Joint Pathology Center
Veterinary Pathology Services

WEDNESDAY SLIDE CONFERENCE 2014-2015

Conference 21

15 April 2015

Guest Moderator:
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CASE I: 13-45574 (JPC 4048670).

Signalment: 6-week-old neutered male mixed breed canine, *Canis familiaris*.

History: The puppy was presented to the referring DVM for wellness exam and vaccination. The puppy was vaccinated with Durammune-5, a combination vaccine against canine distemper, canine adenovirus 2, canine parainfluenza virus, and canine parvovirus at approximately 1 pm. The puppy died the next day and was presented to the diagnostic lab for necropsy examination.

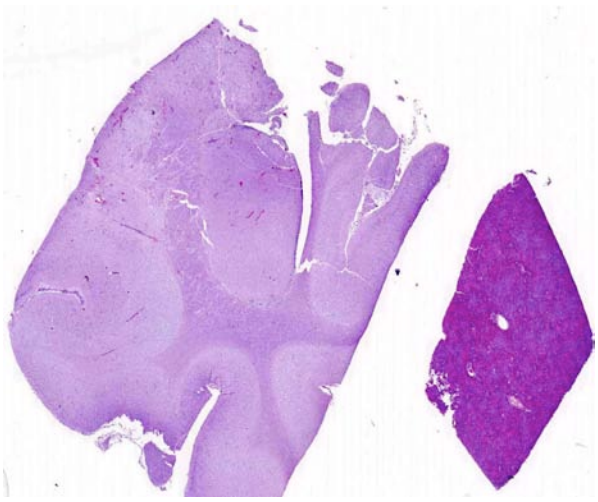
Gross Pathology: The animal was in adequate nutritional condition evidenced by adequate visceral and subcutaneous adipose tissue stores. The oral mucous membranes and subcutaneous tissues were markedly pale. The thymus contained numerous, multifocal, pinpoint, dark red foci (petechial hemorrhages).

The peritoneal cavity contained 20 ml of dark red watery fluid. The intestines were segmentally filled with dark brown, slightly flocculent, viscous digesta. Mesenteric lymph nodes were dark red and moderately enlarged (up to 1.2 cm in diameter). Hepatic parenchyma and brain tissues were grossly unremarkable.

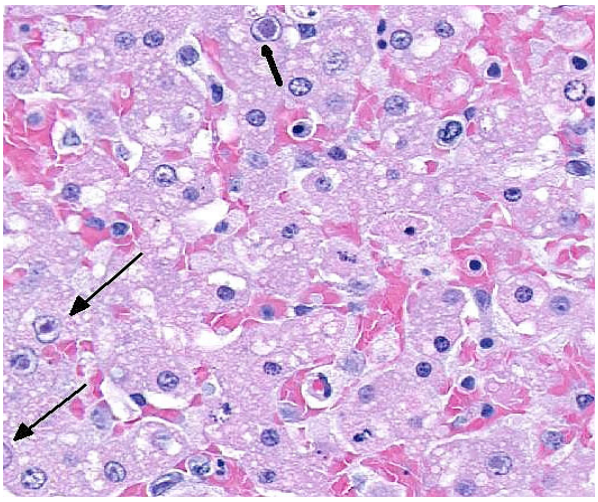
Laboratory Results: *Salmonella* PCR, parvovirus FA, distemper FA were all negative on intestine samples. Bacterial culture revealed heavy growth of *Escherichia coli* and moderate growth of *Proteus* sp. and beta *Escherichia coli* from the intestine. No bacteria were cultured from the spleen or urine. Fecal flotation revealed the presence of *Isospora* sp.

Histopathologic Description: Liver: Diffusely in the liver parenchyma are multiple coalescing foci of hepatocellular swelling and necrosis. These foci are typically centrilobular to midzonal and occasionally extend to periportal areas. Necrotic hepatocytes present with a hypereosinophilic, micro-vacuolated to wispy cytoplasm, and nuclear fragmentation (karyorrhexis), pyknosis or complete lack of nuclear staining. Sinusoids within necrotic foci are frequently expanded by erythrocytes (congestion and/or hemorrhages).

Throughout all zones of the hepatic lobule, numerous hepatocytes, few endothelial cells and rare Kupffer cells contain a large (up to 5 micron), solid amphophilic intranuclear viral inclusion body that marginates the chromatin and is often surrounded by a clear halo (Cowdry type-A).



1-1. Cerebrum and liver, dog: A subgross retiform pattern of hepatic necrosis is visible in the liver. (HE 6X)



1-2. Liver, dog: Hepatocytes at edges of necrotic areas contain large intranuclear adenoviral inclusions (arrows). Within necrotic areas (center), plate architecture is lost and hepatocyte nuclei are pyknotic or karyorrhectic. (HE 340X)

Brain: Multifocally, extending from the caudal brainstem to the thalamus, hypothalamus and basal nuclei, endothelial cells in blood vessels are frequently necrotic and occasionally contain similar intranuclear viral inclusion bodies. Neighboring endothelial cells are enlarged (reactive). The tunica media is often hypereosinophilic and disorganized, and mixed with pyknotic nuclear debris (fibrinoid necrosis). In the surrounding blood vessels Virchow-Robin's spaces contain small numbers of lymphocytes, macrophages, necrotic cells and extravasated erythrocytes (hemorrhage). Similar but less extensive lesions are observed in meninges and cerebral cortex. The cerebellum was not affected.

Other significant histologic changes were identified in the following organs:

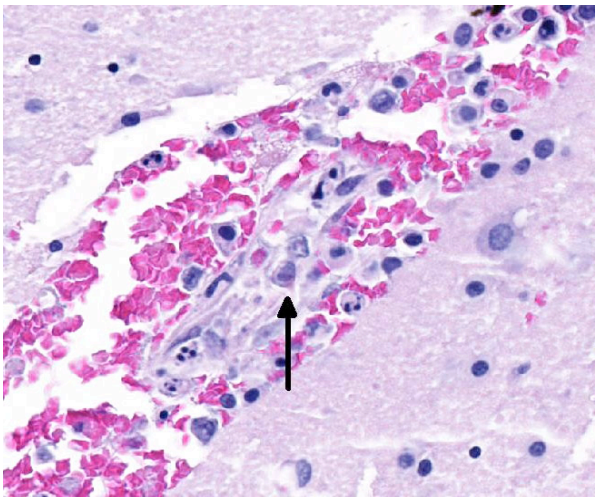
Thymus (hemorrhage and lymphocytolysis), spleen, Peyer's patches and lymph nodes (massive lymphoid and red pulp necrosis with very few inclusions), kidney (inclusions in glomeruli and vascular endothelial cells), heart (rare endothelial inclusions).

Contributor's Morphologic Diagnosis: Liver: Hepatitis, necrotizing, centrilobular to mild zonal, severe, acute with hepatocellular and endothelial intranuclear viral inclusion bodies.

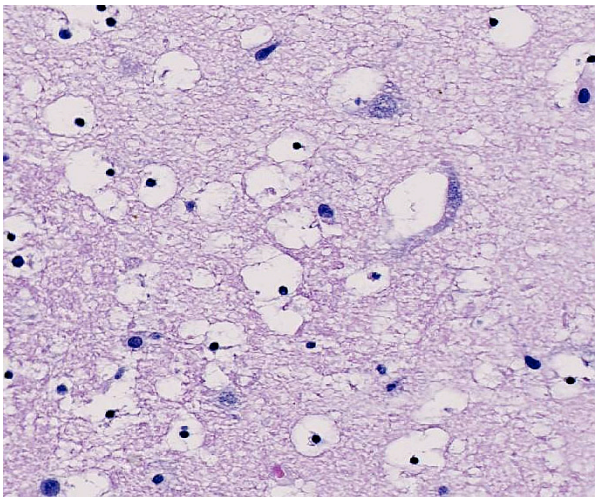
Brain: Encephalitis, multifocal, moderate, acute, with vasculitis, hemorrhages and endothelial intranuclear viral inclusion bodies.

Contributor's Comment: Histopathology is consistent with canine adenovirus type I infection (CAV-1). There is no reported pathogenicity with subcutaneously administered modified live canine adenovirus and the incubation period of adenovirus is typically 4-9 days[7]; therefore, this dog was likely naturally infected with CAV-1 prior to vaccine administration. Vaccination against canine adenovirus has greatly decreased the incidence of infectious canine hepatitis (ICH) cases in domestic dogs, but subclinical infection is prevalent in undomesticated canines, and likely provides a reservoir for infection. The virus is very stable in the environment, and can be excreted in the urine from previously infected animals for up to 9 months.[7] Maternal antibodies are typically protective for puppies until the point at which they are no longer absorbed, typically around 5-7 weeks of age.[7] Maternal antibodies will also inactivate vaccine virus. Therefore, disease may develop in puppies exposed to the virus, whose dam was unvaccinated, who never nursed (were bottle-fed), or who were not vaccinated according to an appropriate schedule.

The pathogenesis of ICH begins with infection with CAV-1 after exposure to infectious saliva, feces, urine, or respiratory secretions. The virus initially localizes in tonsil and regional lymph nodes, finally spreading to the bloodstream approximately four days post infection. Primary targets of circulating CAV-1 include hepatocytes, Kupffer cells, glomerular endothelium, and uvea. Any vascular endothelium is susceptible, causing



1-3. Cerebrum, dog: Multifocally, capillary endothelium contains similar adenoviral inclusions. Adjacent endothelium is necrotic, and erythrocytes are extravasated around the damaged vessel. (HE 360X)



1-4. Cerebrum, dog: In areas adjacent to damaged vasculature, large halos adjacent to neurons and oligodendrocytes suggest marked edema. (HE 256X)

multifocal petechial hemorrhage, and severe widespread endothelial damage leads to disseminated intravascular coagulation (DIC).[7] Although adenovirus was first identified after noting viral inclusions in the brains of foxes with encephalitis, the CNS form is rare. Adenoviral tropism for the CNS has been suggested to be related to viral strain differences.[4]

The earliest clinical sign of ICH is a fever followed by tonsillar enlargement, depression, anorexia, tachycardia, tachypnea, vomiting, diarrhea, abdominal pain/distension (due to fluid accumulation and hepatic enlargement), and hemorrhage if liver damage is severe or endothelial damage is widespread. Neurologic signs (ataxia, hypersalivation, and seizures) may occur if there is CNS involvement. If the animal does not die from severe hepatic failure or DIC, approximately 7-14 days post infection, corneal edema (the classic "blue eye" lesion)[12] and azotemia, hematuria, and proteinuria (secondary to glomerulonephritis) are possible. As was seen in this case, sudden death with no previous clinical signs is possible when CNS infection occurs.[14]

Grossly, hepatic lesions typical of adenoviral infection (swollen mottled liver with gallbladder edema)[5,7] were not noted in this case. However, histologic lesions of multifocal hepatic necrosis, combined with striking intranuclear inclusions in hepatocytes and vascular endothelial cells in the liver and brain suggest etiology consistent with canine adenovirus type 1 (infectious canine hepatitis/CAV-1).

Histologically, typical lesions usually consist of centrilobular to midzonal hepatic necrosis with general sparing of periportal hepatocytes. Cowdry type A inclusions (marginated chromatin and clear halo around the inclusion) are seen in Kupffer cells, hepatocytes, and affected vascular endothelium. Lymphoid organs may be congested with necrosis of lymphoid follicles and intranuclear inclusions in vascular endothelium and histiocytes can be seen. Inclusions may also be found in glomerular or tubular renal epithelium, and central nervous system (CNS) vascular endothelium. Within the CNS, multifocal neuropil hemorrhages, perivascular accumulations of mononuclear cells, mixed with hemorrhage and occasionally fibrin, and intranuclear inclusions in vascular endothelial cells are evident, typically throughout the brainstem and caudate nuclei, often sparing the cerebral and cerebellar cortices.[14] Interestingly, in this case, lesions are noted extending into the cerebral cortex and meninges. Lesions in other organs are typically secondary to vascular endothelial damage and may consist of vascular necrosis, intravascular fibrin thrombi, hemorrhage, and edema.[7,13]

Adenoviral serotypes inducing disease in canines are from the family *Mastadenovirus* and include CAV-1, which causes the disease known as infectious canine hepatitis (ICH), and CAV-2, which is essential for the development of infectious tracheobronchitis (ITB).[7] Other

adenovirus families include *Aviadenovirus* (avian strains) and *Atadenovirus* (mammalian, avian, and some reptilian strains). Adenoviruses are typically host specific and produce multiple notable diseases (Table 1, chelonians, amphibians and fish not included). Typically, most adenoviral infections are subclinical, with serious illness only in young or immunocompromised individuals.[7]

Table 1- Most important adenoviruses, affected species and major pathologic lesions

Species Affected	**Serotypes involved /Disease Name**	**Major Pathologic Findings**
Mastadenoviridae		
Canine Ursidae	CAV-1 Infectious Canine Hepatitis	Intranuclear and intraepithelial inclusions in hepatocytes, Kupffer cells, endothelium and mononuclear cells with secondary necrosis
	CAV-2 Upper respiratory disease conjunctivitis	Important initiator of infectious tracheobronchitis (Kennel Cough)
Feline		Rare, subclinical disease, only 1 confirmed fatal case
Bovine	BADV 3,4,10	Sporadic enteric disease in 1-8 week old calves, tropism for vascular endothelium, lesions are secondary to thrombosis and ischemia
Porcine	PAdV-4- most common in Europe and North America	Typically non-clinical illness, may see pneumonia and enteritis, inclusions are in enterocytes- may be seen in non-clinically affected piglets
Equine	EAdV-1 (worldwide)	May cause pneumonia in SCID (Arabian) foals with intranuclear inclusions in alveolar epithelium, +/- pancreatic degeneration and necrosis with inclusions in pancreatic ducts
	EAdV-2 (Australia)	Diarrhea
Ovine Caprine	OAdV 1-3 GAdV-2	Mild respiratory and GI disease in lambs and kids, inclusions within lamina propria in lambs, in endothelial cells in kids
Humans	Several strains	Respiratory disease and keratoconjunctivitis
Hamsters	Hamster strains	Enteric disease in less than 4 week old animals Intranuclear inclusions in intestinal epithelium Experimentally transmitted adenoviruses from other species can induce neoplasia
Aviadenovirus		
Group I	Chickens Turkeys Geese Ducks Kestrel Pigeons	Inclusion Body Hepatitis	Vertically transmitted, hepatocellular hemorrhage and necrosis with intranuclear hepatocellular inclusions, may also see necrotizing pancreatitis with intranuclear inclusions
	Northern Virginia Quail	Quail Bronchitis	Necrotizing tracheitis, proliferative and necrotizing bronchitis and pneumonia with basophilic intranuclear inclusion in tracheal epithelium
	Chickens Quail	Inclusion Body Ventriculitis	
Group II	Turkey gallinaceous birds psittacine	Turkey Hemorrhagic Enteritis	Fibrino-necrotic membranes lining small intestine, intranuclear inclusions in lymphoblasts and macrophages in spleen, and small intestine lamina propria
	Pheasant	Marble Spleen Disease	Enlarged mottled spleen, congested and edematous lungs, splenic necrosis with large intranuclear inclusions
	Chicken	Group II splenomegaly virus	Usually causes no mortality. Lesions include splenic reticuloendothelial cell hyperplasia with intranuclear inclusions
Atadenovrius			
Group III	Chickens Ducks	Egg Drop Syndrome	Principle site of virus replication is pouch shell gland, if infection occurs before sexual maturity; virus is latent until maturity occurs. Loss of shell color, thin shelled eggs
Bovine		BAdV-5, 6, 7, 8	Enteric disease
Ovine Caprine		OAD -D GAdV-1	Enteric disease
Possums		PAdV- 1	Typically non clinical illness, interest in utilizing virus as a method to control populations as a vector for contraceptive antigens
Squamatids (lizards and snakes)		Agamid AdV-1 (Bearded Dragons), SnAdV-1,2, (snakes), Eublepharid AdV-1 (geckos), Helodermatid AdV-1(gila monsters)	Hepatocellular necrosis with Intranuclear inclusions in hepatocytes. Inclusions also possible in enterocytes, renal epithelium, lung epithelium, myocardial endothelium, glial cells and brain endothelium

JPC Diagnosis: Liver: Degeneration and necrosis, centrilobular to midzonal, multifocal to coalescing, severe, with numerous hepatocyte and endothelial intranuclear viral inclusions.

Cerebrum and thalamus: Vasculitis, necrotizing, diffuse, moderate, with hemorrhage, edema, and numerous endothelial intranuclear viral inclusions.

Conference Comment: This is a great diagnostic case that exhibits the pathognomonic combination

of intranuclear inclusions and brainstem hemorrhages in the dog. The contributor outlined adenoviruses of many species, of which only dogs, bears, oxen, goats, and lizards are mentioned as developing endotheliotropic manifestations of infection. Hemorrhages can occur in multiple organs in these species, and including the kidney, lung, brainstem, and long bones in dogs.[13] Intranuclear inclusions occur most prominently in endothelium and hepatocytes in dogs; however, they may also be observed in Kupffer cells and other differentiated cells.[13] Conference participants deliberated on whether some of the free individual cells with viral inclusions within the sinusoids and large vessels in this case are detached necrotic hepatocytes in the process of exiting the liver into the systemic circulation.

The brain lesions in this case appear to be most severe in the thalamus, where prominent cytotoxic edema of oligodendroglia is evident. Cytotoxic edema occurs due to altered cellular metabolism, often caused by ischemia, and presents as intracellular fluid accumulation. Cells of the CNS vary in their susceptibility to ischemic injury. Neurons are the most sensitive, with oligodendroglia, astrocytes, microglia, and endothelium following in decreasing order.[15] It is curious in this case that neurons are much less severely affected than oligodendroglia, which may allude to irregular or incomplete ischemic damage in this case. Other types of edema that occur within the CNS include vasogenic due to vascular injury, and hydrostatic from elevated pressure, which both results in extracellular fluid accumulation. Also hypo-osmotic edema from plasma microenvironment imbalances can cause both extracellular and intracellular fluid accumulation.[13]

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http://vetmed.illinois.edu/path/

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CASE II: 341368 (JPC 4049166).

Signalment: 6-year-old male Newfoundland Dog, *Canis familiaris.*

History: The animal presented to the small animal hospital at the University of Glasgow with acute tetraparesis following development of left thoracic limb lameness. MR imaging revealed the brainstem to be moderately atrophied with uneven margins. In addition MR imaging revealed that the cervical spinal cord was markedly atrophied with uneven and distorted margins, with an associated compensatory increase of surrounding CSF and faint intramedullary changes most apparent centrally within the cord.

Gross Pathology: On macroscopic examination, the brain was unremarkable but the brainstem and cervical spinal cord were moderately to markedly atrophic with increased CSF within the cervical region in concordance with MRI findings.

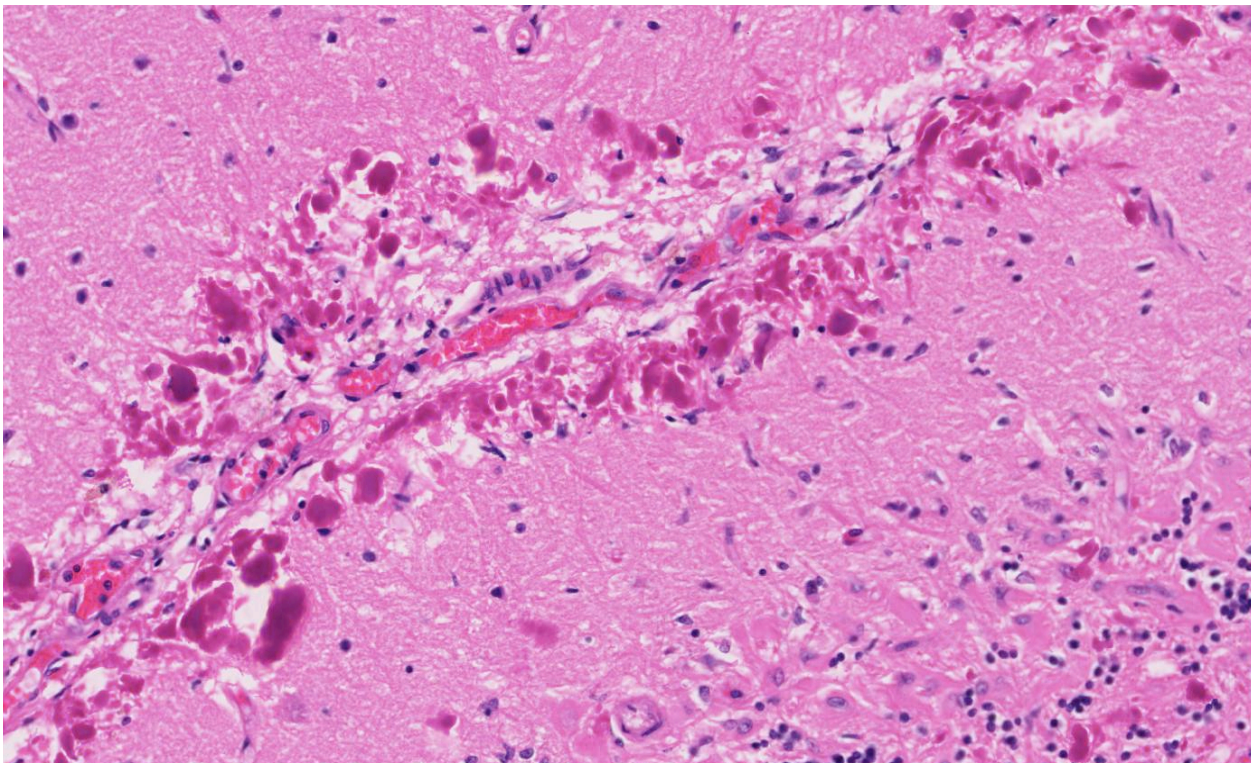
Histopathologic Description: Large numbers of ovoid to irregular, eosinophilic, intra-astrocytic hyaline structures consistent with Rosenthal fibers were distributed throughout the cerebellum, brainstem and spinal cord and to a lesser extent within supratentorial regions. Rosenthal fibers were most prominent within the subependymal and perivascular areas and within the subpial glia limitans, as would be expected for areas which ordinarily contain dense networks of astrocytic processes. Rosenthal fibers were found predominantly within the white matter but also to a lesser extent within the grey matter. Within affected areas, especially in the most severely affected areas of white matter there are also moderate numbers of abnormal astrocytes with large amounts of eosinophilic cytoplasm and marked karyomegaly. Occasional binucleate astrocytes were also noted in severely affected areas. Areas of white matter exhibiting the highest numbers of Rosenthal fibers, including the cerebellum, dorsal medulla oblongata, dorsal cervical spinal cord and piriform lobe, were also characterized by severe rarefaction of the surrounding white matter.

Rosenthal fibers, particularly at their periphery, show moderate GFAP immunostaining and moderate to strong ubiquitin immunostaining.

Contributor's Morphologic Diagnosis: Brain, cerebellum, brainstem and spinal cord: Encephalomyelopathy, multifocal, severe with subpial, perivascular and periependymal Rosenthal fiber accumulation, astrocytosis and astrocytic hypertrophy, consistent with Type II Alexander disease.

Contributor's Comment: The presence of Rosenthal fiber accumulation within the CNS is not a pathognomonic lesion of Alexander-like disease. Rosenthal fibers may be found in a variety of conditions including reactive astrocytosis and in some astrocytomas and the diagnosis of an Alexander-like disease must be based on recognition of the distribution of Rosenthal fibers within the CNS most prominently within the subpial glia limitans and in perivascular and periependymal locations. [13]

Alexander's disease in man is a primary astrocytic disorder with approximately 95% of patients harboring mutations in the GFAP gene. The age of onset is variable with cases reported from the prenatal period through until the sixth decade of life.[7] Alexander's disease is classically divided into infantile (0-2 years), juvenile (2-12 years) and adult (>12 years) onset forms; however, more recently a new classification limited to two categories (type I and type II) has been proposed focusing on lesion distribution and clinical presentation.[10] In the case of the two category classification, system age of onset remained a powerful predictor of disease type. It has been shown that phenotypic pattern and disease course alone more accurately classify cases of Alexander's disease and whereas all type I cases presented at an early age, type II cases occurred at all ages although generally with a later onset than type I cases. Type I disease is typically characterized by early onset commonly with seizures, spasticity, or developmental delays and diagnosis can be made based on the presence of at least four of the following five features on MR imaging: extensive cerebral white matter changes with a frontal predominance, a periventricular rim with high signal on T1-weighted images and low signal on T2-weighted images, abnormalities of the basal ganglia and thalami, brain stem abnormalities, and contrast enhancement of the ventricular lining, periventricular tissue or white matter of the frontal lobes, optic chiasm, fornix, basal ganglia, thalamus, dentate nucleus, or brain stem structures.[10,12] Type II disease is typically



2-1. Cerebellum, dog: Within the cerebellum, and to a lesser degree in the brainstem and cervical spinal cord, numerous brightly eosinophilic astrocyte processes consistent with Rosenthal fibers populate perivascular and subependymal areas. (HE 196X)

later in onset and more often presents with signs of hindbrain dysfunction such as ataxia, palatal myoclonus and dysphagia. MR findings in type II disease show hindbrain predominance with atrophy of the medulla oblongata and cervical spinal cord.[4,5,8,9]

There have been seven previous reports of Alexander's disease in the dog, all of which predate the new human classification system.[1,2,3,6,11,14] Due to the distribution of lesions in this case with pronounced atrophy of the cervical spinal cord, Type II Alexander's disease was diagnosed.

JPC Diagnosis: Cerebellum: Hypertrophy, astrocytic processes, with accumulation of intermediate filament (Rosenthal fibers), diffuse, severe, with Purkinje and granular cell loss. Spinal cord, cervical: Hypertrophy, astrocytic processes, dorsal funiculi and subependymal, with accumulation of intermediate filament (Rosenthal fibers), moderate.

Conference Comment: This is a rarely reported disease in the veterinary literature, thus much of its understanding is derived from the documented cases in people where a functional mutation of the dominant GFAP gene has been identified.[1] The genetic equivalent in dogs has not been determined, although the similarities in presentation between animals and people strongly suggests a correlation. Rosenthal fibers consist of three major chemical components: GFAP, small heat shock proteins, and ubiquitin.[1] Their presence translates into increased expressivity with immunohistochemistry for GFAP, and coupled with their perivascular and periependymal location, are diagnostic for Alexander's disease (AD).[1] In AD, the mutant GFAP proteins are unable to form intermediate filaments and precipitate in aggregrates to cause derangements of astrocytic functions.[9] With the multiple functions of astrocytes, to include regulating the microenvironment of the CNS, repairing injured nervous tissue, and providing structural support;[15] it is reasonable to conclude their dysfunction can result in a variety of central nervous clinical manifestations. Among cases reported in dogs, depression, generalized tremors, progressive tetraparesis, spinal reflex deficits, and ataxia have all been observed.[1,11,14] The contributor described the different classifications of AD, and all previously reported cases in the dog could be considered the juvenile, or type II, form.[1]

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CASE III: 14-69-6 (JPC 4048509).

Signalment: 14-year-old castrated male domestic short haired cat, *Felis catus*.

History: The cat presented with acute onset of seizures and nystagmus progressing to stupor, and was euthanized. It had a subtotal colectomy 3 years previously because of megacolon. One year previously the cat had been treated for constipation, pleural effusion of undetermined cause and pancytopenia, again of undetermined cause. At the time of euthanasia the cat was reportedly negative for FeLV, FIV and *Mycoplasma* infection.

Gross Pathology: The cat was in good nutritional condition. The brain was grossly normal externally and on transverse section. The heart was mildly rounded and had numerous delicate fibrinous and fibrous adhesions between the visceral and parietal pericardial surfaces. Bilaterally there was moderate pulmonary edema.

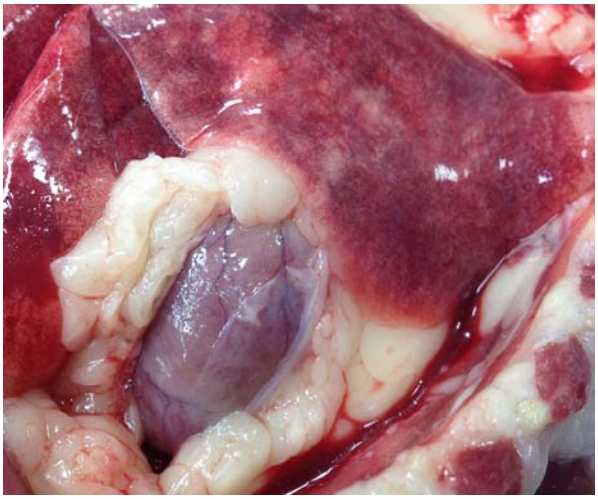
Incidental findings included a unilateral ectopic ureter, hematoma within the urinary bladder wall and abdominal wall musculature caused by cystocentesis, and bilateral polydactyly of the thoracic limbs.

Laboratory Results: None

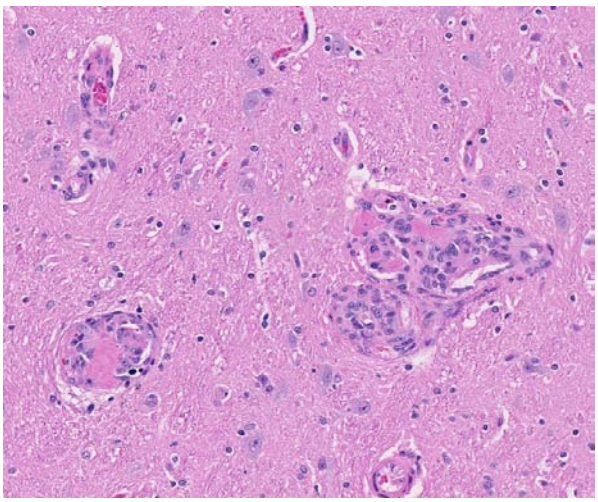
Histopathologic Description: Thalamus and cerebral hemisphere; transverse section. [Depending on the level of the section, different slides contain some or all of the following structures: third ventricle, lateral ventricle, hippocampus, interthalamic adhesion, choroid plexus and ventral meningeal vessels.]

Scattered throughout the entire section, but most numerous in the ventral thalamus and adjacent leptomeningeal blood vessels, are several dozen variably-sized hypercellular foci up to 300 microns in diameter. Most are centered about small to medium-caliber arterioles and consist of mural and luminal proliferations of spindle cells. These form concentric whorls or haphazard tufts that frequently narrow or obliterate the lumen of affected vessels. Multifocally, luminal spindle cells form capillary clefts within which low numbers of red blood cells or fibrin thrombi are present. Spindle cells are bland, with a moderate amount of poorly demarcated smudged to very finely fibrillar eosinophilic cytoplasm. Nuclei are ovoid and pale with vesiculate to stippled chromatin and a single inconspicuous nucleolus. Mitotic figures are very rare. Multifocally, the perivascular (Virchow-Robin) space around both affected and unaffected parenchymal vessels is mildly expanded by clear space or lacy eosinophilic fluid (edema).

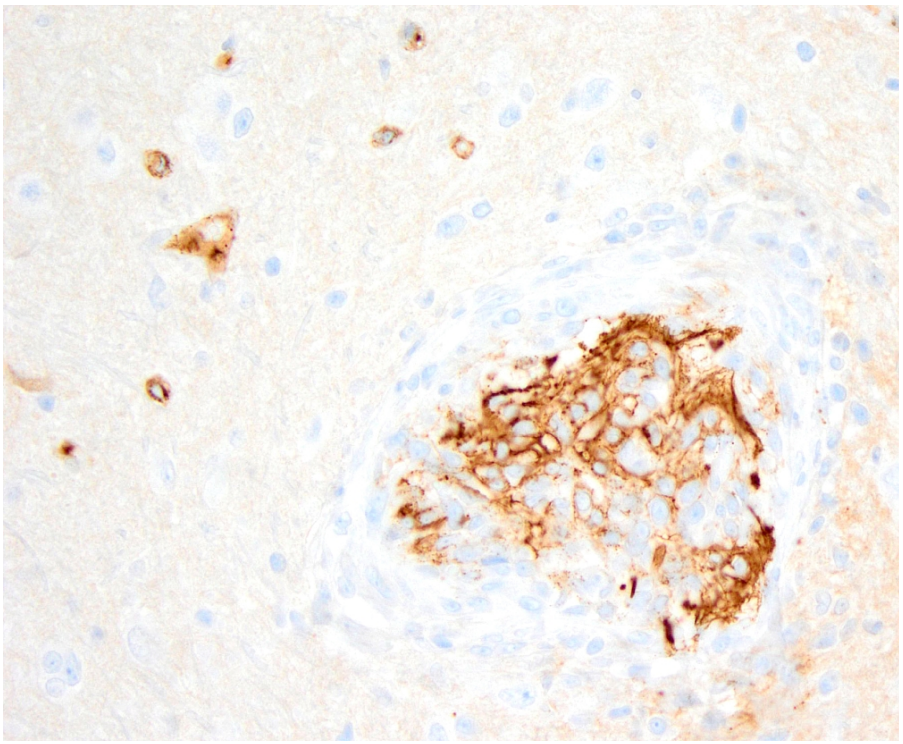
Immunohistochemistry was performed on this section. Approximately 50% of proliferating spindle cells showed strong immunoreactivity for factor VIII-related antigen and the remainder were



3-1. Thoracic cavity, cat: The heart is mildly rounded and has numerous delicate fibrinous and fibrous adhesions between the visceral and parietal pericardial surfaces. Bilaterally, there is moderate pulmonary edema. (Photo courtesy of: Diagnostic Services Unit, Faculty of Veterinary Medicine, University of Calgary, Clinical Skills Building, 11877 85 St. NW,Calgary AB T3R 1J3 http://vet.ucalgary.ca/)



3-2. Thalamus, cat: Thalamic arterioles are expanded by a luminal, occasionally concentric proliferation of spindle cells which narrow the lumen. Affected vessels multifocally contain fibrin thrombi. (HE 144X)



3-3. Thalamus, cat: Within a thalamic arteriole, a proportion of proliferating intraluminal spindle cells exhibit diffuse moderately positive intracytoplasmic staining for Factor VIII-related antigen. (Photo courtesy of: Diagnostic Services Unit, Faculty of Veterinary Medicine, University of Calgary, Clinical Skills Building, 11877 85 St. NW, Calgary AB T3R 1J3 http://vet.ucalgary.ca/ (anti-VWF, 400X)

strongly immunoreactive for smooth muscle actin. IHC for feline coronavirus was also performed. There was no immunoreactivity for feline coronavirus.

Contributor's Morphologic Diagnosis: Brain and leptomeninges: Marked multifocal intraluminal and mural vascular spindle cell proliferation (angioendotheliomatosis) with multifocal thrombosis and mild multifocal perivascular edema.

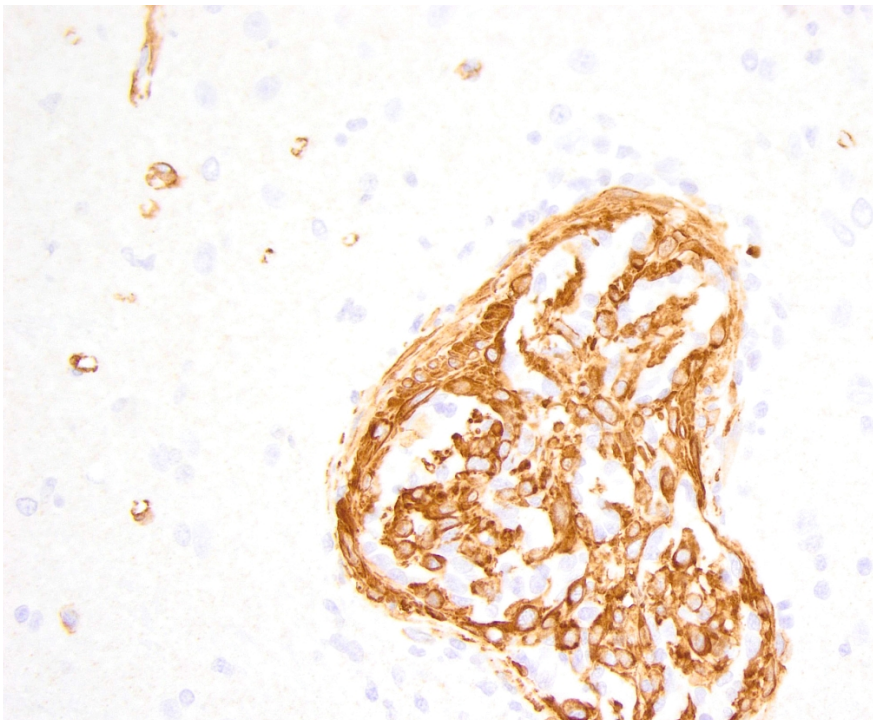
Contributor's Comment: Histologic and immunohistochemical changes are consistent with the condition of feline systemic reactive angioendotheliomatosis (FSRA). This is a rare condition of domestic cats characterized by intravascular proliferation of spindle cells in small blood vessels of many organs.[5] Although not named FSRA until recently,[5] diseases with similar sounding lesions have been described in sporadic case reports since the 1980s.[4,10,11] While FSRA appears to have no counterpart in other domestic species, a multisystemic disease with the same histologic lesions was reported in 2008 in a steer persistently infected by BVDV.[3] Diseases with similar vascular proliferations exist in humans but, unlike FSRA, these are restricted to the skin and are not fatal.[9]

In FSRA, the heart is the most consistently affected organ and myocardial dysfunction is the cause of illness reported in most cats.[5] The myocardial lesions of FSRA were described in an earlier case submitted to the Wednesday Slide Conference (Conference 03-2008; Case 2). In this current case, however, central nervous system disease caused the most important clinical signs, and the case was submitted as a reminder that FSRA is a multisystemic disease with a variety of clinical presentations. As such, FSRA should be considered in the differential diagnosis for cats with neurologic disease.

In this particular case, a specific cause for neurologic signs was not found in the brain sections examined. There was no evidence of obstructive hydrocephalus, severe edema or malacia in any section examined. However, myocardial dysfunction in FSRA is secondary to thrombosis and infarction[5] and it is possible that areas of infarction were present in the brain of this cat but not in sections examined histologically.

In addition to the myocardium and brain, other commonly affected organs in FSRA are the kidneys, spleen, lymph nodes, meninges, eyes and pancreas.[5] In the current cat, the most severely affected organs were the brain and heart, but milder vascular lesions were also present in the kidneys and the tunica muscularis of the gastrointestinal tract. Vascular lesions were not present in the urinary bladder and the mural hemorrhage noted at necropsy was attributed to cystocentesis.

The proliferating cells in FSRA are a mixture of endothelial cells and (presumed) pericytes, as



3-4. Thoracic cavity, cat: Within a thalamic arteriole, a proportion of proliferating intraluminal spindle cells exhibit diffuse strongly positive intracytoplasmic staining for Factor VIII-related antigen. (Photo courtesy of: Diagnostic Services Unit, Faculty of Veterinary Medicine, University of Calgary, Clinical Skills Building, 11877 85 St. NW, Calgary AB T3R 1J3 http://vet.ucalgary.ca/ (anti-SMA, 400X)

JPC Diagnosis: Diencephalon, arterioles: Pericyte and endothelial proliferation, occlusive, diffuse, severe, with necrotizing vasculitis, thrombosis, and mild gliosis.

Conference Comment: This case gives a unique look at a condition more readily recognized in the heart in cats. Conference participants deliberated whether proliferative, neoplastic, inflammatory or other processes could be ruled out based on current knowledge of the entity. Rather than arriving at a consensus, additional questions were raised such as whether the proliferative endothelial cells and pericytes are responsive to growth factors or exhibit decreased sensitivity to inhibitory stimuli. Too few cases of FSRA have been documented to determine a predilection for sex, breed, or age; and some examples offer evidence of possible infectious causes.[1,3,5]

identified by IHC for factor VIII-related antigen[5,10,11,13] and smooth muscle actin,[5,13] respectively. Because of the dual cell population and the lack of cellular atypia, lesions of FSRA are thought to represent an aberrant reactive process rather than neoplasia. (This is discussed in Fuji et al.'s 2005 review,[5] and by the previous submitter of a myocardial FSRA case to the 2008 Wednesday Slide Conference. Since their reviews of the literature, only one further case report on FSRA has been published.[13])

The cause of FSRA is unknown. In humans, certain vasoproliferative disorders are associated with infection by various *Bartonella* species,[6] and several mechanisms by which *Bartonella* spp. might induce endothelial proliferation have been shown.[7,8] Since 2010 a similar link has been investigated in certain vasoproliferative disorders of domestic animals, including FSRA in cats, hemangiopericytoma, hemangiosarcoma and bacillary angiomatosis in dogs and SRA in a steer.[1,2,12] The results of these studies are not conclusive but do suggest that further investigation into *Bartonella* infection and vasoproliferative disorders in domestic animals is justified.

While it consistently affects the heart, FSRA is usually observed in multiple organs of which the kidney, spleen, lymph node, gastrointestinal tract, brain, eye, and pancreas seem to be most common.[5] Regardless of affected organs, the disease is often fatal as the vasoproliferative lesions can induce thrombosis, hemorrhage, and necrosis of the myocardium causing acute myocardial failure.[5] Thrombotic thrombocytopenic purpura (TTP) has also been associated with FSRA, and consists of accumulations of large multidimers of vWF, possibly due to an acquired or genetic defect in vWF metalloprotease.[3] TTP may also be associated with certain drugs, viral infections, pregnancy, and systemic lupus erythematosus and may occur a single episode, relapsing intermittent episodes, or chronic unremitting forms.[3]

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CASE IV: P3900-14 (JPC 4048654).

Signalment: 7-week-old female crossbreed (unknown) porcine, *Sus scrofa domesticus.*

History: Dead pig, suspect meningitis.

Gross Pathology: The pig was in poor body condition with reduced muscle mass and minimal subcutaneous and internal fat stores (weight = 12.5 Kg). Both pinnae showed extensive areas of purple discoloration. The mandibular, cervical, mesenteric and lumbar lymph nodes were edematous and enlarged approximately two times normal size. The trachea contained abundant white froth. The lungs were expanded, rubbery, wet, heavy and non-collapsed (interpreted as interstitial pneumonia); the interlobular septa were expanded with clear gelatinous material (pulmonary edema). The pericardial sac contained approximately 25 ml of clear, yellow, watery fluid (hydropericardium). The epicardial fat was diffusely replaced by clear, translucent gelatinous material (serous atrophy). There was also serous atrophy of the perirenal fat. The kidneys exhibited multifocal to coalescing, 2-5 mm in diameter, white spots scattered throughout the cortex; confluence of these lesions produce expansion and distortion of one renal pole (interpreted as interstitial nephritis). The spleen showed a locally extensive, firm, dry, irregular area of tan discoloration involving the middle third of the organ and extending into the splenic parenchyma (interpreted as infarct). There was an extensive area of subarachnoid hemorrhage over the dorsal surface of the cerebellum. No other gross abnormalities were seen in the rest of the viscera.

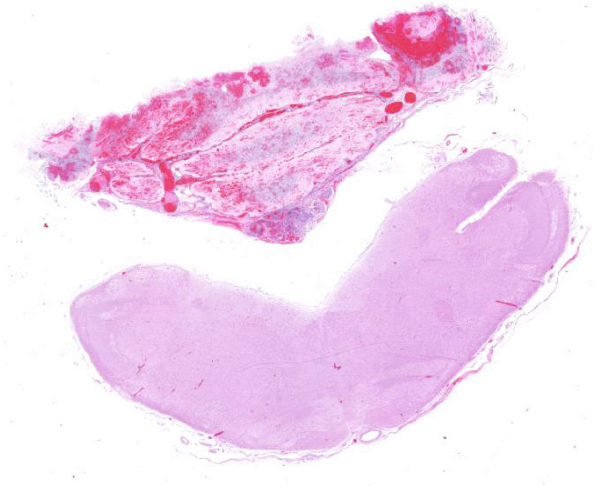
Laboratory Results:

Bacteriology: There was no microbial growth from samples of kidney and spleen. A light growth of mixed flora was recovered from the meninges.

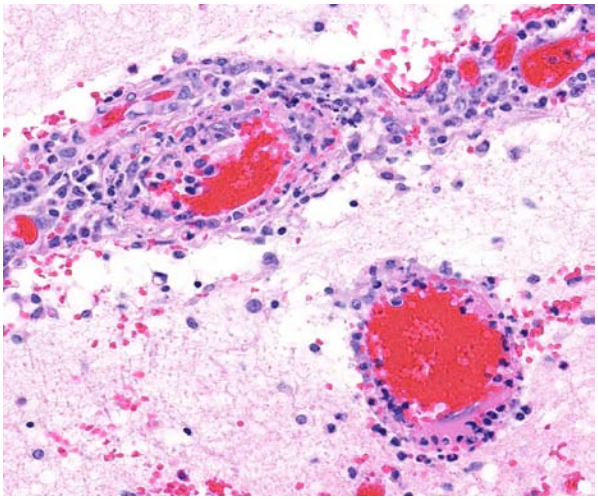
Virology: Ileum and tonsils tested positive for porcine circovirus type 2 by FAT and PCR.

Immunohistochemistry: Porcine circovirus type 2 antigen was present in the inflammatory infiltrate and affected blood vessels of cerebellum, choroid plexus and brain stem (Prairie Diagnostic Services, 52 Campus Dr, Saskatoon, SK. S7N 5B4)

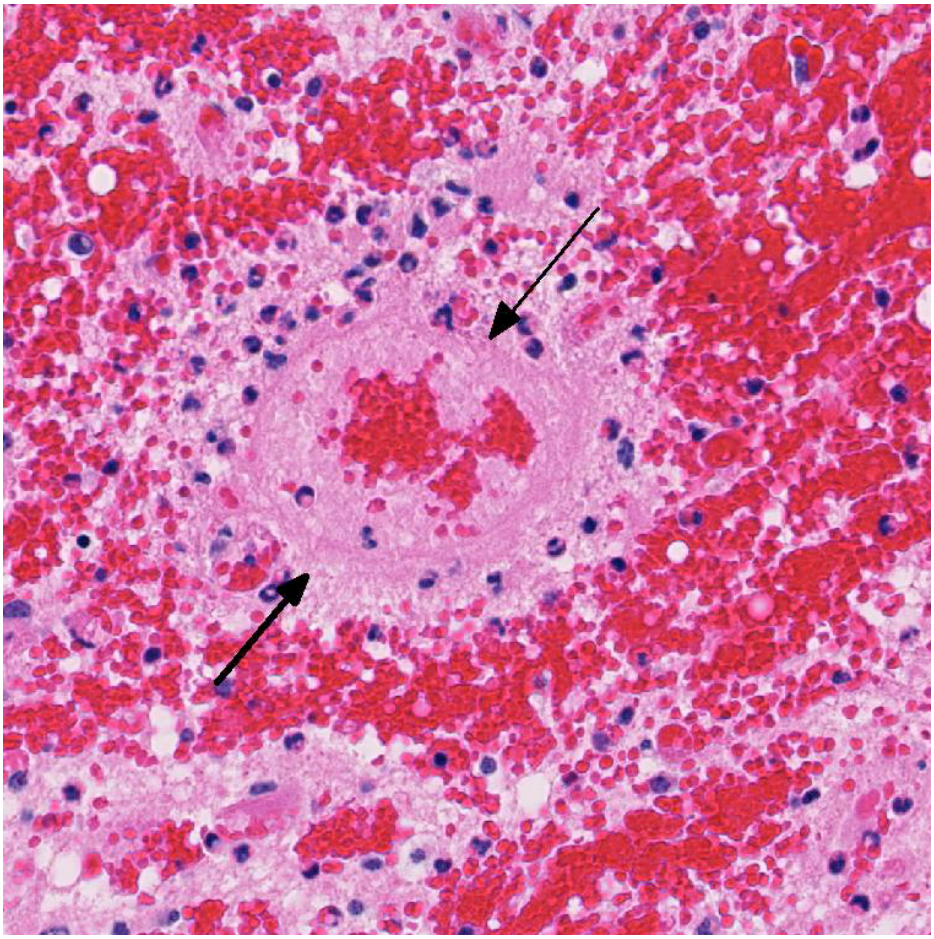
Histopathologic Description: The cerebellum has multifocally extensive areas of hemorrhage, necrosis and edema involving the white and gray matter. The subarachnoid space and the stroma of the choroid plexus (4th ventricle) are markedly expanded with hemorrhage, variable deposits of fibrin, necrotic cell debris, and large collections of macrophages interspersed with many lymphocytes, fewer plasma cells, occasional neutrophils and rare eosinophils. The wall of many blood vessels is infiltrated with scant eosinophilic homogeneous to fibrillar material (fibrinoid degeneration), karyorrhectic debris, and occasional macrophages or neutrophils (vasculitis). Many of these blood vessels and parenchymal capillaries are occluded with fibrin



4-1. Cerebrum, piglet: There is marked hemorrhage throughout the cerebellum. (HE 4X)



4-2. Cerebellum, piglet: Multifocally, vascular walls are necrotic and surrounded by a prominent infiltrate of macrophages, lymphocytes, and fewer plasma cells and neutrophils. (HE 256X)



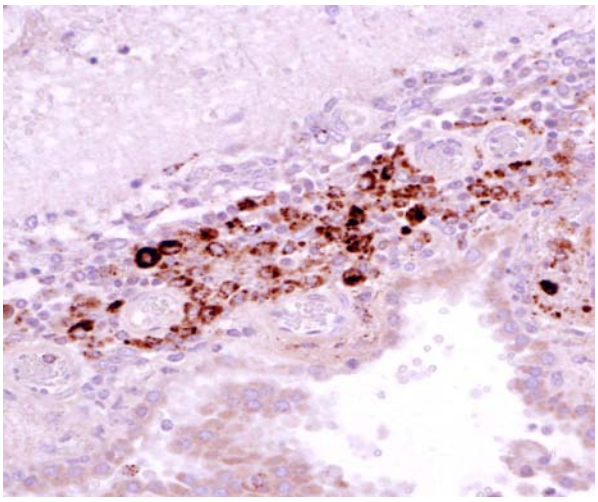
4-3. Cerebellum, piglet: Hemorrhagic infarcts are centered on necrotic vessels. (HE 270X)

thrombi. Within the neuropil are areas of spongiosis (edema) with scattered macrophages and neutrophils. Hypereosinophilic and shrunken neurons with karyolysis or nuclear pyknosis (neuronal necrosis) are seen primarily in the Purkinje and molecular cell layer among the areas of necrosis and hemorrhage. The ventricular space contains variably sized collections of erythrocytes admixed with fibrin, scant cell debris, histiocytes and lymphocytes. Vasculitis is also noted in the adjacent section of brain stem. Porcine circovirus type 2 antigen was present in the inflammatory infiltrate and affected blood vessels.

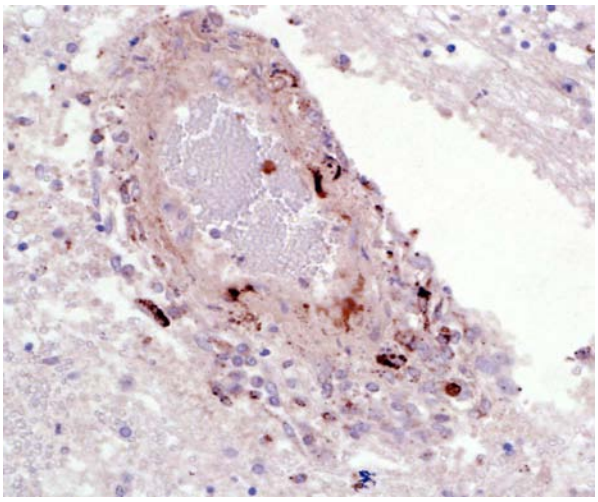
Contributor's Morphologic Diagnosis:
1. Cerebellum, choroid plexus, and brain stem: Vasculitis, fibrinonecrotizing and lymphohistiocytic, severe, diffuse, with severe, multifocal hemorrhage, necrosis, edema and thrombosis.
2. Lungs (not submitted): Interstitial pneumonia, lymphohistiocytic, diffuse, moderate, subacute.
3. Spleen (not submitted): Splenitis, granulomatous, diffuse, severe with locally extensive necrosis, fibrosis, and multifocal mineralization (chronic infarct).
4. Lymph nodes (not submitted): Lymphadenitis, histiocytic, multifocal, moderate, with diffuse lymphoid depletion, and scant intrahistiocytic cytoplasmic botryoid inclusions.
5. Ileum, Peyer's patches (not submitted): Lymphoid depletion, diffuse, severe.
6. Kidney (not submitted): Nephritis, interstitial, lymphohistiocytic, multifocal, moderate, with tubular degeneration, necrosis and regeneration, and interstitial fibrosis.
7. Tonsil (not submitted): Lymphoid depletion, diffuse, severe.

Contributor's Comment: Gross and microscopic findings are consistent with porcine circovirus type 2 (PCV2) infection (Post-weaning multisystemic wasting syndrome). Virology (FAT and PCR) and immunohistochemistry results confirmed the diagnosis. In addition, no significant bacterial isolates were recovered from this animal's samples.

Porcine circovirus (PCV) is a non-enveloped, single-stranded, circular DNA virus classified in the *Ciroviridae* family, genus *Circovirus*. There are two known PCV species, porcine circovirus type 1 (PCV1) and porcine circovirus type 2 (PCV2). PCV1 is non-cytopathic and non-pathogenic in swine. On the other hand, PCV2 is pathogenic in swine and associated with multiple disease entities. PCV2 is globally distributed and most herds are seropositive for anti-PCV2 antibodies.[8] Porcine circovirus type 2 infection



4-4. Cerebellum, piglet: Cells within the perivascular infiltrates are strongly immunopositive for porcine circovirus-2 antigen. (Photo courtesy of: Atlantic Veterinary College, University of Prince Edward Island (http://home.upei.ca/).) (anti-PCV-2, 200X)



4-5. Cerebellum, piglet: Scattered endothelial cells are strongly immunopositive for porcine circovirus-2 antigen. (Photo courtesy of: Atlantic Veterinary College, University of Prince Edward Island (http://home.upei.ca/).) (anti-PCV-2, 400X)

occurs as maternally derived antibodies wane in post-weaned pigs (7-15 weeks of age) and results in either subclinical infection or clinical disease. Clinical disease associated with PCV2 infection can have multiple manifestations which include: post-weaning multisystemic wasting syndrome (PMWS), PCV2-associated respiratory disease, PCV2-associated enteritis, porcine dermatitis and nephropathy syndrome (PDNS), myocarditis/ vasculitis, exudative dermatitis,[1,2] and cerebellar vasculitis.[3,11] Subclinical PCV2 infection may occur in apparently healthy pigs but this type of infection can reduce growth performance and increase susceptibility to other pathogens, or decrease the efficacy of vaccines.[9]

The PMWS is a systemic disease that clinically manifests between 7-15 weeks of age. It is characterized by wasting, dyspnea, lymphadenopathy, diarrhea, pallor and jaundice. Coughing, pyrexia, gastric ulceration, and meningitis have also been reported, but are sporadic.[5] Herd morbidity in PMWS herds is variable with 4-30% of the pigs affected. Mortality rates are often high (20-50%). The most consistent necropsy finding in PMWS pigs is generalized lymphadenopathy. PMWS pigs are frequently coinfected with other common bacterial and viral pathogens, and coinfection often complicates gross findings. Microscopically, lymphoid tissues from PMWS-affected pigs exhibit lymphoid depletion and replacement by histiocytic/granulomatous inflammation. Multinucleated (syncytial) giant cells, epithelioid macrophages and macrophage-associated intracytoplasmic botryoid-like basophilic inclusions are also commonly seen in lymphoid tissues (lymph node, tonsil, Peyer's patches, and spleen). Focal parenchymal coagulative and apoptotic necrosis in lymphoid tissues has also been described. Microscopic lesions in nonlymphoid tissues are characterized by lymphohistiocytic inflammation and include interstitial pneumonia, hepatitis, interstitial nephritis and enteritis/colitis. The diagnosis of PMWS is based on clinical signs of wasting which may or may not include respiratory distress and icterus, lymphoid depletion and granulomatous inflammation, and the presence of PCV2 antigen or nucleic acid associated with microscopic lesions.[12]

PCV2-associated respiratory disease and PCV2-associated enteritis can often overlap with PMWS or be a contributing factor in porcine respiratory disease complex (PRDC) and bacterial enteritis, respectively. Microscopically, there is lymphohistiocytic interstitial pneumonia sometimes associated with type II pneumocyte hypertrophy and hyperplasia, peribronchiolar fibrosis, and associated lymphoid hyperplasia. Within the intestine, the gut associated lymphoid tissue (GALT; Peyer's patches) exhibit similar changes as those described in PMWS. However, the diagnosis of PCV2-associated enteritis is appropriate when there is clinical diarrhea, lymphoid depletion and granulomatous inflammation are present in Peyer's patches but

not in other lymphoid tissues, and PCV2 DNA or antigen can be demonstrated within the lesions.[2]

Porcine dermatitis and nephropathy syndrome is a distinctive, sporadic, acute clinical entity of growing swine characterized by circular to coalescing, red to purple macules or raised papules and plaques that originate on the skin of the hind legs and perineal region. Lesions may become exudative, crusty, and eventually regress leaving dermal scars. Bilateral swollen kidneys with widely disseminated cortical petechial hemorrhages are also commonly observed. Increased mortality is seen in affected pigs older than three months of age. The typical microscopic lesion is necrotizing vasculitis and glomerulonephritis. Small to medium sized dermal and subcutaneous arterioles are cuffed by neutrophils, macrophages, lymphocytes, and plasma cells that are sometimes present within vascular walls. Arterioles are lined by plump endothelial cells, occasionally occluded by fibrin thrombi and walls can display multifocal hyalinization. Kidney sections exhibit distension of urinary spaces by fibrin intermixed with necrotic cellular debris and hemorrhage, periglomerular and interstitial lymphohistiocytic infiltrates, and distension of renal tubules with cellular and proteinaceous casts. Skin and glomerular lesions are characteristic of a type III hypersensitivity reaction with deposition of immune complexes. Multiple viral and bacterial pathogens have been implicated in PDNS, but PCV2 is considered a contributing factor.[2]

A striking finding in this particular case was the cerebellar vasculitis, particularly in absence of significant bacterial isolates. It is known that PCV2 produces nonsuppurative or granulomatous encephalitis with gliosis under experimental conditions and the PCV2 antigen has been identified in brain in these cases. However, in cases of naturally occurring encephalitis, PCV2 has been detected in brains of affected animals always in association with other pathogens that can cause encephalitis alone.[7] Cerebellar hemorrhage, edema and necrosis, resulting from necrotizing and lymphohistiocytic vasculitis (and thrombosis) is an uncommon feature that has also been previously described associated with PCV2 infection.[3,11] PVC2 antigen has been demonstrated in the inflammatory infiltrate and affected blood vessels as in this particular case. Similar to this case, the reported PCV2-associated cerebellar vasculitis exhibited some characteristics of PMWS and also changes consistent with PDNS[9] suggesting that a type III hypersensitivity reaction with deposition of immune complexes, as it has been considered in PDNS, might be involved in the pathogenesis of this lesion.

JPC Diagnosis: Cerebellum: Vasculitis, necrotizing, diffuse, severe, with thrombosis and multifocal to coalescing cerebellar necrosis.

Conference Comment: Despite the decreasing prevalence of PCV2 due to a successful vaccination campaign, it remains an important disease of swine throughout the world. This case serves as a reminder of maintaining PCV2 on the differential list for a multitude of different lesions in swine, as neural pathology associated with PCV2 infection occurs infrequently and is considered to be of minor importance.[8] PCV2 has the potential to cause disease in nine organ systems in various ways through its overlapping PCV-associated disease (PCVAD) manifestations outlined by the contributor. Perhaps most notably, PCV2 causes lymphoid depletion and histiocytic inflammation of lymphoid tissues.[8] This consistent lesion led some researchers to look for a porcine lentivirus during the initial presentation of PMWS just 20 years ago.[4]

The presence of vasculitis and fibrin in this case led many participants toward an etiology of *Streptococcus suis* or *Hemophilus parasuis*. Other differentials to consider for lymphohistiocytic encephalitis and cerebellar hemorrhage include *porcine parvovirus, porcine reproductive and respiratory syndrome virus,* and *hemagglutinating encephalomyelitis virus*.[8] Lymphohistiocytic and necrotizing vasculitis is well documented in PCV2-systemic disease, where it occurs most commonly in the mesenteric lymph nodes and kidney though many other organs may also be affected.[10] The virus appears to have a direct cytopathic effect on vascular endothelium, myocytes, and pericytes in these instances, although an indirect mechanism such as a hypersensitivity reaction may also be possible.[10]

Contributing Institution: Atlantic Veterinary College, University of Prince Edward Island (http://home.upei.ca/)

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