



WEDNESDAY SLIDE CONFERENCE 2013-2014

Conference 22

09 April 2014

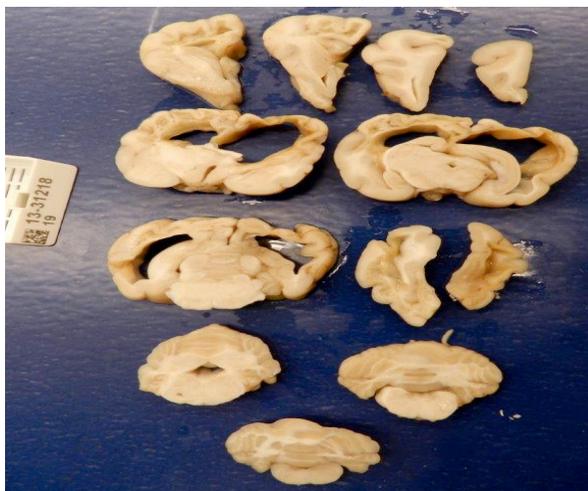
CASE I: 13-31218 (JPC 4033968).

Signalment: 4.5-year-old female spayed Yorkshire terrier, (*Canis familiaris*).

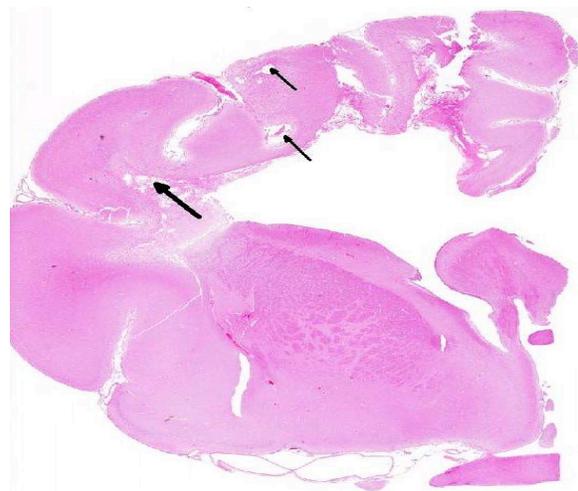
History: A 4.5 year-old, spayed female Yorkshire terrier dog was referred to the University of Illinois Veterinary Teaching Hospital for

neurologic evaluation. The animal had become blind and was circling to the right six months prior to presentation to the hospital. One week prior to presentation, the animal had become ataxic and unable to right itself after falling.

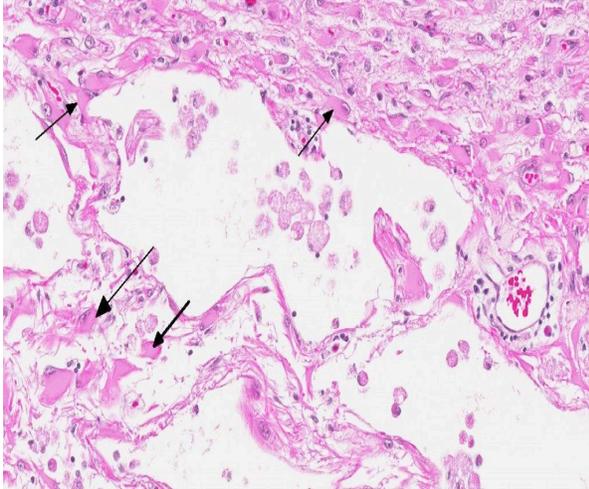
On initial neurologic examination, the animal had a left head turn and tilt, thoracolumbar kyphosis



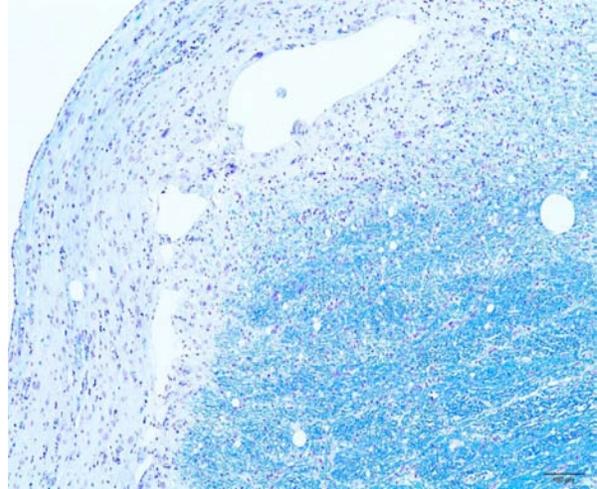
1-1. Cerebrum, dog: The ventricles are markedly dilated. There were multiple, 1 mm to 8 mm in diameter, gray to pink, depressed foci in the periventricular areas and within the cortical white matter and are associated with thinning of the cortical grey matter. (Photo courtesy of: Department of Pathobiology, College of Veterinary Medicine, University of Illinois Urbana-Champaign, 2001 S. Lincoln Ave., Urbana, IL 61801 <http://vetmed.illinois.edu/path/>)



1-2. Cerebrum, dog: There are multiple areas of cavitation within the cortical white matter. (HE 0.63X)



1-3. Cerebrum, dog: Cavitated areas contain few Gitter cells and are bounded by gemistocytic astrocytes (arrows). (HE 140X)

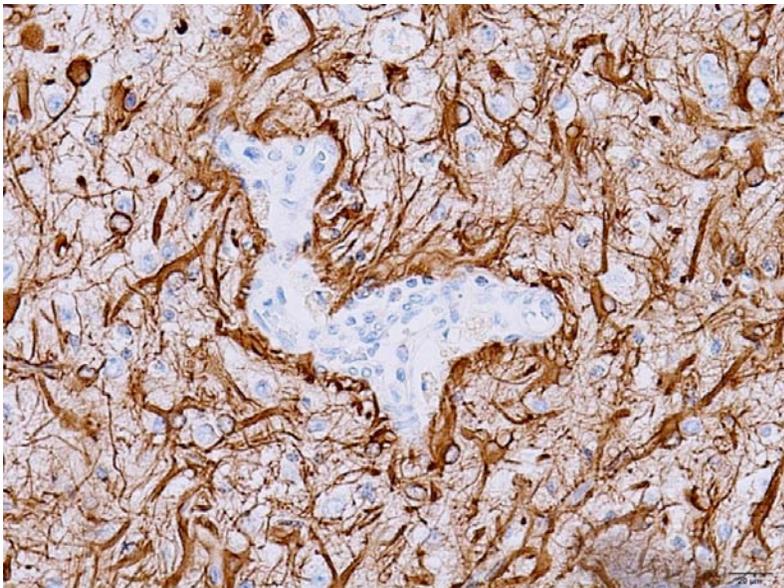


1-4. Cerebrum, dog: A Luxol fast blue stain for myelin shows the absence of myelin in cavitated areas. (Photo courtesy of: Department of Pathobiology, College of Veterinary Medicine, University of Illinois Urbana-Champaign, 2001 S. Lincoln Ave., Urbana, IL 61801 <http://vetmed.illinois.edu/path/>)

and extensor rigidity of the pelvic limbs. The animal was tetraplegic but could move all limbs when supported ventrally. The animal would alligator roll to the left when attempting to stand. Placing responses and hopping were absent in all four limbs. Muscle tone was increased in all four limbs, most markedly in the pelvic limbs. Spinal reflexes were increased in the pelvic limbs (with a crossed extensor). Menace response was absent in both eyes and there was a resting ventrolateral strabismus in the left eye. Pain could be elicited

on palpation over the calvarium and cervical spine. Complete blood count, chemistry profile and preprandial and postprandial bile acids testing showed no significant abnormalities.

The animal's neurologic status improved somewhat after treatment with prednisone, and the animal was no longer painful. Two weeks after starting the steroid medication, a neurologic examination showed no change to the cranial nerve deficits and a continued head tilt and turn; however, the animal was able to walk again (with tetraparesis and tetrataxia). The animal continued to show improvement on steroids for six weeks but then began to show worsening neurologic symptoms. At final examination, the animal's demeanor was dull, and it was unable to stand with or without support. Proprioception was decreased to absent in all four limbs. In addition to previously observed cranial nerve symptoms, the animal now had mild anisocoria (left > right) and positional slow rotary nystagmus. The owner elected euthanasia.



1-5. Cerebrum, dog: A glial fibrillary acidic protein (GFAP) stain highlights the numerous astrocytes and their processes in tissue bordering areas of cavitation. (Photo courtesy of: Department of Pathobiology, College of Veterinary Medicine, University of Illinois Urbana-Champaign, 2001 S. Lincoln Ave., Urbana, IL 61801 <http://vetmed.illinois.edu/path/>)

Gross Pathology: On necropsy, the animal was in fair to poor nutritional condition, with mottled dark pink to red lungs (congestion),

mild tonsillar atrophy, and moderate cardiomegaly. On opening of the calvarium, the right hemisphere of the brain was fluctuant. The exterior of the cerebral cortex was moderately to markedly thinned, and partially translucent. On coronal incision into the cerebral hemispheres, a large amount of clear, slightly yellow fluid was released from the markedly distended ventricles. There were multiple, 1 mm to 8 mm in diameter, gray to pink, depressed foci in the periventricular areas and within the cortical white matter. Extending from the frontal to the occipital cerebral cortex, these white matter lesions were irregular, bilateral but non-symmetrical, and often associated with thinning of the cortical grey matter. Lesions were more severe in the right hemisphere than the left. There was a focal, 1 mm in diameter cavitation in the left metencephalon. Other areas of the brain (i.e. cerebellum, retina, optic nerve) were not affected.

Laboratory Results:

CBC:

	Value	Reference Range	Units
HCT	55.8%	35-52%	
MCHC	31.3	32.0-36.0	g/dL
Eosinophils	0.081x10 ³	0.1-1.0 x10 ³	/μL

- Anisocytosis: 1+
- Polychromasia: rare
- Target cells: 4+

Chemistry:

	Value	Reference Range	Units
Globulin	2.6	2.7-4.4	g/dL
Alb/Glob ratio	1.3	0.6-1.1	
ALT	93	8-65	U/L
Total T4	14.3	15.0-48.0	nmol/L
Bile acids (preprandial)	15.5	0.0-7.5	nmol/L
Bile acids (postprandial)	16.0	0.0-25.0	nmol/L

Microbiology:

Aerobic culture:

- Brain: *Pasteurella multocida* – few
- Brain: Alpha strep non-Enterococcus – rare
- Brain: *Escherichia coli* - rare

Anaerobic culture:

- Brain: *Clostridium perfringens* - v. few
- Brain: *Prevotella* - few

Histopathologic Description: The cerebral white matter was severely affected by bilateral but asymmetric white matter degeneration. Loss of white matter ranged from 75% to nearly 100%, generally decreasing in a cranial to caudal direction through the cerebral hemispheres. Degeneration was characterized by loss of tissue substance with formation of pseudo-cysts delineated by numerous reactive astrocytes (gemistocytes) admixed with foamy macrophages (gitter cells) and few lymphocytes. The ventricles were markedly enlarged (compensatory hydrocephalus). Staining with GFAP for astrocytes revealed a marked gliosis throughout the affected areas. The Virchow-Robin space of occasional blood vessels was expanded by a mild infiltrate of lymphocytes, plasma cells, and occasional macrophages. The loss of white matter was verified by an almost complete lack of staining for myelin with Luxol fast blue within affected areas. In less severely affected white matter areas, like the corpus callosum, marked and abrupt areas of demyelination were often noted. Within the brain stem, similar multifocal loss of white matter was identified in the dorsal thalamus, geniculate area, and mesencephalon. One focal area of cavitation was noted in the metencephalon. The occasional neurons encountered within degenerate areas appeared unaffected. No histopathologic lesions were noted within gray matter adjacent to areas of white matter degeneration.

Contributor’s Morphologic Diagnosis: Brain, cerebrum: Severe, necrotizing, leukoencephalitis with marked astrogliosis and compensatory hydrocephalus.

Contributor’s Comment: Necrotizing leukoencephalitis of Yorkshire Terriers (NLE) is a rare, idiopathic, inflammatory disease of the central nervous system. It is characterized by infiltration by inflammatory cells into the white matter of the cerebrum and brainstem, with consequent widespread cavitation necrosis, demyelination, perivascular lymphoplasmacytic cuffing and glial scarring. Active lesions are characterized by marked lymphohistiocytosis, glial activation, and infiltration by numerous

gitter cells and gemistocytes. Quiescent, chronic lesions are characterized by marked cavitation, advanced gliosis, and a relative paucity of inflammatory and gitter cells.¹¹ Lymphoplasmacytic cuffing in the case under discussion was relatively mild, but in other reported cases of NLE, perivascular lymphoplasmacytic exudate has been marked and extensive.^{4,7,11} NLE is relatively sparing of the cerebral cortex and meninges, and predominantly affects periventricular cerebral white matter, including the centrum semiovale, thalamocortical fibers, internal capsule and thalamus.⁷

NLE is commonly grouped with Necrotizing Meningoencephalitis (NME) or pug dog encephalitis⁷ in veterinary literature. While breed predilection and lesion topography vary between the two diseases (NME affects gray and white matter primarily in the cerebral cortex, hippocampus and thalamus,⁴ while NLE affects the cerebra and brainstem), the hallmark of both diseases is lymphoplasmacytic meningoencephalitis and bilateral, asymmetric, cerebral necrosis.⁷ There is some debate as to whether these diseases are two distinct entities or one disease with a similar pathogenesis but histopathologic differences as a result of minor genetic differences between breeds, modifying genes and/or variations in antigenic exposures.⁷

NLE was first described in Yorkshire terriers in 1993,⁹ and has since been diagnosed in French bulldogs as well.^{6,8} It primarily affects young adult dogs, with a mean age of onset of 4.5 years (range, 4 months to 10 years old).⁸ It appears to affect male and female dogs equally.⁹ Clinical signs on initial presentation are referable to the location of the cerebral lesions, and commonly include visual deficits or blindness, depression, seizures, circling, ataxia and head tilt.⁶ Conventional treatment is with immunosuppressive doses of glucocorticoids. Survival after diagnosis varies between 3 and 18 months² and the disease is invariably progressive and fatal.

The etiology of NLE is poorly understood. No infectious agents have ever been identified in association with NLE; PCR screening in dogs with histopathologic diagnoses of NLE and NME for the presence of degenerate herpesvirus, adenovirus, and canine parvovirus viral proteins have revealed no viral proteins,¹ and IHC staining

for *Toxoplasma gondii* and *Neospora caninum* are routinely negative. However, negative PCR results for viruses does not rule out the possibility of a viral trigger for the disease via molecular mimicry or the possibility that a pathogen is present at undetectable levels in the presence of a self-perpetuating immune response, a phenomenon that has been described for flavivirus infections.⁷ Genetics may play a role in pathogenesis, as the disease is breed specific, and a strong familial inheritance pattern was detected in pugs with NME.⁷ There is likely an immune-mediated component to NLE, as evidenced by the variable but generally positive response of the disease to treatment with glucocorticosteroids. In one case report of NLE, major infiltration of necrotic areas by cytotoxic T-lymphocytes, IgG producing plasma cells, macrophages and microglial cells was identified, suggesting a possible delayed T-cell immune response in the pathogenesis of the disease.³ It is most likely that NLE is a multifactorial disorder caused by an as yet unknown combination of the factors above.

Diagnosis of NLE can be made on a combination of factors: age, breed affected, clinical signs that can be localized to the cerebra and brainstem, and a chronic, progressive course should all be considered when making a diagnosis. MRI imaging can be a very helpful diagnostic tool, and allows the diagnosis of NLE with a high degree of suspicion based on lesion localization, lesion appearance in different sequences and contrast enhancement.¹¹ Protein levels and cell counts in the CSF may also be increased in cases of NLE,^{5,6} but this is a non-specific finding and should only be used in conjunction with the factors above in making a diagnosis.

JPC Diagnosis: Cerebrum, frontal cortex: Leukoencephalitis, necrotizing, multifocal, severe with hydrocephalus *ex vacuo* and numerous gemistocytic astrocytes.

Conference Comment: Small/toy breeds are susceptible to several potentially overlapping, idiopathic encephalitides which are poorly understood. Necrotizing leukoencephalitis (NLE) of the periventricular cerebral white matter (and brainstem) is described in Yorkshire terriers and occasionally French bulldogs and is discussed comprehensively by the contributor. Necrotizing meningoencephalitis (NME) is a similar syndrome, known historically as “pug dog

encephalitis,” that is reported in various toy breeds including the pug, Maltese terrier, chihuahua, Yorkshire terrier, Pekingese, West Highland white terrier, Boston terrier, Japanese spitz, and miniature pinscher. In contrast to NLE, NME typically affects the leptomeninges, cerebral hemispheres and subcortical white matter, with loss of the anatomic demarcation between gray and white matter.⁷ Granulomatous meningoencephalitis (GME) is a progressive, generally fatal neurologic disease of unknown origin that typically affects toy and terrier breeds; it is characterized by focal (mass-like) or disseminated perivascular accumulations of histiocytes, lymphocytes and plasma cells, primarily within the white matter of the brain, spinal cord and the optic nerve.^{4,7} Due to considerable overlap in the clinical presentation of these conditions, some researchers suggest that the terminology meningoencephalitis of unknown etiology (MUE) may be preferable for an antemortem diagnosis of idiopathic meningoencephalitis without concurrent histopathology. Although the etiopathogeneses for these disorders remain elusive, immunosuppressive therapy is the mainstay of treatment, suggesting that an aberrant immune response directed against the CNS may play a role in the development of idiopathic canine meningoencephalitis.⁷ A similar, fatal condition, known as Alaskan husky encephalopathy (AHE) affects young huskies, and is characterized by bilateral thalamic necrosis and cavitation. AHE is thought to be similar to Leigh syndrome, which is a group of diseases in humans attributed to mutations in either nuclear or mitochondrial DNA. A recent study found a mutation in the gene encoding a thiamine transporter protein (SLC19A3.1) plays a critical role in the pathogenesis of AHE.¹⁰

The microscopic lesions in this case, particularly their cavitating nature and specific location within the white matter, are most consistent with the condition known as necrotizing leukoencephalitis of Yorkshire terriers (NLE). Conference participants speculated that the mild perivascular and leptomeningeal inflammation was likely a reactive change secondary to marked necrosis and that the presence of hydrocephalus *ex vacuo* was probably due to the filling of the large pseudocysts with CSF.

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CASE II: 13/326 (JPC 4033975).

Signalment: 3-year-old female domestic cat, (*Felis catus*).

History: The cat had three episodes of seizures with increasing severity during a period of one month. There was loss of proprioception and loss of vision after an episode with cluster attacks, but both proprioception and vision showed some improvement the following days. The cat was dehydrated at admission, but after rehydration the hematocrit was still very high (see below). The cat was euthanized. The differential diagnosis included encephalitis due to dry form of feline infectious peritonitis, *Toxoplasma*, neoplasia or polycythemia.

Gross Pathology: The cat was not macroscopically dehydrated (normal position of eyes in orbits). The heart was moderately rounded in shape and the right side was moderately dilated. Between the atria there was a persistent foramen ovale that measured 8 mm in diameter. The lungs were congested and edematous with moderate amounts of red colored mucus in the bronchi. In the stomach there was one nematode and in the small intestine there was one tapeworm. Colonic contents were moderately increased in amount and drier than normal. The renal cortices contained numerous petechiae on the cut surface. The texture of the cortex was normal. The size of the spleen was normal. Bone marrow was diffusely red. In formalin fixed brain there were bilateral mildly accentuated vascular structures on the cut surface of the hippocampus.

Laboratory Results:

Complete blood count:

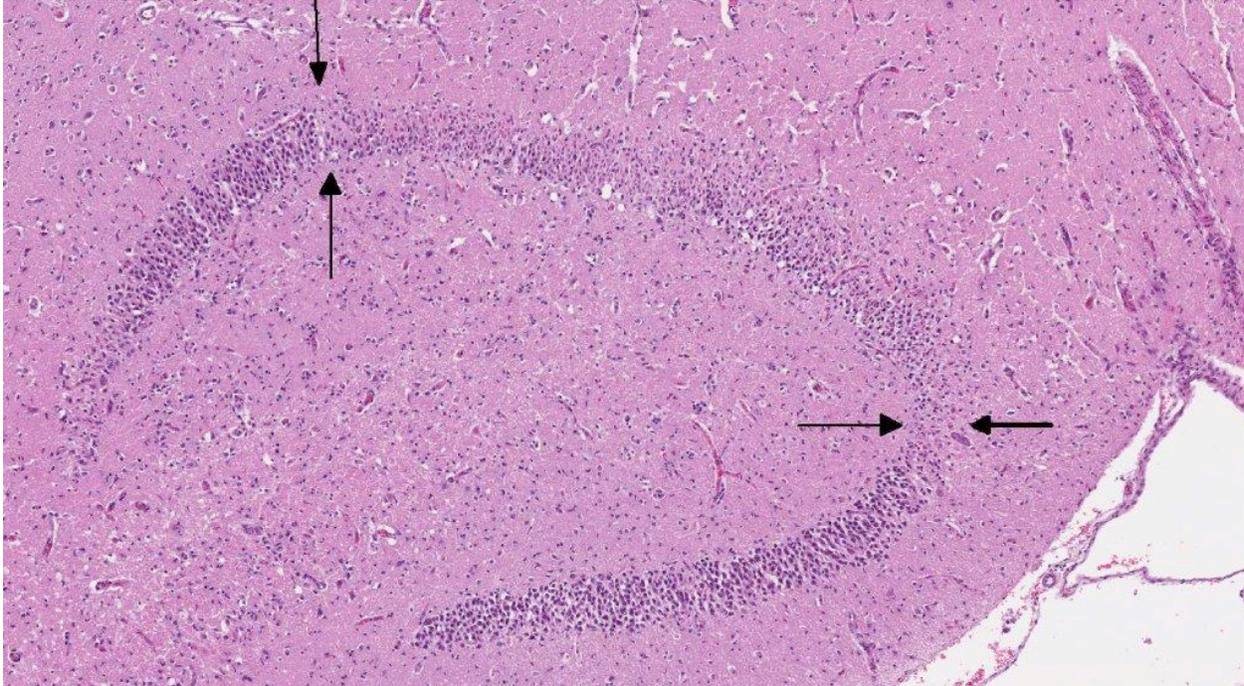
RBC: 20.56 (5-10)
HGB: 239 (80-150)
HCT: 0.72 (0.24-0.45)
MCV: 35.1 (40-52)
RDW: 18.5 (13-17)
Lymphocytes: 0.2 (1.5-7.0)

Conclusion: marked erythrocytosis and marked lymphopenia

Histopathologic Description: In the brain there was bilateral and nearly diffuse neuronal necrosis in the hippocampus. The necrosis affected both the dentate gyrus and the pyramidal neurons. There were some segments with intact neurons in the dentate gyrus, but most neurons were necrotic with a shrunken hypereosinophilic appearance with a pyknotic or karyolytic nucleus. There were some mitotic figures probably representing proliferating glial cells. There was mild multifocal rarefaction and vacuolation of the neuropil and proliferation of vessels with hypertrophied endothelial cells. A similar but small focus of necrosis was detected in the pyriforme lobe. Otherwise, the brain was unremarkable, except for one vessel with perivascular infiltrates of



2-1. Hippocampus, cat: The neuronal population of the hippocampus is less prominent than normal (HE 0.63X)



2-2. Hippocampus, cat: A segmental area of hypercellularity (between arrows) is present within the hippocampal neurons. There is also a prominent gliosis within the hippocampus as a whole. (HE 75X)

lymphocytes in the cerebral cortex laterally to the thalamus.

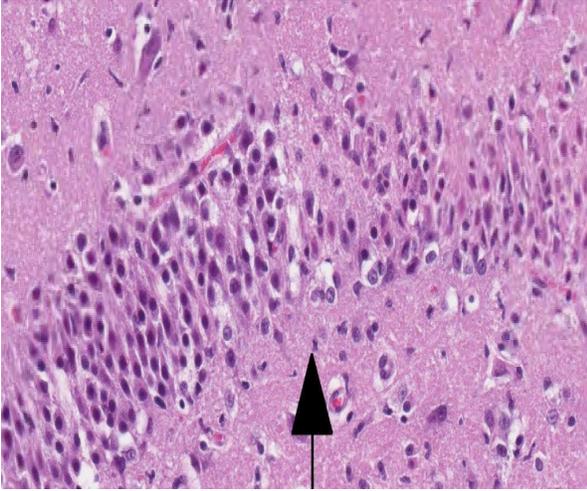
Other relevant histological findings: In the lungs there was severe congestion and edema. Pulmonary vessels were normal. There was moderate acute congestion in the liver. Although renal cortical petechiae were detected macroscopically, this could not be confirmed histologically, but the glomerular capillaries were engorged with blood. Cell density of bone marrow was moderately increased with mixed cell types but dominated by erythroid cells of mature stages.

Contributor's Morphologic Diagnosis: Brain, hippocampus: Neuronal necrosis, subtotal, bilateral, subacute.

Contributor's Comment: Feline hippocampal necrosis is a neurological disorder with unknown cause, characterized by generalized or complex-partial seizures of acute onset and rapid progression.³ Fatzer et al described the findings in 38 domestic cats suffering from the disease.³ Most cats were between 1-6 years old, and there was no breed or sex predisposition. The typical distribution of the lesions is severe involvement of the hippocampus with sparing of the remaining

parts of the brain, except for the pyramidal lobes in some cases.^{3,10} Histopathologic findings are acidophilic neuronal necrosis that may be diffuse in severe cases, gliosis, and proliferated vessels with hypertrophied endothelial cells.^{3,10} The hippocampal lesions in this case were consistent with the findings described by Fatzer et al.³ Some cases may have perivascular lymphohistiocytic infiltrates,³ but this was only present around one vessel in this case and in a location not related to the necrotic lesions.

The polycythemia observed in this cat was interpreted to be an absolute polycythemia (primary or secondary) and not a relative polycythemia due to dehydration, since the cat presented with a high hematocrit (0.72) even after rehydration. The rare disease primary polycythemia (polycythemia vera) must be distinguished from secondary polycythemia which is more common. In primary polycythemia, the bone marrow has a very high cellularity with little remaining fat. Aspirated marrow has a synchronous trilineage hyperplasia with a myeloid:erythroid ratio of near 1.0.⁹ This cat had had a moderately cellular bone marrow with a dominance of mature erythroid cells, possibly indicating a secondary polycythemia. Measurement of blood oxygen levels would be



2-3. Hippocampus, cat: Higher magnification of Figure 2-2, demonstrating marked neuronal loss. In addition, many of the remaining neurons are shrunken, eosinophilic, and/or pyknotic (degeneration and necrosis). (HE 160X)

helpful differentiating between primary and secondary polycythemia, but this was not performed in this case. A cause of secondary polycythemia is vascular anomalies causing anoxia. This cat had a persistent foramen ovale of 8 mm in diameter, a lesion usually not causing anoxia unless the blood flow through the atrial defect switches from left-right to right-left (Eisenmenger syndrome).⁵ Pulmonary hypertension may be the result of heart malformations causing left to right shunting of blood and increased blood flow to the lungs.¹ Vascular lesions in the lungs due to pulmonary hypertension were not detected in this cat; neither acute lesions consisting of endothelial degeneration, fibrinoid necrosis and vasculitis, nor chronic lesions consisting of remodeling of pulmonary arterioles with thickening of the tunica intima and hypertrophy of the media were noted.¹ Interestingly, hypoxia due to patent foramen ovale in the absence of pulmonary hypertension is described in humans.⁴ It is not clear to what degree the cardiac and hematological abnormalities contributed to the hippocampal necrosis in this cat. Of the 38 cats described by Fatzer et al, no similar hematological abnormalities were described; however, it is unclear whether hematological examinations were performed on all cats.

JPC Diagnosis: Cerebrum, hippocampus and piriform lobe: Neuronal necrosis, multifocal, subacute, with edema, gliosis and neovascularization.

Conference Comment: Conference participants briefly discussed the differential diagnosis for the histological findings, including ischemic encephalopathy, neuronal toxicity and rabies viral infection. Within the central nervous system, neurons and oligodendroglia are the most sensitive to ischemia, while blood vessels are more resistant and may survive in necrotic areas. In general, the grey matter is more sensitive to hypoxia than the white matter; specifically neurons of the hippocampus (especially the CA1 region) and the deeper laminae of the cerebral cortex, as well as Purkinje cells, are the most sensitive to ischemic necrosis.⁶ Ischemic necrosis following fibrocartilagenous embolus (FCE) is a possible explanation for the lesions in this case; however, FCE is rare in cats, and when it occurs, it is asymmetric and typically affects the spinal cord, rather than the brain.² Feline ischemic encephalopathy (FIE) is quite similar to feline hippocampal necrosis, and has been associated with aberrant migration of *Cuterebra* spp. larvae. This condition is characterized by severe necrotizing lesions and infarction of areas of the cerebrum supplied by the middle cerebral artery, and thus often involves the hippocampus and piriform lobe; however, in contrast to feline hippocampal necrosis, which is bilateral and symmetric, the lesions in FIE are typically unilateral or asymmetric with spontaneous resolution and often partial to total recovery.^{3,6}

Due to its use of glutamate (or possibly aspartate) as an excitatory neurotransmitter, the hippocampus is also particularly vulnerable to neuronal excitotoxicity, which may have played a role in the pathogenesis of this case. Glutamate is toxic to neurons and is normally cleared rapidly by glial cells. Conditions such as ischemia, hypoxia, seizures, and hypoglycemia promote a cascade of unregulated events including endogenous glutamate release, activation of glutamate receptors, decreased clearance of glutamate, and opening of voltage gated calcium channels, ultimately resulting in neuronal degeneration and necrosis; this is known as endogenous neuronal excitotoxicity.^{6,8} A comparable neurotoxic condition has been described in marine mammals and seabirds in association with exposure to domoic acid (an analog of L-glutamate) following harmful algal blooms.⁸

In contrast to the microscopic lesions in this case, which are confined to the hippocampus, the lymphoplasmacytic perivascular cuffing, focal gliosis and neuronal intracytoplasmic viral inclusions (Negri bodies) commonly associated with rabies virus tend to be most severe from the pons to the hypothalamus and within the cervical spinal cord.⁶ Nevertheless, definitive diagnosis of feline hippocampal necrosis in this case (versus rabies viral infection) was complicated for some participants by identification of scattered eosinophilic, intracytoplasmic “rabies-like” inclusions. The occurrence of intracytoplasmic neuronal inclusions indistinguishable from Negri bodies is a fairly common incidental finding in older dogs and cats which must be differentiated from true viral inclusions with laboratory diagnostics such as fluorescent antibody testing.⁷

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CASE III: AFIP Case 1 (JPC 4003089).

Signalment: 1-year-old intact male Argentinian Mastiff dog, (*Canis familiaris*).

History: The dog had an approximately 1-week history of hindlimb ataxia. Upon referral to the Boren Veterinary Medical Teaching Hospital, CT imaging revealed a mass in the L1-L2 spinal cord. Dorsal laminectomy was performed, and the mass was considered non-resectable. The dog was euthanized.

Gross Pathology: Over the dorsal vertebral processes, centered on the thoracolumbar junction, is a 12 cm long incision that is closed with surgical staples. Subcutaneous tissue deep to the incision is dark red and contains large aggregates of friable, dark red material (clot, fibrin). The right dorsal pedicles and lamina of the lumbar vertebrae 1 and 2 are absent (surgical artifact), and the surrounding tissue is dark red. Dura overlying the mass is mostly intact with a single small defect (surgical artifact). At the level of L1-L2, the spinal cord is moderately enlarged and dark brown to red. Protruding from subdural space into the spinal cord is a 1 cm diameter, well-demarcated, soft, white mass. The tissue immediately surrounding the mass is markedly expanded by abundant dark red material (hemorrhage).

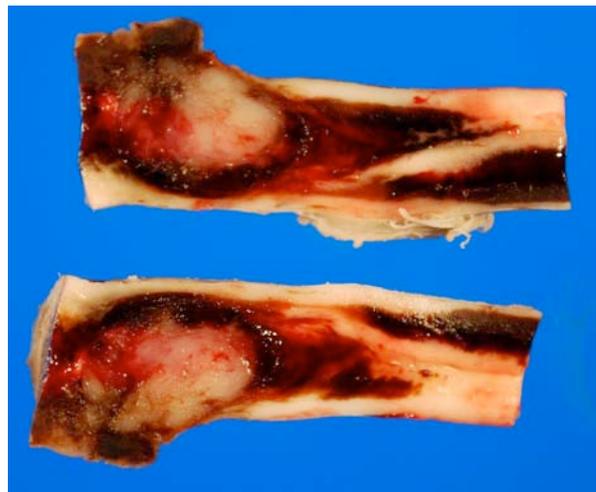
Histopathologic Description: Spinal cord, L1-L2: Expanding from within and beneath the dura and infiltrating the underlying spinal cord is a densely cellular, well-demarcated, partially encapsulated neoplasm. Neoplastic cells are of two distinct cell populations. One population forms tubules lined by cuboidal cells that have a small amount of eosinophilic cytoplasm and a single round nucleus with finely stippled chromatin. Surrounding the neoplastic tubules are sheets of polygonal blastemal cells that have minimal cytoplasm and a round, deeply basophilic nucleus with slight vesicular chromatin. The mitotic rate is high with 25 mitoses in 10 high-powered fields. Surrounding the neoplasm is abundant hemorrhage that extends cranially and caudally, obliterating large portions of the spinal cord and surrounding few remaining neurons. Scattered throughout the areas of hemorrhage are few small aggregate of neutrophils. Cranial and caudal to the mass, white matter tracts are markedly vacuolated with many spheroids.

Immunostaining of the mass demonstrates that neoplastic epithelial cells are immunoreactive on staining with cytokeratin and mesenchymal cells are immunoreactive on staining with vimentin. Neoplastic cells are not immunoreactive on staining with neuron specific enolase or glial fibrillary acidic protein.

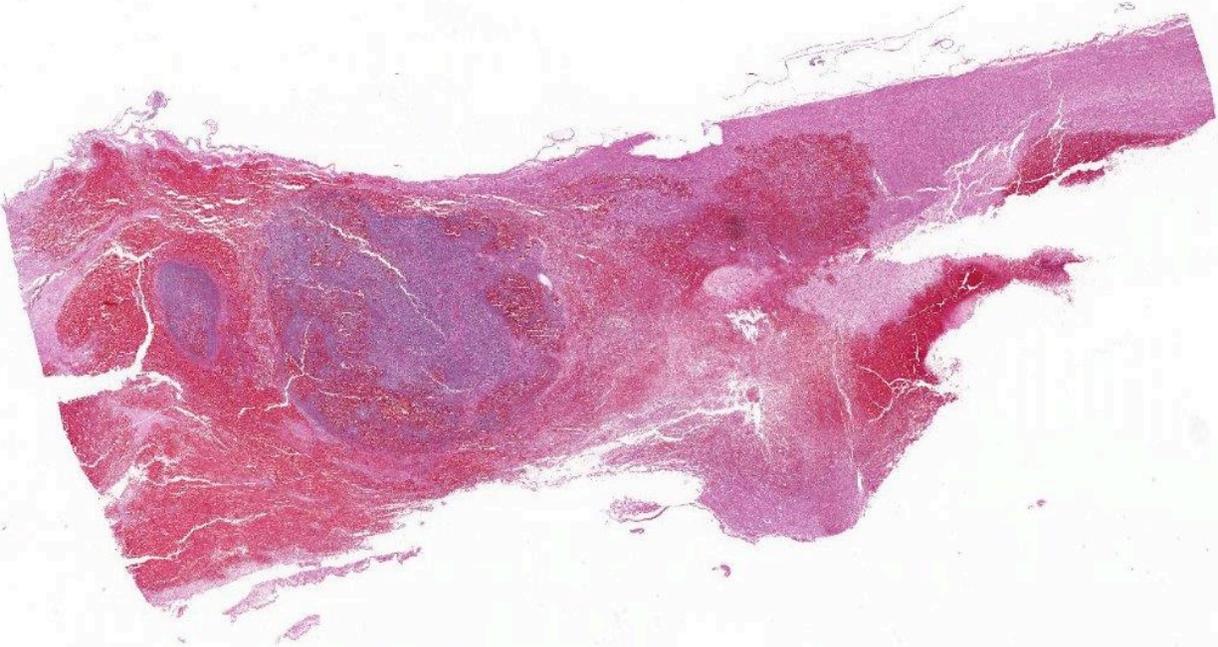
Contributor's Morphologic Diagnosis: Spinal cord, L1-L2: Nephroblastoma.



3-1. Spinal cord, dog: A large mass disrupts the normal architecture of the spinal cord. (Photo courtesy of: Oklahoma State University, Department of Veterinary Pathobiology, Room 250 McElroy Hall, Stillwater, OK 74078 <http://www.cvhs.okstate.edu>)



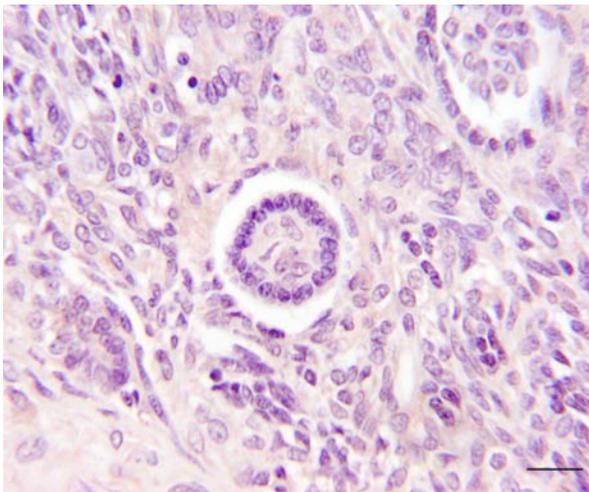
3-2. Spinal cord, dog: Cut surface of the spinal cord reveals a large, white mass with abundant surrounding hemorrhage. (Photo courtesy of: Oklahoma State University, Department of Veterinary Pathobiology, Room 250 McElroy Hall, Stillwater, OK 74078 <http://www.cvhs.okstate.edu>)



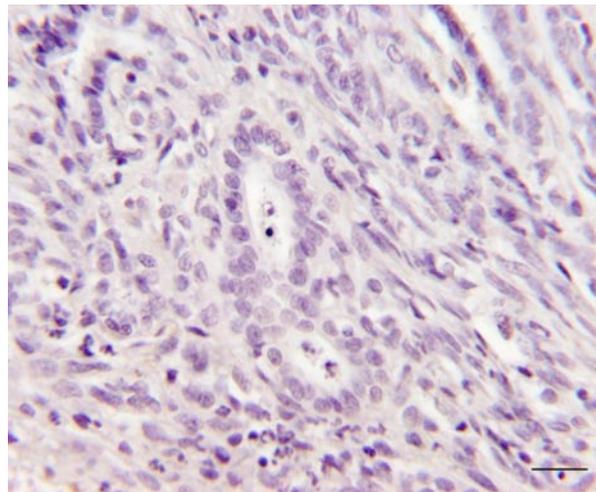
3-3. Spinal cord, dog: Section of neoplasm demonstrating the abundant hemorrhage associated with this neoplasm. (HE 0.63X)

Contributor's Comment: Spinal nephroblastomas are rare neoplasms that occur in young dogs, and German Shepherds may be over-represented.² These neoplasms typically arise at the thoracolumbar junction and are thought to arise from ectopic rests of embryonal renal tissue entrapped in the subdural space.² Metastasis is not typical⁴ though possible intraspinal metastasis has been reported.⁵ Affected animals typically present with hindlimb ataxia, paresis, and proprioceptive deficits.^{4,5}

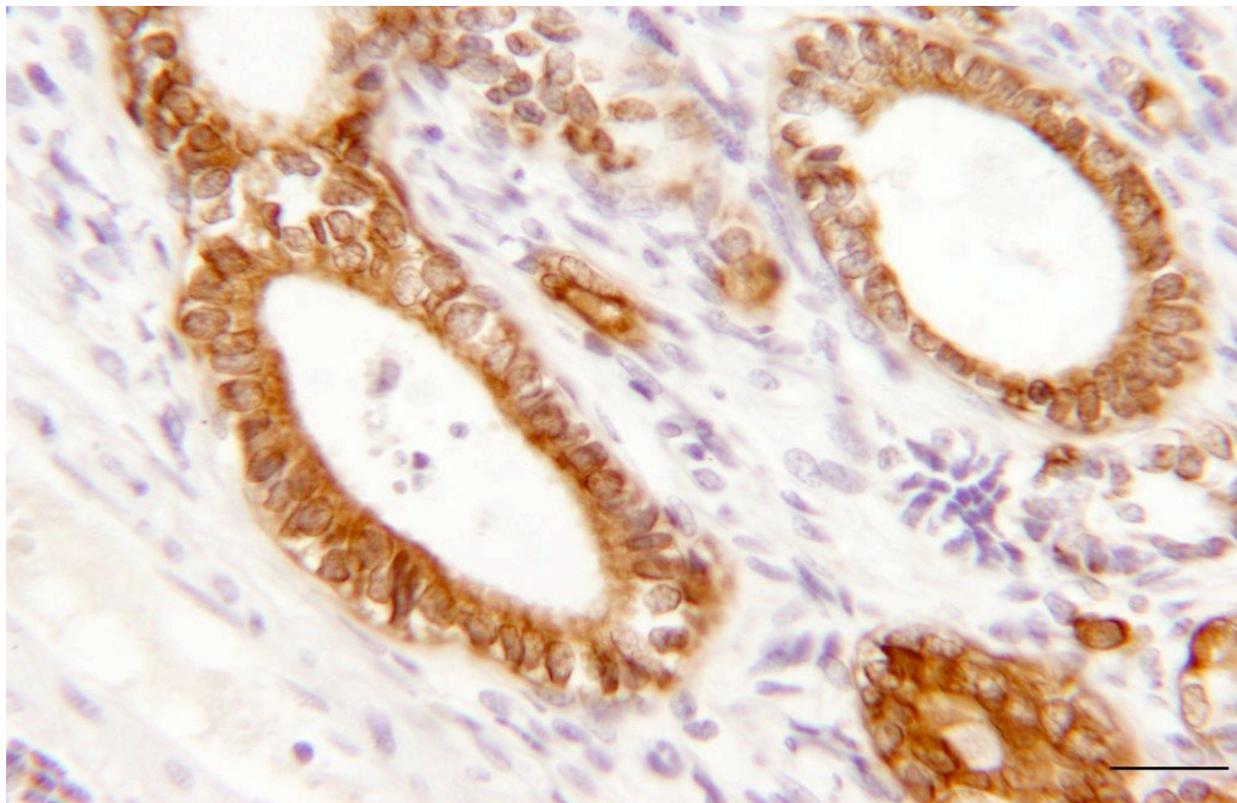
The classic histomorphology of spinal nephroblastoma is similar to that of renal nephroblastoma. Neoplastic cells form embryonic glomeruli, primitive tubules, and primitive acini, surrounded by a mesenchymal stroma.² Cytologic evaluation shows a characteristic triphasic pattern with mesenchymal cells, epithelial cells, and undifferentiated hyperchromatic cells.¹ The submitted neoplasm demonstrates characteristic primitive tubules,



3-4. Spinal cord, dog: Scattered throughout the neoplasm are structures resembling embryonic glomeruli. (Photo courtesy of: Oklahoma State University, Department of Veterinary Pathobiology, Room 250 McElroy Hall, Stillwater, OK 74078 <http://www.cvhs.okstate.edu>)



3-5. Spinal cord, dog: In other areas, neoplastic cells form primitive tubules. (Photo courtesy of: Oklahoma State University, Department of Veterinary Pathobiology, Room 250 McElroy Hall, Stillwater, OK 74078 <http://www.cvhs.okstate.edu>)



3-6. Spinal cord, dog: Neoplastic cells with an epithelial phenotype demonstrate cyokeratin immunopositivity, while surrounding blastemal cells do not. (Photo courtesy of: Oklahoma State University, Department of Veterinary Pathobiology, Room 250 McElroy Hall, Stillwater, OK 74078 <http://www.cvhs.okstate.edu>)

acini, and mesenchymal stroma, though it lacks classic embryonic glomeruloid structures.

Differential diagnoses include ependymoma, primitive neuroectodermal tumor, or poorly differentiated astrocytoma.⁵ Immunohistochemistry can aid in establishing a definitive diagnosis. The epithelial cells within spinal nephroblastomas are immunopositive for cyokeratin, and the blastemal cells and stroma are immunopositive for vimentin.^{2,5} The neoplastic cells are immunonegative for NSE, GFAP, neurofilament, or chromogranin.^{2,5} In addition, these neoplasms may be immunopositive on staining with a nephroblastoma-specific marker, Wilm's tumor gene protein product (WT1).³ Immunostaining of this neoplasm was consistent with spinal nephroblastoma; immunostaining for Wilm's tumor gene protein product was not performed.

JPC Diagnosis: Spinal cord: Nephroblastoma.

Conference Comment: Nephroblastoma, also known as Wilms' tumor, is an important human

pediatric neoplasm. The term "blastoma" defines the neoplastic population as embryonic, rather than mature terminally differentiated cells; histologically, nephroblastoma recapitulates the embryologic development of the kidney.¹ The protein product of the Wilms' tumor suppressor gene-1 (WT-1) is a DNA binding protein important in normal renal development; inactivation of this gene likely prevents differentiation of primitive metanephric cells and is documented in some pediatric nephroblastomas.³ A similar intradural extramedullary spinal cord neoplasm occurs between the tenth thoracic (T10) and second lumbar (L2) spinal cord segments in large breed dogs, typically less than three years old, and is thus referred to as thoracolumbar spinal tumor of young dogs.⁵ Although the histogenesis of this tumor has not been firmly established, it is thought to originate from ectopic metanephric blastema trapped between the dura and the developing spinal cord.⁵ The Wilms' tumor gene protein product, WT1, has been identified immunohistochemically in some of these "canine spinal cord nephroblastomas."³ As noted by the

contributor, the microscopic features (a poorly differentiated blastemal component, mesenchymal stroma, and an epithelial component forming tubules and vague glomeruloid structures) and immunohistochemical staining characteristics (cytokeratin positive epithelial cells and vimentin positive blastemal and mesenchymal cells) in this case are consistent canine spinal cord nephroblastoma (or perhaps more accurately, thoracolumbar spinal tumor of young dogs); however, there is significant slide variation and tissue identification for some conference participants was difficult, as some sections did not contain any identifiable spinal cord.

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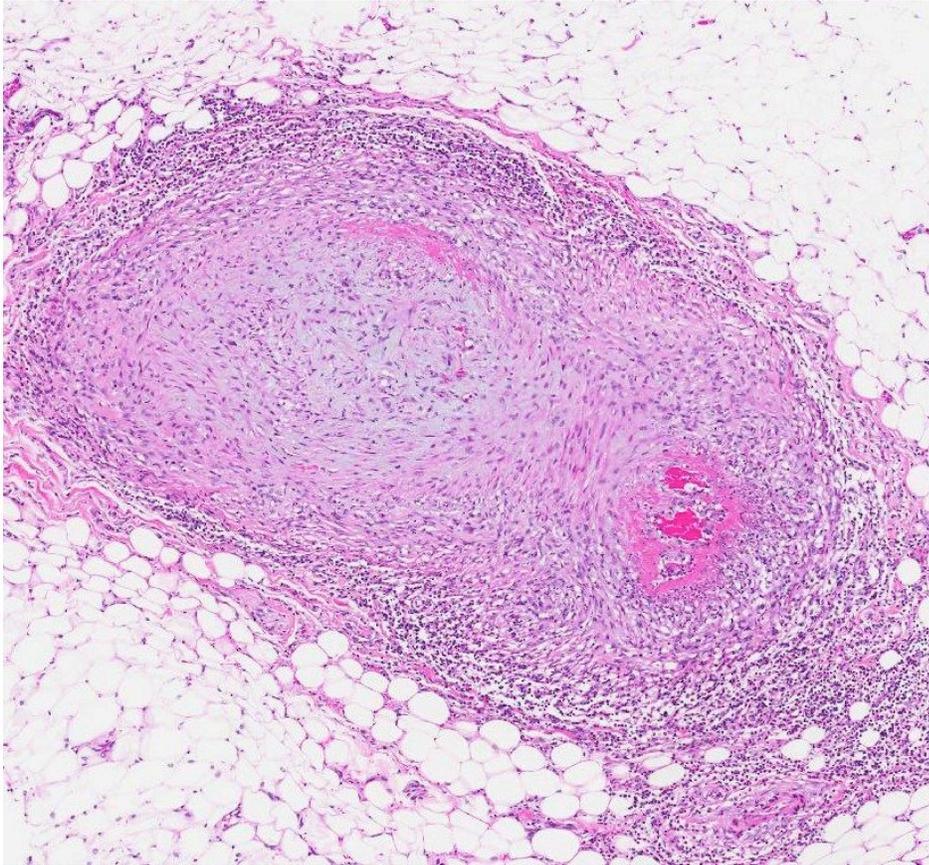
CASE IV: NC-10-667-4 (JPC 3175517).

Signalment: 12-year-old spayed female beagle dog (*Canis familiaris*).

History: This beagle presented with a 2-year history of chronic pancreatitis and a 24-hour history of icterus. She had a 3/6 heart murmur, elevated liver enzymes, and elevated BUN/creatinine. Abdominal ultrasound revealed pancreatitis, gastritis, enteritis, and lymphadenopathy. A moderate to severe, unstructured interstitial pattern was noted in the caudodorsal lungs on radiographs, especially in the hilar region, leading to a clinical differential diagnosis of pulmonary lymphoma or other hematogenous disease. An alveolar pattern was noted along the cranial margin of the right caudal lung lobe. Cytology of the liver showed few bile plugs, and was considered indicative of cholestasis. The dog was subsequently euthanized due suspected severe pancreatitis and a poor, long-term prognosis.

Gross Pathology: The body of a female beagle in good body condition (body condition score: 6/9) and in a state of mild autolysis was presented for necropsy. Icterus was evident in the sclera, mucous membranes, and shaved skin.

The ventral pylorus was adhered to the left ventral abdominal wall by bands of dense, tan fibrous tissue. The liver was firm with irregular, rounded margins and contained approximately 10-12, 0.2 cm to 3.5 cm diameter, fluid-filled cysts (suspect biliary cysts). The gall bladder was moderately enlarged and contained variably-sized clumps of dark green, inspissated bile. The pancreas was atrophied, pale, firm, and nodular. The mucosa of both the small and large intestines was moderately thickened and the jejunum was corrugated. The kidneys contained multiple cysts that were approximately 0.2 cm in diameter and contained clear fluid. These cysts were present throughout the parenchyma and along the capsular surface. Multiple pale, tan, round, 0.5 mm diameter foci were scattered regularly throughout the cortical tissue.

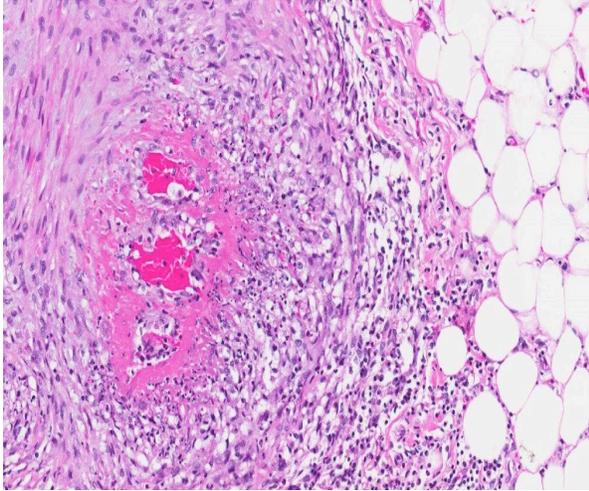


4-1. Mediastinum, dog: Arterioles are tortuous, with extrusion of bright red protein into the subintimal layers (fibrinoid necrosis). (HE 50X)

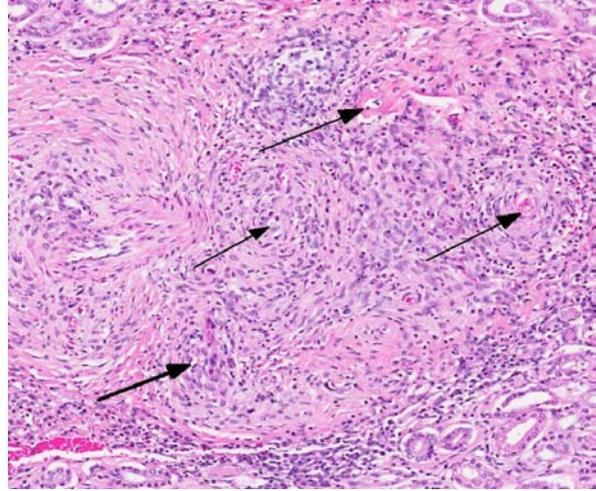
Five to ten milliliters of clear, serosanguineous fluid were in the pleural space. The lungs were markedly congested and oozed blood on cut surface. The heart was rounded and the septal leaflets of the mitral valve were moderately thickened by smooth, variably-sized nodules (nodular endocardiosis).

Laboratory Results: Anaerobic and aerobic bacterial cultures of the peritoneal fluid obtained in the clinic were negative.

Histopathologic Description: In multiple tissues, including the heart, kidney, liver, spleen,



4-2. Mediastinum, dog: Higher magnification of Figure 4.1. The arteriolar wall is infiltrated by large numbers of degenerate neutrophils and histiocytes, admixed with bright red protein and cellular debris. In addition, smooth muscle cells are variably hypertrophic and or necrotic, and admixed with numerous fibroblasts (fibrinoid necrosis). (HE 175X)



4-3. Kidney, dog: Similar proliferative lesions are present within small renal arterioles. (HE 150X)

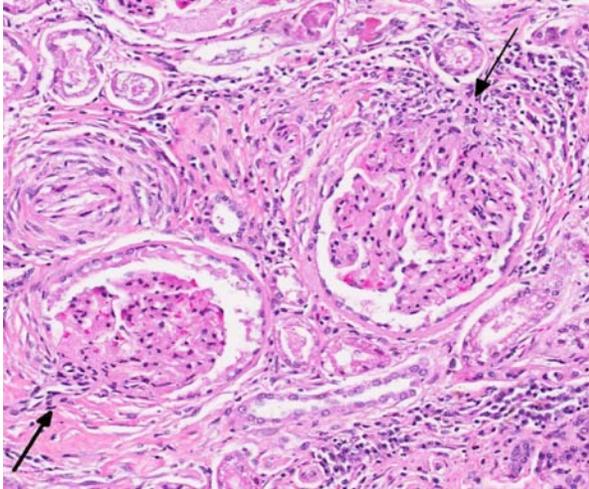
pancreas, stomach, and intestine, the tunica media of medium to small arteries was variably inflamed and necrotic. Affected vessels had multifocal regions of smooth muscle hypertrophy, fibrosis, and luminal obstruction. In most medium-sized vessels, the wall was infiltrated and moderately to markedly expanded by neutrophils, lymphocytes, plasma cells, and occasional macrophages and eosinophils. The tunica media often contained several nodules composed of hypertrophied smooth myocytes and chronic, swirling fibrosis. In other vessels, the tunica media contained regions of fibrinoid degeneration characterized by brightly eosinophilic, amorphous material with admixed pyknotic nuclear debris, faded smooth muscle cells with karyolysis, and regions of brightly eosinophilic fibrin deposition. The necrosis spanned the internal elastic lamina, which was segmentally fragmented and lost, and also involved the intima. The intima was multifocally, moderately expanded by fibrosis. In occasional vessels, a portion of the lumen contained brightly eosinophilic fibrin, with occasional reorganization and recanalization. Mild numbers of red blood cells diapedesed into the adjacent tissues. Inflammatory infiltrates extended into the perivascular connective tissues with associated vacuolated, lightly eosinophilic edema fluid.

The walls of arteries throughout the kidney and perirenal fat were markedly expanded by hypertrophied smooth myocytes, fibrosis, and

infiltrating neutrophils and lymphocytes, leading to the obstruction of the vascular lumens (as described above). Affected vessels were surrounded by moderate, streaming fibrosis. Moderate to marked interstitial lymphoplasmacytic infiltrates were scattered throughout the renal parenchyma. Bowman's capsule was moderately expanded in the majority of the glomeruli, as was the mesangium of several glomerular tufts. Glomerular tufts occasionally adhered to the capsule (synechia). Multifocally, the tubular epithelium was variably swollen, vacuolated or attenuated, and hyper eosinophilic, suggestive of early epithelial degeneration. Occasional tubules were dilated and contained glassy, amorphous, lightly eosinophilic material. A few, scattered tubules were markedly dilated by a flocculent, eosinophilic material. In both kidneys, the connective tissues around the renal pelvises were moderately to markedly infiltrated by lymphocytes and plasma cells.

Within the heart, the coronary arteries and vessels in the pericardial fat were multifocally, markedly affected by the vascular changes described above. Multifocally, the myocardium was mildly infiltrated by mature fat. In one section of myocardium, the myofibers were mildly separated by a fine fibrous connective tissue.

The lobules within the pancreas were moderately to markedly separated by dense fibrosis, which occasionally invaded into the lobules, isolating



4-4. Kidney, dog: Basement membranes are markedly expanded and there is mild to moderate hypertrophy of parietal epithelium with periglomerular fibrosis (membranous glomerulonephritis). Afferent arterioles are sclerotic and inflamed. (HE 175X)

small islands of acini. Multifocal, mild aggregates of lymphocytes were apparent within the fibrosis. Multifocal vessels in the pancreatic parenchyma and the adjacent mesentery were effaced by the previously described inflammatory process (pancreas not submitted).

Contributor's Morphologic Diagnosis: Small to medium arteries: Multifocal, moderate to marked, neutrophilic, lymphoplasmacytic, and fibrinonecrotic to fibrosing polyarteritis.

Kidney:

1. Moderate, global, diffuse membranoproliferative glomerulopathy
2. Multifocal, moderate lymphoplasmacytic interstitial nephritis
3. Acute tubular degeneration and multifocal tubular proteinosis

Heart:

1. Mild, multifocal fatty infiltration
2. Focal, mild myocardial fibrosis

Pancreas (not submitted): Moderate, chronic-active, fibrosing pancreatitis

Contributor's Comment: This dog was diagnosed with a necrotizing polyarteritis that involved multiple organs, including the heart, kidney, spleen, stomach, intestine, liver, lung, lymph node, and pancreas. Interestingly, this animal showed no clinical signs that were directly related to vasculitis and the evenly-spaced, raised,

pinpoint foci in the kidneys, the irregular margins of the liver, the chronic peritonitis, and the thickened intestines were the only apparent gross lesions that were interpreted to be associated with this disease process.

Vasculitis is defined as the invasion of vessel walls by inflammatory cells with associated vascular damage, which can include fibrin deposition, collagen degeneration, and necrosis.^{5,6} In animals and humans, vasculitis can be categorized as immune-mediated, infectious, toxic, hemodynamic-mediated, or idiopathic.^{1,4,5} Infectious causes of vasculitis in dogs include canine distemper virus, bacterial septicemia and endotoxemia, rickettsial organisms, mycotic infections, protozoal organisms, and rarely helminths.⁵ In this patient, infectious causes were considered unlikely based on the lack of an organism seen histologically, the negative peritoneal culture, and the lack of any other histologic or gross features associated with an infectious organism.

Immune-mediated vasculitis is a differential diagnosis for the vascular changes in this dog, though such immune-mediated reactions are less common in dogs than in humans.^{1,5} The main pathologic processes that can lead to immune-mediated vasculitis include antibody/antigen complex deposition secondary to an infection or a hypersensitivity response, anti-neutrophil cytoplasmic antibodies, or anti-endothelial cell antibodies.⁴ One type of vasculitis that is thought to be immune-mediated is polyarteritis nodosa. Polyarteritis nodosa is rarely described in dogs and is considered to be similar to idiopathic juvenile polyarteritis (discussed below). This condition is characterized by segmental, necrotizing vasculitis of small to medium sized arteries. Arterioles, capillaries, and venules are typically not involved, and glomerulonephritis is not present.⁵ Type IV hypersensitivity-associated vasculitis is also an immune-mediated vasculitis that has also been described as affecting small vessels (though sparing muscular arteries) and is characterized by a non-necrotizing, mononuclear vasculitis.¹ Hypersensitivity vasculitides commonly occur in the skin, and have been associated with systemic lupus erythematosus in dogs.^{3,5} Drug reactions occasionally cause type III hypersensitivities, which result from the deposition of antibody/antigen complexes within small vessels, leading to a necrotizing vasculitis.⁵

The skin was not examined histologically in this dog.

Toxic damage to the endothelium or to the vascular smooth muscle cells caused by medications has been reported to lead to a necrotizing vasculitis. This form of vasculitis affects small to medium arteries in multiple organs, and is characterized by transmural segmental fibrinoid necrosis and neutrophilic inflammation, which also affects surrounding tissues. Focal medial scarring and adventitial fibrosis has also been described.¹ Toxic vasculitis is difficult to differentiate from polyarteritis nodosa. Medications can also lead to vascular damage caused by excessive hemodynamic activity. For example, dogs have been reported to be sensitive to vasodilators and positive inotropes, and develop vascular lesions associated with their use. The acute histologic features of this lesion include segmental medial necrosis and hemorrhage of the coronary arteries. Chronic changes include smooth muscle hyperplasia of the intima and adventitial fibroplasia, and medial degeneration, necrosis, and variable inflammation.¹ There was no history of vasodilator or positive inotrope use in this dog.

In most cases of vasculitis in dogs, the cause is unknown. Some idiopathic vasculitides appear to occur more commonly in certain breeds. For example, several authors have described a juvenile polyarteritis in beagle dogs.^{1,2,5,8,9} This syndrome occurred primarily in young beagle dogs (<40 months of age). These dogs developed sudden-onset fever, anorexia, and a hunched stance that waxed and waned. However, in one study, affected beagles did not show any clinical signs.⁹ Histologically, acutely affected small to medium-sized muscular arteries were characterized by necrotizing vasculitis with occasional fibrinoid change and perivascular nodules predominately composed of neutrophils with multifocal accumulations of macrophages, lymphocytes and plasma cells. Affected organs included the extramural coronary arteries, cervical spinal cord, and the cranial mediastinum. Less commonly affected organs included thyroid glands, thymus, lymph nodes, stomach, small intestine, esophagus, urinary bladder, epididymis, gall bladder, lung, and diaphragm. Few dogs exhibit severe, diffuse, membranoproliferative glomerulonephritis.^{8,9} Hemorrhage and necrosis

were not associated with the vascular lesions in these studies.¹

In this case of necrotizing polyarteritis, beagle pain syndrome was considered unlikely due to the age of the patient. Additionally, based on the histologic features described above, including the presence of necrotizing vasculitis in multiple organs, the minimal associated necrosis and hemorrhage, and the restriction of the lesions to the small and medium muscular arteries, type IV hypersensitivity reactions were considered less likely. These lesions typically spare muscular arteries, typically occur in the skin, and generally do not have associated fibrinoid necrosis. Vasculitis secondary to excessive hemodynamic activity was also unlikely, because these lesions are often restricted to coronary arteries, and are less likely to have associated inflammation. Interestingly, this dog had a history of chronic pancreatitis, which may have caused or at least contributed to the vasculitis and the glomerulopathy through the production of circulating antigen/ antibody complexes. As a result, a toxic vasculitis, an immune-mediated vasculitis, or an idiopathic vasculitis remain the most likely differentials for this patient.

JPC Diagnosis: 1. Kidney, heart and adjacent vessels: Arteritis, necrotizing and proliferative, chronic, diffuse, severe with fibrinoid change.
2. Kidney: Glomerulonephritis, membranoproliferative, diffuse, moderate, with multifocal tubular necrosis and lymphoplasmacytic interstitial nephritis.

Conference Comment: Although the specific etiopathogenesis is not clear, this case provides an excellent example of canine polyarteritis combined with other renal changes. The contributor provides a thorough summary of the histological findings, differential diagnosis and proposed pathogeneses associated with vasculitis in dogs. Conference participants discussed the differential diagnosis for this case, including immune-mediated vasculitis, which led to a brief review of mechanisms of immunologically mediated hypersensitivity reactions (see table 1).

Type I, or immediate type hypersensitivity reactions involve an initial sensitization phase to an allergen or parasite, as well as an effector phase upon secondary or prolonged initial

exposure, mediated by IgE antibody cross-linking, mast cell degranulation (resulting in release of vasoactive amines and other mediators) and, in late phase reactions, recruitment of inflammatory cells, especially eosinophils. Type I hypersensitivity is associated with anaphylaxis, and is characterized by increased vascular permeability (edema) and dilation (hypotension), smooth muscle contraction (bronchospasm), mucus production and inflammation. Interestingly, the guinea pig is the species most sensitive to the development of anaphylaxis.

Type II, or cytotoxic hypersensitivity reactions occur following the development of antibodies against cell surface antigens or receptors, with subsequent phagocytosis or lysis of the target cell by activated complement or Fc receptors, as well as recruitment of leukocytes. Due to the presence of numerous blood group surface antigens and a predilection for absorbing drugs and antigens associated with infectious agents or tumors, erythrocytes are particularly prone to this type of antibody-mediated hypersensitivity reaction (e.g. autoimmune hemolytic anemia and foal neonatal isoerythrolysis). Furthermore, antibodies directed against cell surface receptors can either activate or inhibit cell function. For instance, binding of antibody to the thyroid stimulating hormone (TSH) receptor activates thyroid follicular epithelial cells, resulting in hyperthyroidism, while antibody binding the acetylcholine neurotransmitter receptor at the neuromuscular junction inhibits cell function, resulting in myasthenia gravis.⁷

Type III hypersensitivity reactions, as noted by the contributor, can incite necrotizing vasculitis via formation and deposition of antigen-antibody complexes which lead to complement activation, recruitment of leukocytes, release of free radicals, proteolytic enzymes and other toxic molecules. In order for deposition of antigen-antibody complexes to occur, there must be a slight antigen excess with the formation of intermediate sized complexes; deposition tends to occur at sites where blood is filtered at high pressure, such as glomeruli, joints, small vessels, the heart, the skin, or the serosa. Examples include systemic lupus erythematosus, equine infectious anemia and acute glomerulonephritis.⁹

Type IV hypersensitivity reactions, also known as cell mediated or delayed-type, are mediated by

Table 1. Mechanisms of Immunologically Mediated Hypersensitivity Reactions.⁷

Type	Prototype Disorder	Immune Mechanisms	Pathologic Lesions
Type I (immediate) hypersensitivity	Anaphylaxis; allergies; bronchial asthma	Cross linking of IgE antibody, mast cell degranulation → release of vasoactive amines and other mediators; recruitment of inflammatory cells (late-phase reaction)	Vascular dilation, edema, smooth muscle contraction, mucus production, inflammation
Type II (antibody-mediated/cytotoxic) hypersensitivity	Autoimmune hemolytic anemia; neonatal isoerythrolysis	Production of IgG, IgM → binds to antigen on target cell or tissue → phagocytosis or lysis of target cell by activated complement or Fc receptors; recruitment of leukocytes	Cell lysis; inflammation
Type III (immune complex-mediated) hypersensitivity	Systemic lupus erythematosus; glomerulonephritis; serum sickness; Arthus reaction	Deposition of antigen-antibody complexes → complement activation → recruitment of leukocytes → release of enzymes and other toxic molecules	Necrotizing vasculitis (fibrinoid necrosis); inflammation
Type IV (cell-mediated/delayed-type) hypersensitivity	Contact dermatitis; transplant rejection; tuberculosis; Johne's disease	Activated T lymphocytes: 1. Release of cytokines and macrophage activation 2. T cell-mediated cytotoxicity	Perivascular cellular infiltrates; edema; cell destruction; granuloma formation

CD4⁺ or CD8⁺ T-lymphocytes (see WSC 2013-2014, conference 2, case 2 for a review of CD4⁺ T-lymphocyte mediated hypersensitivity). CD8⁺ T-lymphocytes are activated by antigen expressed in the context of MHC I and are directly cytotoxic to target cells via granzyme A/perforin (which leads to caspase-independent apoptosis), granzyme B (leading to caspase-dependent apoptosis) or Fas:Fas ligand interactions (which induces extrinsic apoptosis). Tuberculosis, Johne's disease, allograft rejection and allergic contact dermatitis are all diseases associated with primary type IV hypersensitivity reactions.⁷

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