
At necropsy, major lesions were observed in the heart, which was enlarged and showed on the epicardial surface multifocal pale to slightly white areas, ranging from 0.5-1 cm in diameter, which extended through the myocardium on the cut surface. These pale areas were more pronounced in the right and left ventricles, occasionally presenting a gritty texture. Mild hydropericardium and pulmonary edema were also observed.

Laboratory Results:
RT-PCR: samples of liver, lymph node, and heart tested positive for Encephalomyocarditis virus. Brain sample tested negative.

Microscopic Description:
Heart, left ventricle: in the myocardium, multifocally, there are areas of necrosis of the cardiomyocytes, characterized by hypereosinophilia, loss of cellular detail, nuclear karyolysis and pyknosis, associated with non-



Heart, pig: One section of ventricle is submitted for examination. Serpiginous areas of mineralization are evident at subgross magnification. (HE, 10X)

suppurative inflammation, composed of macrophages, lymphocytes and plasma cells. This inflammatory infiltrate frequently replaces the necrotic cardiomyocytes and infiltrates the myocardial interstitium. In some areas, there is deposition of intracytoplasmic basophilic granular material in necrotic cardiomyocytes (highlighted by Von Kossa histochemistry - mineralization). Additionally, mild fibrous connective tissue proliferation is also present in the myocardial interstitium.

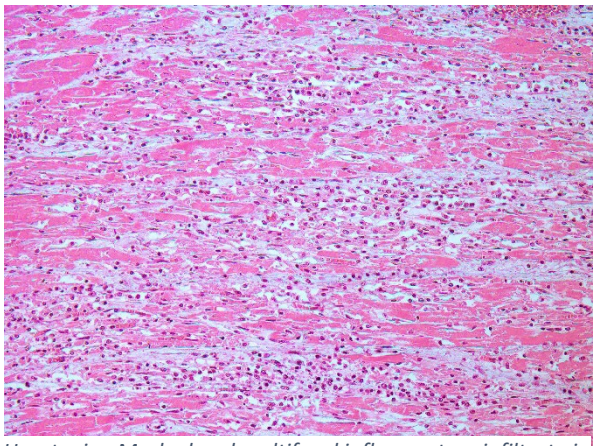
Contributor's Morphologic Diagnosis:

Myocarditis, necrotizing and lymphoplasmohistiocytic, multifocal, moderate, with dystrophic mineralization.

Contributor's Comment: The *Picornaviridae* family consists of small, non-enveloped, single-stranded RNA viruses, which include the *Cardiovirus* genus. Encephalomyocarditis virus (EMCV) is classified within the genus *Cardiovirus*, specifically as *Cardiovirus* A (the genus *Cardiovirus* comprises six species named A to F).[5,9]

EMCV is cause of myocarditis in several wildlife species, including non-human primates, as well as domestic animals, particularly swine, and humans.[1,3,4,6,11] Although the name 'encephalomyocarditis' originates from the initial association of the virus with brain and cardiac lesions, encephalitis is not consistently observed in natural EMCV infections in pigs.[8,12] Encephalitis mainly occurs in experimental infections in mice and swine fetuses, whereas myocarditis is a frequent lesion in both natural and experimental infections.[1,8,12]

Rats and mice serve as reservoir species for EMCV, spreading the virus and causing outbreaks in susceptible animals.[3,7,8] Several dead black rats (*Rattus rattus*) from the reported farms were subjected to necropsy, revealing positive RT-PCR results for EMCV in fecal samples. Accordingly, the presence of rodent infestation at the farms where the outbreak occurred indicates a failure of the control system and suggests rodents as potential reservoir and disseminator of EMCV in this report. On the other hand, EMCV infection is usually subclinical and may demonstrate that recovered pigs play an important

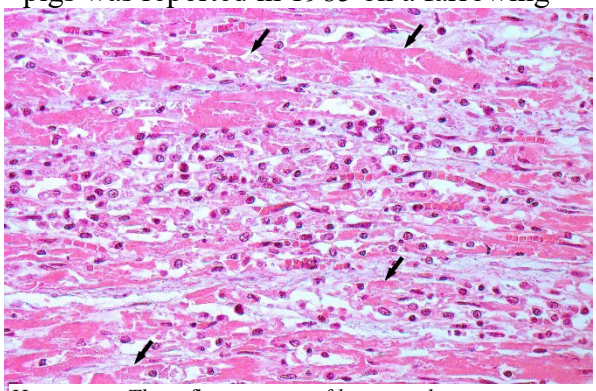


Heart, pig. Marked and multifocal inflammatory infiltrate is observed in the interstitium and dissecting cardiac fibers. (HE, 200X) (Photo courtesy of Faculdade de Veterinária, Universidade Federal do Rio Grande do Sul, Setor de Patologia Veterinária, Universidade Federal do Rio Grande do Sul, Setor de Patologia Veterinária, http://www.ufrgs.br/patologia).

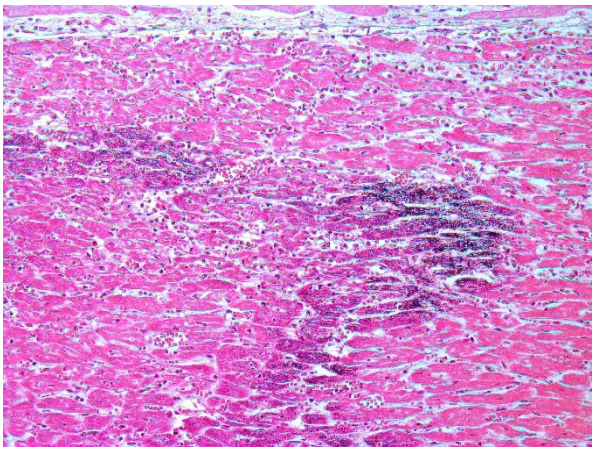
role in the dissemination of EMCV. Therefore, in addition to controlling rodents, it is crucial to identify subclinical animals for more effective disease control.[2]

EMCV infection can result in characteristic myocardial lesions, with a pattern of viral myocarditis (non-suppurative inflammation), myocardial necrosis, and marked dystrophic mineralization which are clues for histopathological diagnosis.[8,12] However, some differential diagnoses should be considerate such as *Aphthovirus* infection, *Parvovirus* infection, and vitamin E/selenium (VitE/Sel) deficiency.[12,14] VitE/Sel deficiency is the most important differential diagnosis for commercial pigs and can also lead to cardiac mineralization patterns similar to those seen in EMCV infection. However, VitE/Sel deficiency is more common in nursery pigs compared to finishing pigs, and other lesions such as cardiac hemorrhages, hepatic necrosis, and muscular necrosis may be present in this condition, which are useful for pathological differentiation.[10,12] Additionally, RT-PCR detection of EMCV is crucial to confirm the diagnosis.[8]

In Brazil, the first occurrence of EMCV in pigs was reported in 1985 on a farrowing



Heart, pig. The inflammatory infiltrate replaces necrotic cardiomyocytes and is composed of lymphocytes, plasma cells, and macrophages. Note necrotic cardiomyocytes (black arrows), characterized by loss of cellular details and cross striations, nuclear karyolysis and pyknosis.(HE, 400X) (Photo courtesy of Faculdade de Veterinária, Universidade Federal do Rio Grande do Sul, Setor de Patologia Veterinária, http://www.ufrgs.br/patologia).



Heart, pig. Necrotic cardiomyocytes showing deposition of intracytoplasmic basophilic granular material (dystrophic mineralization). (HE, 200X) (Photo courtesy of Faculdade de Veterinária, Universidade Federal do Rio Grande do Sul, Setor de Patologia Veterinária, http://www.ufrgs.br/patologia).

farm in the southern region, affecting one sow and resulting in the death of 9 out of 10 piglets.[13] After a 38-year gap with no further documented cases, an outbreak in growing-finishing pigs occurred in 2023.[8] The phylogenetic analysis of the VP1 gene from the EMCV identified in this outbreak, showed that the samples contained similar strains that had their closest relatives identified in humans in Peru.[6,8] However, epidemiological, serological, and field studies on the distribution of EMCV in Brazil are limited, and more research is needed to understand the real impact of EMCV.

Contributing Institution:

Faculdade de Veterinária
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http://www.ufrgs.br/patologia

JPC Morphologic Diagnosis: Heart, ventricle: Pancarditis, necrotizing and lymphohistiocytic, monophasic, subacute, multifocal, marked.

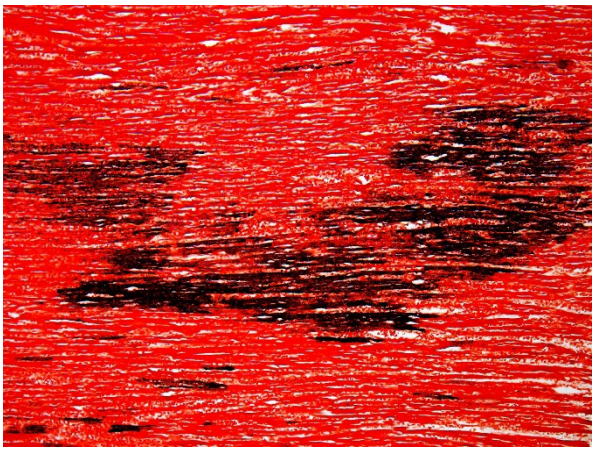
JPC Comment: This week's moderator was Dr. Patty Pesavento from the University of

California-Davis, who explored viral and vascular pathology with conference participants. We enjoyed discussing this first case as its descriptive features reinforced the underlying pathogenesis of EMCV. Dr. Pesavento's first question to the group challenged them to consider the target cell for the virus – is it the myocyte or something else?

The answer in this case is probably both. Prior research has shown that vascular cell adhesion molecule 1 (VCAM1) is the necessary receptor for EMCV infection,[16] though other sialylated surface glycoproteins may play a role depending on EMCV strain. Supporting this interpretation of endothelial cells within capillaries being a target is the distribution of changes across all layers of the heart (i.e. pancardial) and regionally distinctive areas of necrosis and mineralization that are suggestive of damage to small-caliber blood vessels. A Movat's pentachrome stain highlights that much of the increased clear space in section reflects edema versus fibrosis.

We appreciate the contributors' morphologic diagnosis and added a single modifier to qualify the necrosis as monophasic in this case. The dystrophic mineralization in this case is remarkable and we speculate that the punctate basophilic foci may represent mineralization of organelles (mitochondria) secondary to ATP depletion and calcium dysregulation.

The contributor provides several good differential diagnoses for this case. Other important rule outs for porcine myocarditis (pancarditis) include porcine circovirus 2, porcine parvovirus, and toxin ingestion such as cottonseed (gossypol).[12] Dr. Pesavento also noted two other important scenarios related to transmission of EMCV for participants to be aware of. As rodents are a common nuisance in zoological parks, they may contaminate feed and water with virus, or in select cases, be ingested directly by primates or other species.[3] Finally, EMCV has been shown to persist within the porcine myocardium, which presents an unusual hazard for xenotransplantation of hearts to cardiac patients.[15] As recipients are highly immunosuppressed, the potential for subsequent permissive replication and spread to the CNS leading to severe encephalitis should not be overlooked.



Heart, pig. Von Kossa-positive intracytoplasmic basophilic granular material (mineralization - calcium). (Von Kossa, 200X) (Photo courtesy of Faculdade de Veterinária, Universidade Federal do Rio Grande do Sul, Setor de Patologia Veterinária, http://www.ufrgs.br/patologia).

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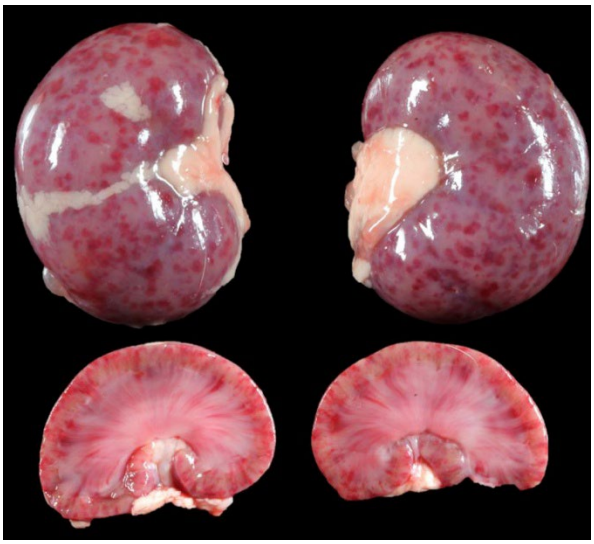
CASE II:

Signalment:
3-week-old male Bulldog (*Canis familiaris*)

History:
The puppy was born by caesarean section and was from a litter of eight. At 18 days old it was found shaking, anorexic and lethargic and was



Kidney, puppy: There were multifocal to coalescing petechial to ecchymotic hemorrhages in the renal cortex that on cut surface extended into the renal parenchyma. (Photo courtesy of: Massey University School of Veterinary Science)

treated empirically with amoxicillin and dexamethasone. The puppy deteriorated and within 48 hours was hospitalized and placed in an oxygen tent. A serosanguinous nasal discharge and regurgitation of milk from the nose and mouth were present. The puppy was the second of the litter to die; a third puppy was unwell at the time this puppy was presented for postmortem examination.

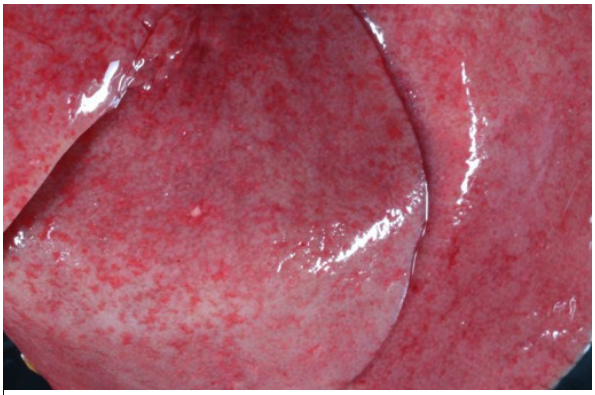
Gross Pathology:

The 3-week-old male Bulldog puppy was in only adequate body condition (total body weight 735g). On external examination, a moderate amount of white fluid (milk) was present in the nasal passages. On internal examination, there were multifocal to coalescing petechial to ecchymotic hemorrhages throughout the renal cortex that on cut surface extended into the renal parenchyma. The liver was diffusely pale and had multifocal petechial hemorrhages, and multifocal 1 mm pitted areas on the capsular surface. No other gross lesions were present elsewhere.

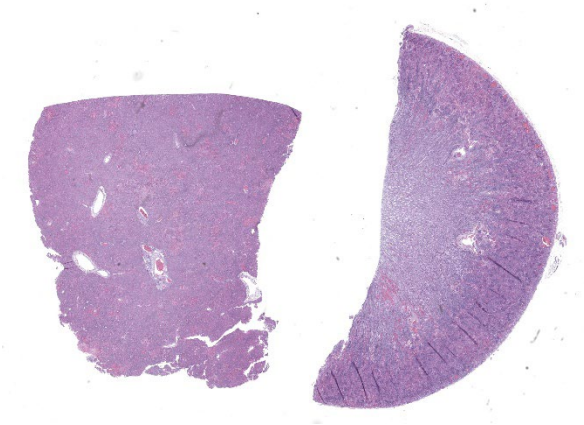
Microscopic Description:

Kidney: Affecting approximately 30% of the renal parenchyma, with lesions predominantly localized in the cortex, are multifocal randomly distributed foci of coagulative necrosis characterized by tinctorial aberrations and retention of cellular architecture, with accumulations of cellular and karyorrhectic debris admixed with haemorrhage, fibrin and edema. Renal tubular epithelial cells within these areas are degenerate with swollen, pale and vacuolated cytoplasm, or necrotic with hypereosinophilic cytoplasm and nuclear pyknosis and occasional sloughing into luminal spaces. Rare 2-4 um eosinophilic, intranuclear viral inclusions are present within renal tubular epithelial cells. Multifocally, glomeruli rarely display segmental necrosis, characterized by hypereosinophilia, loss of cellular detail and the presence of karyorrhectic debris. Visceral and parietal epithelium are hypertrophied in affected glomeruli.

Liver: Within the liver, there is multifocal random hepatocellular necrosis, characterized by loss of normal architecture and replacement by cellular and karyorrhectic debris, hemorrhage and low numbers of neutrophils and macrophages. Rarely, hepatocytes adjacent to



Liver, puppy. The liver was diffusely pale and had multifocal petechial hemorrhages, and multifocal 1 mm pitted areas on the capsular surface. (Photo courtesy of: Massey University School of Veterinary Science)



Liver, kidney, puppy: One section of liver and one of kidney are submitted for examination. Areas of hepatic necrosis and renal hemorrhage are evidence at subgross magnification. (HE, 11X)

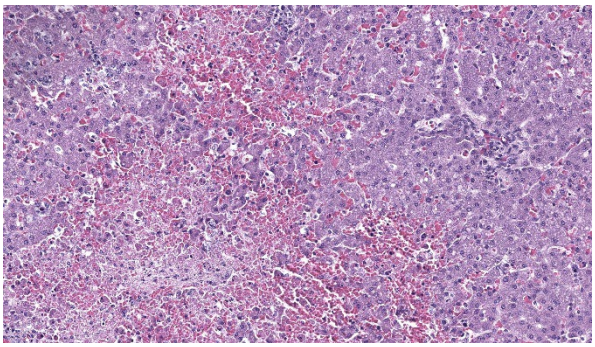
areas of necrosis have 2-4 um, eosinophilic intranuclear viral inclusion bodies, which are surrounded by a clear halo and peripheralize nuclear chromatin. Periportal areas are mildly expanded by edema and low numbers of neutrophils and macrophages. Diffusely, small and medium arteriolar walls are moderately expanded by edema, with endothelial cells showing a spectrum of cell degeneration and necrosis including nuclear and cytoplasmic swelling, pyknosis, karyorrhexis and karyolysis.

Contributor's Morphologic Diagnosis:
Kidney: Severe, acute, multifocal, necrohemorrhagic nephritis with rare epithelial intranuclear viral inclusions.

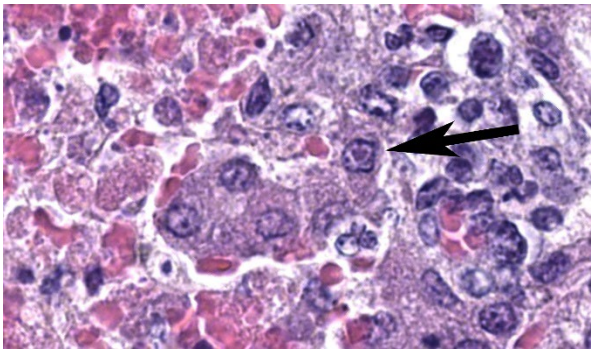
Liver: Severe, acute, multifocal random, necrohemorrhagic hepatitis with rare epithelial intranuclear viral inclusions and multifocal arteriolar endothelial necrosis.

Contributor's Comment: The lesions in this case are consistent with acute infection with canine herpesvirus-1 (CaHV-1). CaHV-1 is an Alphaherpesvirus which infects both domestic and wild canids and was first described as a cause of neonatal puppy mortality in the 1960s.[2] It has a worldwide distribution and is antigenically similar to other Alphaherpesviruses of veterinary significance including feline herpesvirus-1, phocid herpesvirus-1 and equine herpesvirus-1 and 4.[2,4]

CaHV-1 is inactivated in temperatures over 40ºC (104ºF) and is readily broken down in the environment. Neonatal puppies aged less than 3 weeks of age become infected through direct contact and inhalation or ingestion of infected oronasal or genital secretions during passage through the birth canal, postnatal grooming by the dam or through contact with other shedding hosts including littermates.[2,3,8] Following exposure, it is thought that CaHV-1 infects epithelial cells of the oropharynx and lymphocytes in the tonsils. Leukocyte trafficking in lymphocytes spreads the virus systemically, where it targets endothelial cells indiscriminately and epithelial cells of several organ systems including the kidney, spleen, lung and liver.[8] Gross lesions in neonates are considered diagnostic and include miliary necrosis and petechial hemorrhages in multiple organs, particularly the kidneys.[1,8] This is further confirmed by demonstration of intranuclear viral inclusion bodies, though other relevant diagnostic tests include virus isolation, immunofluorescence, and polymerase chain reaction.[1] There may be pleural or peritoneal effusions, splenomegaly, lymphadenomegaly,



Liver, puppy. There are large areas of coagulative necrosis scattered randomly throughout the hepatic parenchyma. (HE, 301X)



Liver, puppy: At the periphery of necrotic foci, rare hepatocellular nuclei contain a single rhomboidal 2-4um intranuclear inclusion. (HE, 850X)

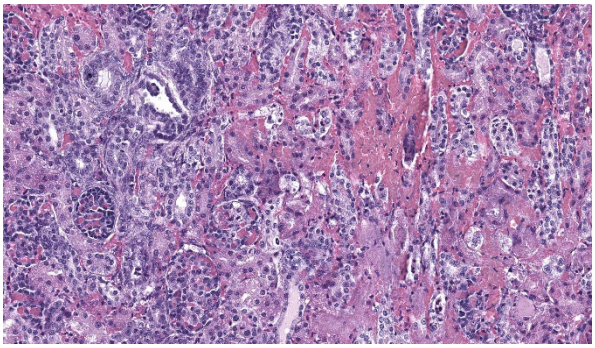
and wet lungs with froth in the airways.[7] This puppy also had a severe necrotizing bronchopneumonia with intranuclear inclusion bodies in the bronchiolar epithelial cells.

Ocular lesions may not always be obvious if the affected puppy's eyelids are not yet open (after 10-14 days) and include panuveitis, retinitis and optic neuritis. Puppies that survive infection may have blindness, cataracts, optic nerve atrophy, and retinal degeneration or dysplasia.[3] Meningoencephalitis may also be seen, with lesions including multifocal glial nodules and cerebellar cortical necrosis without significant inflammation.[5]

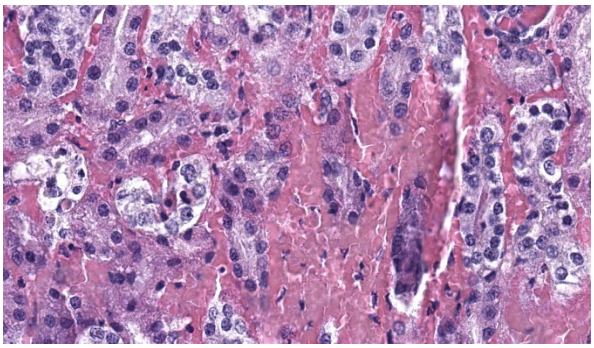
An incubation period of 3-10 days is followed by 1-3 days of nonspecific clinical signs including vomiting, inappetence and abdominal pain.[2,7] The mortality rate can be up to 100% in some litters, with neonatal susceptibility thought to be due to a combination of immune naivety and a lower body temperature which improves the ability of CaHV-1 to enter cells, replicate and spread.[2,8] Infected puppies may shed virus within respiratory and ocular secretions, saliva, urine and on mucosal surfaces, and thus serve as a source of virus for other littermates. Puppies that are infected after 3 weeks of age or those that have been exposed to maternally derived antibody are generally resistant to disease.[3]

Infection of adult dogs and older puppies is associated with mild upper respiratory tract disease; CaHV-1 is yet to be shown to be a primary pathogen in canine infectious tracheobronchitis.[1,7] Severe fibrinonecrotic or hemorrhagic bronchopneumonia leading to respiratory distress and death has been occasionally reported in adult dogs.[6] Infection of a naïve dam during pregnancy can result in placental necrosis with mid-gestational abortion and stillbirths or weak puppies that die soon thereafter. Development of maternal antibody prevents disease in subsequent litters. Adult animals may also show lymphoid hyperplasia and hyperemia of the genital mucous membranes.[2]

CaHV-1 can establish latency within canids, existing within the trigeminal ganglia, lumbosacral ganglia, tonsils and parotid salivary glands. Recrudescence of infection can occur at times of physiological stress or treatment with immunosuppressive doses of corticosteroids. These animals may serve as a source of infection within breeding colonies,[2,3] and can shed virus from mucosal surfaces including those not involved in producing clinical disease.[3]. Serological studies may be of use in determining prevalence in kennels and at-risk breeding stock.[1]



Kidney, puppy: There are areas of hemorrhage and tubular necrosis scattered throughout the cortex. (HE, 252X)



Kidney, puppy. Higher magnification of an area of interstitial hemorrhage and tubular necrosis. (HE, 350X)

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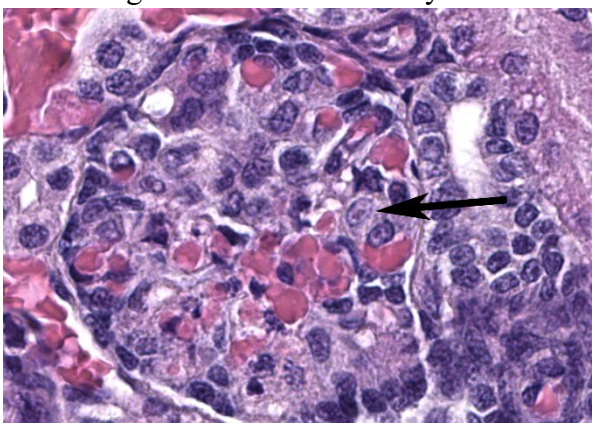
JPC Morphologic Diagnosis: 1. Liver: Hepatitis, necrotizing, multifocal to coalescing and random, moderate, with rare hepatocellular intranuclear viral inclusions.

2. Kidney: Nephritis, necrotizing, tubular and glomerular, multifocal, moderate.

JPC Comment: This second case is a double feature, with the contributor kindly sharing features of CaHV-1 in two separate tissues with us. Microscopic features of the virus were classic for alphaherpesviruses, with Dr. Pesavento remarking that changing the signalment of the animal to another (e.g. horse, cow) would still bring conference participants to consider their respective alphaherpesvirus (EHV-1, BHV1) accordingly. Canine adenovirus and sepsis are other important rule outs for this case. Adenovirus would also have intranuclear inclusions and centrilobular hepatic necrosis (due to ischemia and endotheliotropism) while CaHV-1 is more hepatotropic – animal age is therefore helpful in weighting these differentials. Bacterial sepsis should reflect a greater number of neutrophils which can be confirmed via a simple touch impression on the necropsy floor. Dr. Pesavento emphasized this point in her preconference lecture to participants and urged anatomic pathologists to develop basic familiarity with cytology and incorporate it to drive case management decisions during case prosection.

This case has overlap with Case 4 of this conference and both are best reviewed together. Here, intranuclear inclusions were sparse (especially in the kidney) though the constellation of microscopic features were nonetheless suggestive of CaHV-1. The gross image of the kidney reinforces this differential – we debated whether the subcapsular hemorrhage correlated with the expansion of the renal interstitium microscopically, though distinguishing between simple congestion versus hemorrhage was characteristically difficult.



Kidney, puppy: Rare podocyte nuclei contain intranuclear viral inclusions. (HE, 1405X).

Dr. Pesavento highlighted several subtle slide features that pointed to this animal being very young, including fetal glomeruli with cuboidal epithelium, thinned renal cortex (decreased corticomedullary ratio) and decreased space between glomeruli, and smaller overall size of hepatocytes. From low magnification, the increased basophilia (colloquially, 'blueness') reflects these developing

cells and the active transcription of nucleic acids therein.

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CASE III:

Signalment:
14-day-old, Angus calf, Bovine, *Bos taurus*. Male.

History:
Six out of fifty 2–3-week-old, Angus calves were found dead with other calves presenting with lethargy, tachypnea, hypersalivation, circling, tremors, and seizures, with rapid deterioration preceding to death. Calves were otherwise in good body condition. No abnormalities of calves were observed at birth. These calves originated from artificially inseminated heifers.

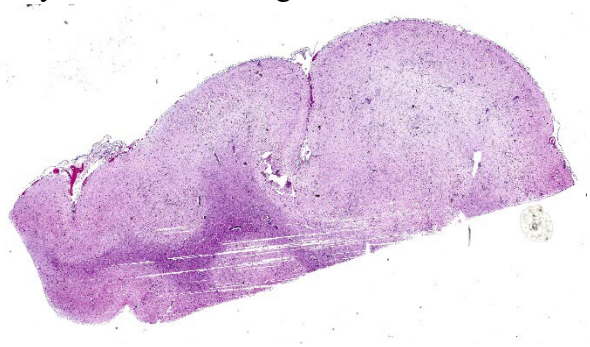
Laboratory Results:
Bovine herpesvirus real time PCR positive on fresh brain

Bovine herpesvirus-5 real time PCR positive on fresh brain

Listeria spp. selective culture on fresh brain negative

Chlamydia pecorum real time PCR on brain dry swab negative

Aqueous humor urea, glucose, β-hydroxybutyrate, calcium, magnesium, nitrate, nitrite



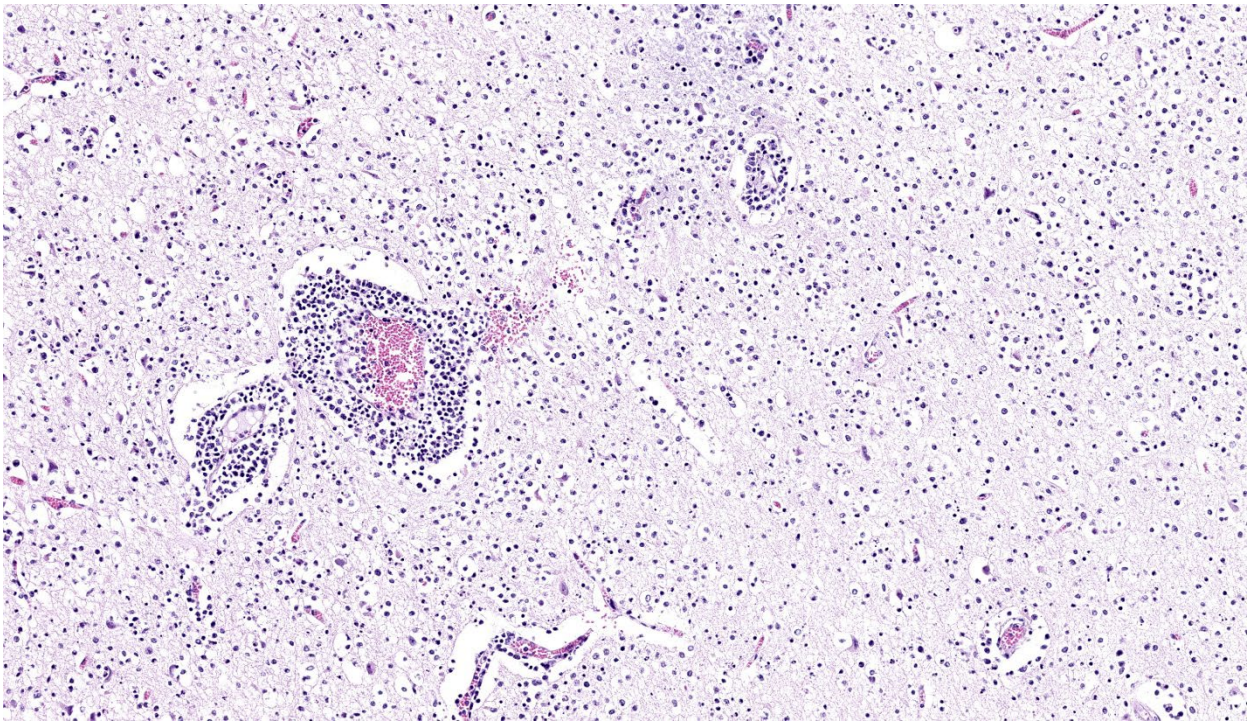
Cerebrum, calf: One section of cerebrum is submitted for examination. Prominent perivascular cuffs are present at subgross magnification. (HE, 8X)

analytes within normal limits. Aqueous humor potassium is elevated (likely due to delayed post-mortem sampling or vitreous contamination).

Contributor's Microscopic Description: Brain; rostral cerebrum:

Multifocally, the meninges contain small numbers of lymphocytes, occasional macrophages and extravasated erythrocytes (hemorrhage), and rare neutrophils. Frequently, blood vessels in the white and to a lesser extent the gray matter are cuffed by up to 4-5 layers of lymphocytes, macrophages, and rare plasma cells. Occasional scattered neurons are shrunken, angular, hypereosinophilic, and have pyknotic or karyorrhectic nuclei (neuronal necrosis), rarely surrounded by up to 5 glial cells (satellitosis) and karyorrhectic nuclear debris. Multifocal patches in the gray matter have moderate numbers of neurons and rare astrocytes contain large, basophilic to amphophilic, intranuclear viral inclusions which peripheralise the chromatin (. Multifocally in the gray and white matter, there are abundant glial cells (gliosis), with astrocytes with vesiculated nuclei, which are often paired or clustered, frequently with karyorrhectic nuclei (glial cell necrosis) with large amounts of karyorrhectic nuclear debris scattered throughout the neuropil. Extensively within the gray matter and extending into the white matter, blood vessels, neurons, and glial cells are surrounded by clear spaces (edema) with frequent small, irregular clear spaces expanding the neuropil (spongiosis).

Contributor's Morphologic Diagnosis: Brain, rostral cerebrum: Meningoencephalitis, lymphohistiocytic, subacute, multifocal, severe with multifocal neuronal and glial cell

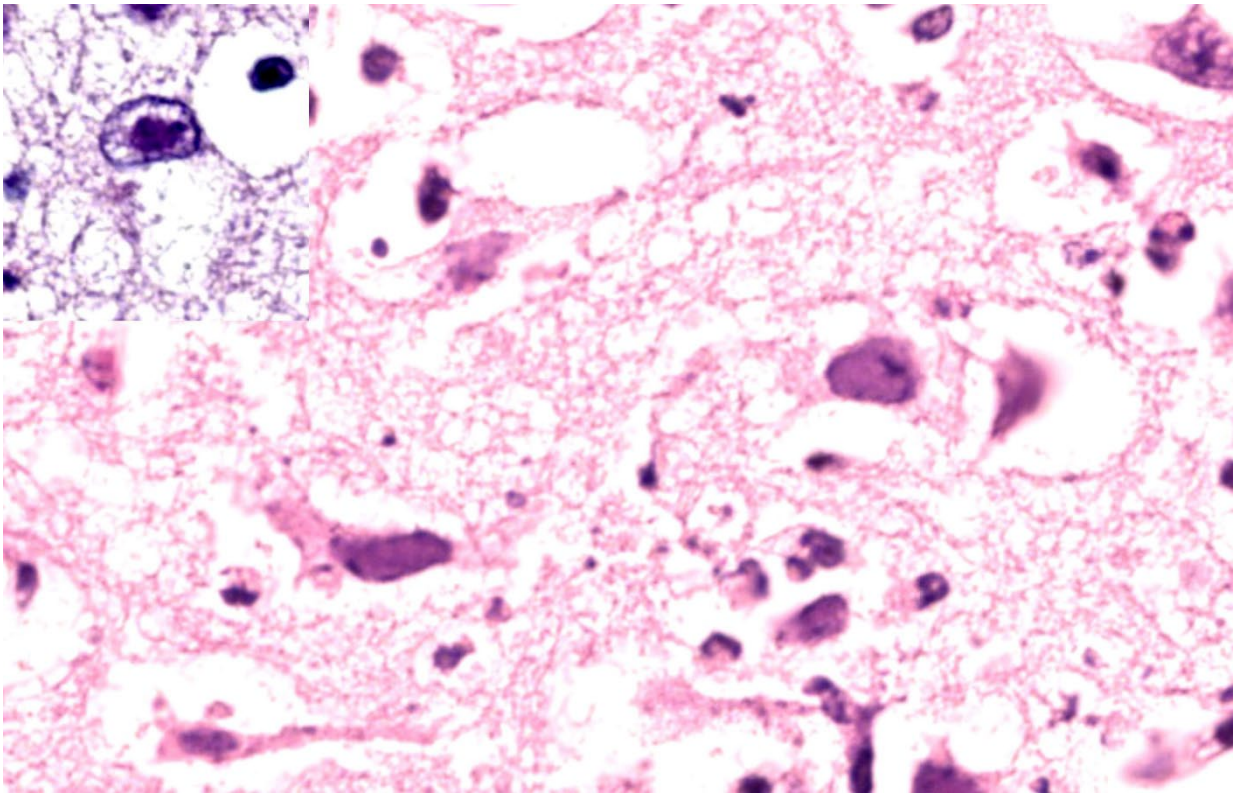


Cerebrum, calf: There are prominent cuffs of lymphocytes, macrophages, and fewer neutrophils, which infiltrate the adjacent parenchyma. There is also edema and gliosis, with prominent astrocytes and numerous microglia. (HE, 178X)

Contributor's Comment: Bovine herpesvirus-5 (BoHV-5) is an alphaherpesvirus known to cause meningoencephalitis in young cattle. BoHV-5 is closely related to BoHV-1 (the causative agent of bovine infectious rhinotracheitis) and was originally considered to be a "neurogenic variant of BoHV-1" or "BoHV-1.3".[4] After further comparative studies with different strains of BoHV-1, it was determined that this virus had distinct and differing genomic and antigenic properties and was reclassified as BoHV-5 by the International Committee on Taxonomy of Viruses in 1992.[4,10] BoHV-5 encephalitis outbreaks have been reported mostly in South American countries such as Brazil and Argentina, but also sporadically in other countries including Australia, and within North America and Europe.[4,9] BoHV-5 is part of a group of herpesviruses known to cause specific disease syndromes in bovines summarized in table 1 below.

BoHV-5 associated encephalitis is a typically a sporadic disease, but occasional outbreaks can occur in groups of calves and yearlings.[7] Morbidity can reach up to 50% and few symptomatic individuals survive.[7] The incubation period is approximately 1-2 weeks followed by presentation of clinical signs including depression, anorexia, weakness, proceeding to neurological signs such as circling, head pressing, incoordination, blindness, muscular tremors, convulsions, paddling, and death.[4,7] Nasal and ocular discharges have also been reported in some outbreaks of BoHV-5 associated disease, mimicking the classical clinical presentation of BoHV-1.[7]

Both BoHV-1 and -5 have many commonalities in their pathogenesis including the ability



Cerebrum, calf: Herpesviral inclusions peripheralize the chromatin with neurons and an astrocytes (inset, top left) contains a viral inclusion surrounded by a clear halo (HE, 800X)

to infect epithelial cells at the portal of entry, establish latency in the trigeminal ganglia, and can be reactivated by natural or experimental stressors.[4,7] BoHV-5 associated disease differs from that of BoHV-1 as they have different neuroinvasion and neurovirulence capabilities with BoHV-1 rarely causing encephalitis.[7] The exact pathogenesis of BoHV-5 is unknown. Transmission occurs via direct contact, aerosolization, or indirect spread through contaminated feed and water, or semen.[4,7] Following inoculation, BoHV-5 infects and replicates within epithelial cells at the portal of entry (e.g., nasal or vaginal mucosa).[4] Several possibilities for BoHV-5 neural invasion are being investigated including local spread from infected nasal epithelial cells with intra-axonal transport via the trigeminal or olfactory pathways, or by hematogenous viremic spread.[4,6] Once BoHV-5 has gained entry to the central nervous system, it can cause acute meningoencephalitis or become latent within the sensory ganglia, with possible reactivation and clinical recrudescence induced at times of stress.[11]

The characteristic histopathological changes associated with BoHV-5 are non-suppurative meningoencephalitis with mononuclear perivascular cuffing, gliosis, satellitosis, neuronophagia, trigeminal ganglioneuritis, and neuronal necrosis and degeneration.[7] Malacia is reported variably across literature, can take a laminar cortical necrosis pattern of polioencephalomalacia (PEM), and is proposed to occur dependent on strain neurovirulence or individual susceptibility.[1,3] Intranuclear alphaherpesviral inclusion bodies are occasionally present in degenerate neurons and astrocytes.[7] Histopathological changes are most severe within the frontal cortex, with milder changes described variably within the diencephalon, parietal and occipital cortices, cerebellum, basal nuclei, and brain stem.[2] In our case, milder changes were observed within the dorsal cerebrum, thalamus, and brainstem.

Possible histological differential diagnoses of BoHV-5 meningoencephalitis in calves include BoHV-1 infection, rabies, or malignant catarrhal fever, listeriosis, sporadic bovine encephalomyelitis (caused by *Chlamydia pecorum*), or less likely PEM causes such as lead or sulfur toxicity, thiamine deficiency, or salt poisoning.[5]

Table 1: Outline of bovine diseases associated with bovine herpes viral infections.

Bovine herpesvirus type	**Subfamily**	**Disease associations**
BoHV-1[6-8]	Alpha	• Infectious bovine rhinotracheitis (IBR) • Infectious pustular vulvovaginitis (IPV) and balanoposthitis (IPB) • Meningoencephalomyelitis • Systemic disease in neonates • Abortion • Bronchopneumonia
BoHV-2[6,7]	Alpha	• Pseudolumpy skin disease Ulcerative mammillitis
BoHV-4 ("Bovine cy-	Gamma	• Metritis • Abortion • "Epivag" syndrome in-

tomegalovirus")[8]		cluding: vaginitis, salpingitis, oophoritis or epididymitis • Mammillitis • Pneumonia • Enteritis
BoHV-5[6,7]	Alpha	• Meningoencephalitis

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JPC Morphologic Diagnosis: Cerebrum: Meningoencephalitis, lymphohistiocytic, subacute, diffuse, moderate, with neuronal necrosis and glial and neuronal intranuclear viral inclusions.

JPC Comment: The third case of this conference is yet another alphaherpesvirus and does not disappoint. Recent (and quite timely) publication[12] reviewing bovine herpesviral meningoencephalitis was a welcome addition to our discussion. Gross images from that publication nicely highlight the predominant frontal lobe distribution of BoHV-5, to include the sometimes dramatic malacia that the contributor notes above. We considered many of the same differential diagnoses that the contributor helpfully notes, but would also add rabies (though 5 animals is a bit of a stretch), bovine astrovirus, West Nile virus, and listeriosis as other broader differentials for bovine meningoencephalitis. Dr. Pesavento emphasized low power evaluation of any brain section for symmetry, position of the midline, distribution of features (to include portion of the brain examined), and loss of parenchyma to help sort (or rule out) these possibilities. Intranuclear viral inclusions were fairly generous in this case which aided in recognition of the etiological agent.

Mild neutrophilic inflammation was an unexpected finding in this calf's brain given the primary viral etiology. We considered a secondary process such as sepsis, though there is little lymphoid necrosis present within perivascular lymphoid cuffs and neutrophils are well within the parenchyma itself. One potential explanation is the young age (14 days) of this animal and insufficient time course to develop and deploy other innate/adaptive immune cells in large numbers akin to some of the NOD/Rag1/ILrg2 fully immunodeficient mice we have considered in conference this year (see Conference 11, Case 3 for one such example). We anticipate that in a slightly older animal histopathologic features would reflect non-suppurative meningoencephalitis alone.

Conference discussion of this case concluded with review of vascular features. In comparison to Case 4, this brain lacked changes in major blood vessels, though there was capillary damage coincident with eosinophilic fluid which we interpreted as true edema to accompany the spongiosis noted (versus processing artifact alone). Dr. Pesavento reminded conference goers that Factor VIII IHC is a potentially useful IHC marker for vascular damage as it also labels platelets, with the resulting perivascular aggregate serving as a reliable label when other markers (e.g. CD31) might be difficult to interpret alone.

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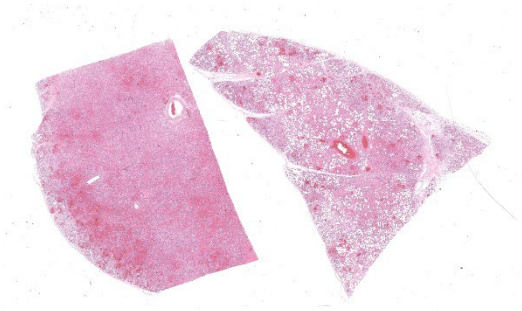
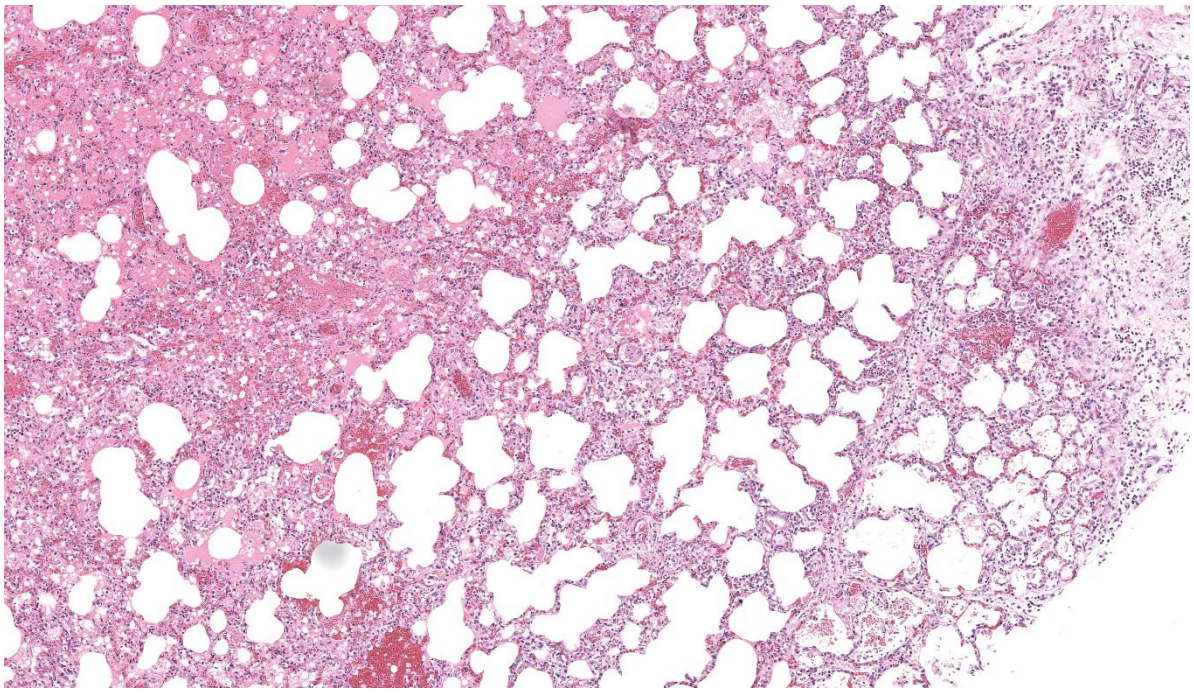
CASE IV:

Signalment:
10 day-old, female, Standardbred horse, *Equus caballus,* equine

History:
In the late spring of 2023, five, 3-4 day old foals in a Standardbred breeding farm developed clinical signs of pneumonia over a period of several weeks. Four of these foals did not respond to antibiotic treatment and died



Lung, foal: Two sections of lung, varying in lesion severity, are submitted for examination. At this magnification, there is abundant hemorrhage and edema within both sections. (HE, 6X)



Lung, foal: There is diffuse interstitial pneumonia with thickening of alveolar septa and abundant alveolar edema and hemorrhage. (HE, 171X)

at approximately 8-10 days of age. Two of these foals were necropsied and both exhibited severe acute interstitial pneumonia and severe edema, with microscopic features most consistent with acute diffuse alveolar damage. Equine herpesviruses 1 and 4, and equine influenza type A were not detected in PCR testing of lungs samples from both foals. No clinical abnormalities were noted in the dams of these foals, or in any other horses on the farm.

The last of these foals (the 5th one reported) was noted to be lethargic and tachypneic at 4 days of age. This filly was treated with ceftiofur sodium, gentamicin, flunixin meglumine, dexamethasone, furosemide, and oxygen therapy. Radiographs of the thorax revealed abnormalities consistent with interstitial pneumonia. Despite treatment, the foal's condition progressively worsened until she suddenly decompensated and began agonal breathing early morning, 6 days after clinical signs were first noted. The filly was humanely euthanized with IV Euthanyl and submitted for necropsy.

Gross Pathology:

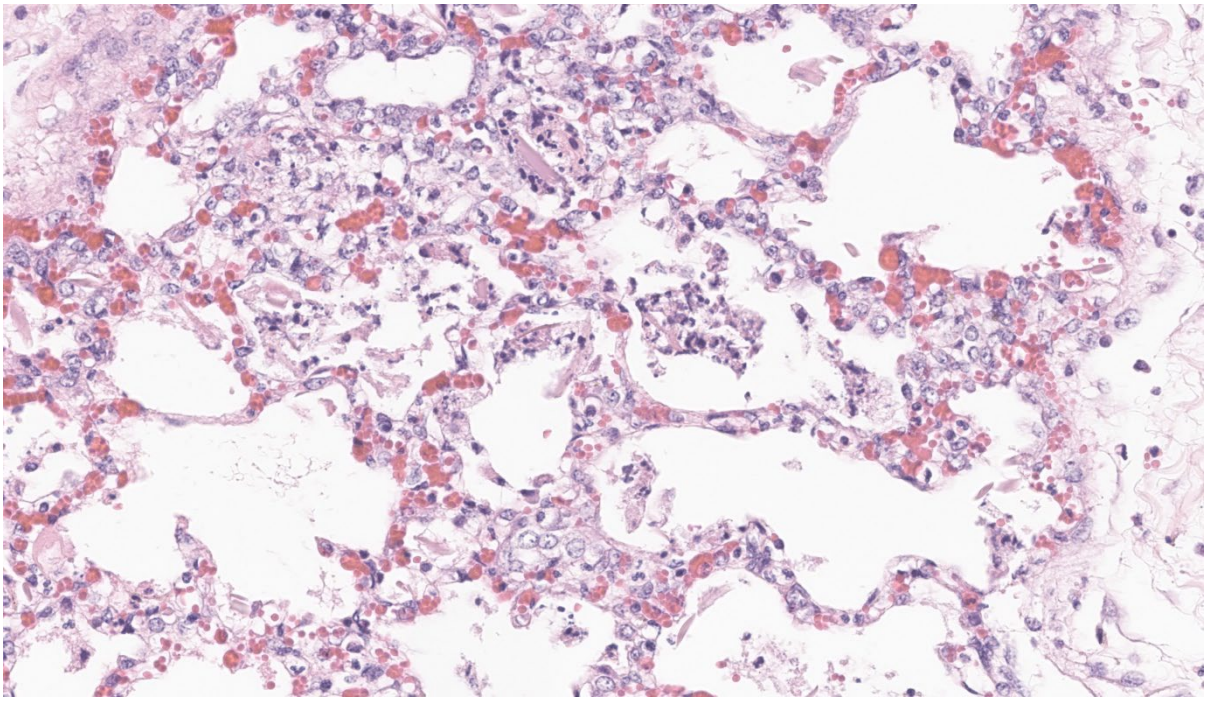
The filly was thin. The lungs were moderately expanded, diffusely dark pink to red, rubbery in texture, and failed to collapse. Large amounts of white froth were noted in the trachea. Small amounts of clear yellow tinged fluid were present in the pericardial sac. The remaining carcass was grossly unremarkable.

Laboratory Results:

Aerobic culture of the lung yielded no microbial growth. Samples of lung from this foal, and from both previously necropsied foals from this farm, were submitted for the equine respiratory pathogen PCR panel offered by the Cornell University Animal Health Diagnostic Centre. Equine adenoviruses 1 and 2,

Equine herpesviruses 1 and 4, Equine rhinitis viruses A and B, and influenza virus matrix, were not detected. Streptococcus equi was also not detected. Equine arteritis virus (EAV) was detected in lung samples from all three foals. Virus isolation from lung samples from each of these foals using cloned monkey cell lines was performed and EAV isolates were recovered from all three samples. Preliminary genomic sequencing of these isolates reveals that this virus has 97% homology with American Type Culture Collection (ATCC) reference strains of EAV isolated in North America approximately 30 years ago. Additional genomic sequencing and phylogenetic analysis of these isolates are ongoing.

Microscopic Description:
The most significant microscopic abnormalities were present in sections of lung which exhibited diffuse filling of most alveoli with dark pink, proteinaceous fluid admixed with occasional small deposits of amorphous fibrinoid debris, small bits of pyknotic cell debris, few degenerate neutrophils, small numbers of macrophages, and frequent erythrocytes. In a few areas, a thin layer of fibrinoid debris lines alveoli (hyaline membranes). In areas, scattered keratin squames are also noted in alveoli (attributed to terminal aspiration). Inter-alveolar septa are often mildly thickened and moderately congested. In areas where alveolar fibrin deposits are more prominent, plump polygonal cells with pale vesicular nuclei partially line alveoli (early type II pneumocyte hyperplasia). The epithelium lining of bronchi and bronchioles is generally intact. In a few scattered small and medium caliber arteries, there are foci where sparse cell debris, sometimes accompanied by small amounts of dense, hyalinized fibrinoid material, and occasional pyknotic nuclei partially effaces the tunica media.



Lung, foal: High magnification of alveolar septa which are expanded by varying combinations and concentrations of congestion, edema, fibrin, septal macrophage hypertrophy. Neutrophils, cellular debris, and scattered type II pneumocyte hyperplasia. (HE,554X)

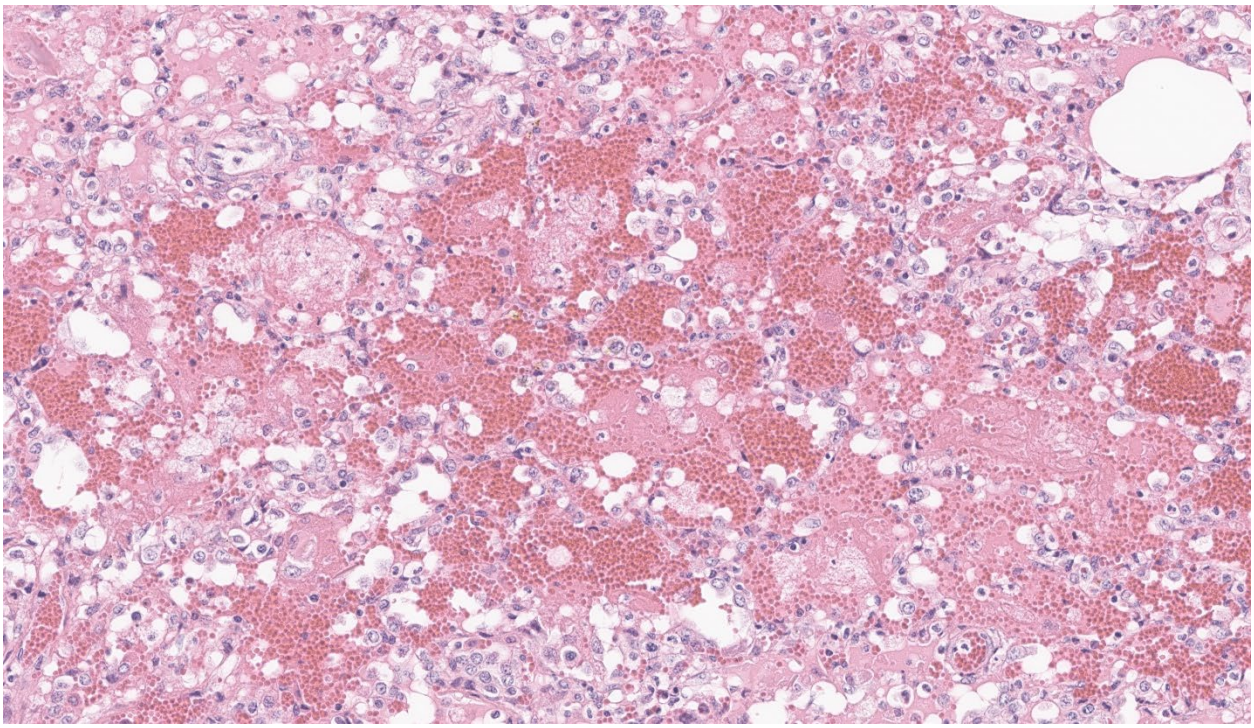
No significant microscopic abnormalities are noted in sections of kidney, liver, brain, adrenal gland, spleen, heart, or intestine.

Contributor's Morphologic Diagnosis:
Lung:

1. Severe, acute, fibrinous, interstitial pneumonia with marked pulmonary edema, multifocal type II pneumocyte hypertrophy and hyperplasia, and few scattered foci of mild, peracute, vascular, fibrinoid necrosis
2. Multifocal, intra-alveolar keratin squames (attributed to terminal or agonal aspiration)

Contributor's Comment: The clinical signs described in this foal are attributed to respiratory failure resulting from severe acute interstitial pneumonia and pulmonary edema. The microscopic appearance of these lung lesions were consistent with diffuse alveolar damage due to diffuse injury to type I pneumocytes and/or endothelial cells in alveolar septa. In acute stages of diffuse alveolar damage, pulmonary edema, exudation of fibrin into alveoli, and the formation of hyaline membranes (aggregates of fibrin, other serum proteins and cell debris) that line alveoli lumina are the first lesions typically apparent, rapidly followed by type II pneumocyte hyperplasia. If the affected individual survives long enough, interstitial fibrosis may be seen. These lesions often clinically manifest as acute respiratory distress syndrome (ARDS) in humans and animals. This clinical condition presents as acute onset pulmonary edema resulting in hypoxemia that does not respond to oxygen supplementation, with no evidence of concurrent left atrial enlargement (or primary left heart failure).[1]

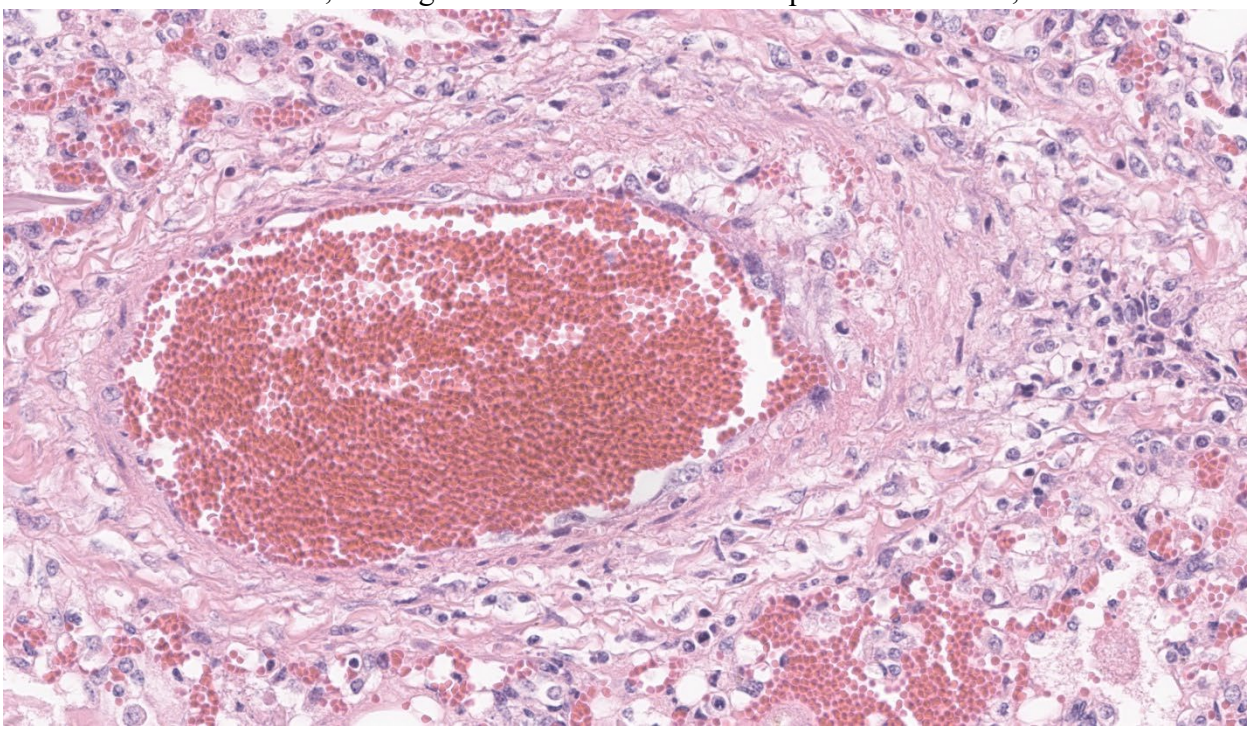
Diffuse alveolar damage has been associated with a wide range of etiologies in animals.[1]



Lung, foal: There are large areas in which alveoli are flooded with hemorrhage and edema (HE, 381X)

In this case, given the microscopic appearance of lesions, the clinical history, and involvement of multiple animals, an infectious etiology (most likely a viral infection) was highly suspected. Initial PCR testing of lung samples from this foal and the two other necropsied horses for equine herpesvirus 1 and 4 and equine influenza virus were negative which prompted additional PCR testing for a wider range of respiratory pathogens including equine adenoviruses, equine rhinitis viruses and equine arteritis virus (EAV). Only EAV was detected in each of the examined samples and this outbreak of acute interstitial pneumonia in foals was attributed to infection with this pathogen.

Equine arteritis virus (EAV) is a small enveloped, RNA, non-arthropod-borne virus in the family Arteriviridae, and the order Nidovirales and causes a condition termed equine viral arteritis. EAV was first isolated from an outbreak of respiratory disease and abortion in a Standardbred breeding farm in Bucyrus, Iowa in 1953.[8] Since then, serologic studies have revealed a worldwide distribution of EAV, although several counties including Iceland, Singapore, Japan, and New Zealand may be free of the virus.[5] The virus is highly species specific and infection is limited to equids such as horses, donkeys, mules and zebra. In the United States, a very high percentage of Standardbreds have been found to be seropositive (70-90%), compared to other breeds (such as Thoroughbreds), while in some European countries, the seroprevalence of EAV in some Warmblood stallions is very high. Most infections in adult horses are inapparent or cause mild clinical signs and are rarely fatal.[8] Most infections involve mares bred to a persistently infected stallion. Very young, old, or debilitated and immunosuppressed horses may develop more severe clinical signs, and rarely develop fatal disease. Clinical signs in adult infected horses most commonly consist of pyrexia, depression, anorexia, dependent edema, conjunctivitis, periorbital and supraorbital edema, respiratory distress and leukopenia.[8] After infection and a period of viremia, the virus is



Lung, foal: There is segmental necrosis of the wall of an arteriole with necrosis of smooth muscle cells, infiltrations of neutrophils, cell debris, mural hemorrhage and edema, and adventitial edema. (HE, 571X)

widely disseminated and is replicating in macrophages and endothelial cells within 3 days. Clinical signs of EAV infection are the result of endothelial injury and increased vascular permeability resulting in edema, congestion and hemorrhage in subcutaneous tissues, lymph node and viscera.[3,8]

Abortion is another common manifestation of EAV infections in horses. In natural outbreaks, abortion rates of less than 10% to 71% of infected mares have been reported. Mares are typically between 3 and 10 months of gestation when abortion occurs. In these cases, the fetus and placenta are often expelled without premonitory signs and may be autolyzed or well preserved. Lesions in the fetus are often not seen, and when present, may consist of mild interstitial pneumonia, mild perivascular lymphoplasmacytic infiltrates, and fetal membranes may appear edematous. Rarely, vasculitis may be seen in the allantochorion and in fetal visceral sites.[3] In most cases of EAV infection, abortion is likely largely due to acute vasculitis, edema and hemorrhage within the uterus resulting in impaired placental perfusion and hypoxia. Hypoxic injury may also cause decreased placental progesterone production and local release of prostaglandins that would also promote premature placental separation and fetal death.[3] Interestingly, abortions were not noted during this outbreak, possibly due to the late stage of gestation when the mares were infected. Alternatively, it is also possible that the strain of EAV virus in this outbreak had a low abortigenic potential.[7]

Equine arteritis virus infection resulting in severe, fulminating, interstitial pneumonia has been reported in neonatal foals and was the primary presentation of affected horses on this farm.[3,7,8] The prognosis for affected foals despite aggressive treatment, is poor and most infections in neonatal foals are fatal. This cluster of cases would suggest that the dams were infected just days prior to parturition or that foals were exposed to the virus in the first few days of life. Intestinal lesions have also been reported in affected foals but no such lesions were noted in our cases.

Transmission of the majority of EAV infections is via venereal and respiratory routes. Transmission of EAV through indirect contact with contaminated fomites may occur, but is generally not considered a major contributor to the spread of disease. However, the latter was implicated as a contributing factor in the spread of EAV infection in an outbreak in a veterinary teaching hospital.[2] Persistently infected carrier stallions are the reservoir responsible for maintenance of EAV in equine populations. Once infected, stallions harbor the virus in the ampulla of the vas deferens, other accessary sex glands, and in portions of the lower genitourinary tract, from where they shed virus in semen for weeks to months to years. Some stallions may shed virus in semen for the rest of their lives. Maintenance of the carrier state in stallions appears to be testosterone dependent and currently, the only effective means of eliminating infection in these horses is via surgical castration[8]. Carrier stallions may infect mares via natural breeding and via artificial insemination of infected semen. Once infected, a recently bred mare (or a recently infected stallion) may develop clinical signs and shed virus in respiratory secretions within 7-10 days[7]. Horizontal transmission of the virus via aerosolized respiratory secretions to other close contacts is a common cause of spread within the herd.[7,8] In cases where mares have aborted due to EAV infection, exposure to the fetus, placenta and placental fluids is another potential source of infection.[7] Infected mares, geldings and foals less than 6 months of age, clear the virus 28 days post-infection.[7,8]

Although several reports of outbreaks of EAV infection can be found in the literature, those primarily involving significant disease only in neonates are rare. One such case report[4] has features similar to that described in our cases. Affected foals also presented with severe, acute, fatal interstitial pneumonia with no obvious clinical signs were noticed in the mares. In the mentioned reference, each of the affected foals were thought to be immunocompromised to some degree, due to colostrum deprivation, death of the dam, or prematurity, which may have contributed to the severity of disease noted. Interestingly, in our cases, no such factors appeared to be at play, but each of the three affected foals necropsied were deficient in selenium. All had liver levels of less than 0.20 ppm wet weight (0.20 ppm is the lowest amount of selenium our assay can accurately quantify): adequate reference range of selenium in equine liver is 0.30-1.00 ppm. There were no lesions of white muscle disease (or nutritional myopathy) in any of the necropsied foals. However, selenium is an important essential trace element involved with a wide variety of physiologic processes in animals, including normal immune system function, regulation of growth and development, protection against oxidative stress and has antimicrobial (including antiviral) effects.[6] It is interesting to speculate that selenium deficiency in the dams and affected foals may have played a role in the severity of disease seen in the foals in this outbreak of equine viral arteritis.

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JPC Morphologic Diagnosis: Cerebrum: Meningoencephalitis, lymphohistiocytic, subacute, diffuse, moderate, with neuronal necrosis and glial and neuronal intranuclear viral inclusions.

JPC Comment: The contributor provides a spectacular slide to accompany a thorough summary of EVA and a putative cause for the changes observed in this case. Dr. Pesavento was excited to review this case as equine viral arteritis is a rare submission to the WSC and the microscopic features gave us much to discuss. The inclusion of squamous epithelial cells is an unexpected secondary feature to explore – we considered the contributor's interpretation of agonal inspiration and also wondered about perinatal fetal stress (and inhalation of amniotic contents) as several participants pointed out possible meconium as well. Within this section, we also note segmental fibrinoid necrosis of larger arterioles that highlight the route of entry of EAV and subsequent genesis of the abundant edema present.

Differential diagnoses for this case included other viruses such as Hendra virus (paramyxovirus), equine herpesvirus 1, African horse sickness (orbivirus), and equine infectious anemia virus (lentivirus) which share overlapping gross and microscopic features, to include the prolific pulmonary edema seen in this case. Discriminating features include time course of the disease and geography (i.e. current transboundary diseases). Syncytial cells within the bronchiolar epithelium did resemble viral syncytia of paramyxoviruses, though we attributed this change to increased turnover of lung epithelial cells due to viral effects versus direct infection as bronchiolar epithelial cells lacked direct cytopathic changes. For this reason, we differed from the contributor and did not label this pneumonia as 'bronchointerstitial'. Other potential

vasculocentric ruleouts include leptospirosis, purpura hemorrhagica, and plant toxicity such as hoary alyssum (*Berteroa incana*).

Finally, we briefly revisited the concepts of diffuse alveolar damage and interstitial pneumonia which we previously debated in Conference 9, Case 2 of the current conference year (in a dog). That case also featured large balls of fibrin filling alveoli, allowing us to introduce the term 'fibrinous and organizing pneumonia'. The present case is decidedly more acute, with few cells embedded within the fibrin meshwork and little evidence of reorganization. Dr. Pesavento also drew the distinction between diffuse alveolar damage (a histologic finding) and interstitial pneumonia (interstitial lung disease) itself which is used more broadly (and sometimes, confusingly) between veterinary pathologists. For a more complete review of this topic, we direct the reader to an excellent and recent publication.[9]

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