



WEDNESDAY SLIDE CONFERENCE 2015-2016

C o n f e r e n c e 10

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Mark Butt, DVM, , DACVP

Tox Path Specialists, LLC
Frederick, MD

CASE I: S 696/14 (JPC 4067275).

Signalment: Canine, Staffordshire terrier, 3.5 years (*Canis lupus familiaris*)

History: The dog had developed progressive neurological and behavioral dysfunction for the last six months. The dog was finally euthanized with severe ataxia.

Gross Pathology: Necropsy revealed no relevant lesions; the central nervous system and vertebral column appeared normal.

Laboratory Results: None

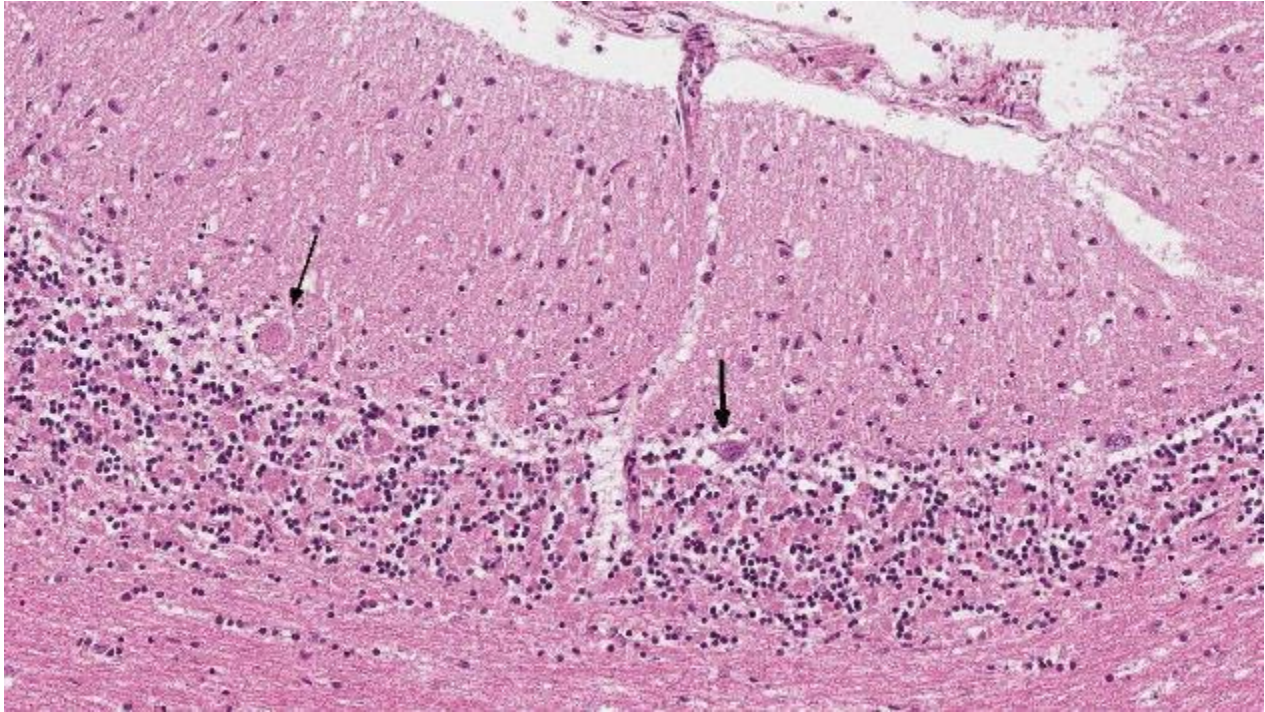
Histopathologic Description: Cerebellum: There is marked diffuse loss of Purkinje cells with remaining Purkinje cells containing abundant, lightly eosinophilic to amphophilic, granular to globular, cytoplasmic material, which often displaces the nuclei peripherally. Multifocally, Purkinje cells and neurons of the deep cerebellar nuclei are shrunken, hypereosinophilic and angular or swollen and rounded, with hyperchromatic or pyknotic nuclei (neuronal degeneration and necrosis). Rarely, large round clear spaces in the

Purkinje cell layer (empty baskets) are present. Almost diffusely, the granular cell layer is hypocellular (neuronal atrophy).

Contributor's Morphologic Diagnosis: Cerebellum: Purkinje cell degeneration, necrosis and loss, multifocal, moderate, with cerebellar atrophy and abundant neuronal intracytoplasmic granular pigment.

Contributor's Comment: The neuronal ceroid-lipofuscinoses are inherited lysosomal storage diseases also referred to as Batten's disease. In humans they represent the most common group of progressive encephalopathies in children. In addition to humans, the disease is documented in sheep,²⁹ goats,⁷ cattle,¹³ horses,³¹ mice,⁸ cats³³ and several breeds of dogs.¹⁶ Table 1 summarizes published cases.

The disease is characterized by accumulation of granules in the cytoplasm of most nerve cells and, to a lesser extent, of many other cell types. The granules are autofluorescent, periodic acid-Schiff (PAS), Luxol Fast Blue and Sudan black B positive and resistant to lipid solvents. Consequences include



Cerebellum, dog. Rare Purkinje cells remain (arrow), and the underlying granular cell layer is markedly hypocellular. (HE, 78X)

progressive selective neuronal loss with secondary astrocytic proliferation and hypertrophy as well as infiltration by macrophages.

The disease is clinically classified by age of onset into early (up to 1.5 years) and late (up to 9 years) onset forms. It is additionally categorized according to the defective genes associated with the disease (see Table 1). All forms result in progressive neurodegeneration of the central nervous system, but clinical symptoms are variable depending on breed, age and individual factors. Affected dogs change their behavior, become blind, and suffer from progressive proprioceptive and motor deficits, seizures and ataxia.

Gross lesions are often absent; especially in cases with early onset, marked cerebral atrophy may be apparent with often a brown tinge in severely affected areas.

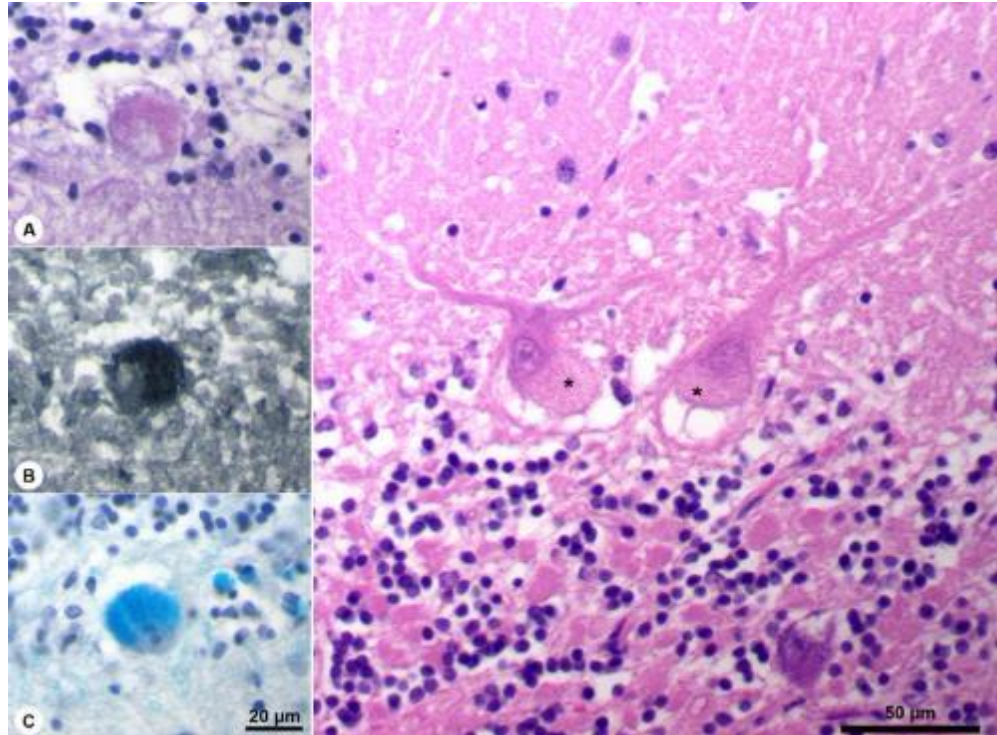
JPC Diagnosis: Cerebellum, brainstem: Purkinje cell degeneration and loss, diffuse, marked with intracellular ceroid accumulation and granular cell loss.

Conference Comment: The primary lesion in this case, as described by conference participants, is the striking (70-80%) loss of Purkinje cells, and overall the conference description was similar to the contributor's description. In addition to the change described above, hypocellularity within the granular cell layer, spongiosis within the white matter and the presence of spheroids were also described. There was discussion regarding the presence of dilated axons within the granular cell layer and whether they truly represent dilated axons or only appear dilated due to the loss of granular cells. The moderator noted the presence and function of Bergmann glial cells, proliferation of which may be seen within the granular and Purkinje cell layers in cases of Purkinje cell loss or injury; their processes

can be visualized within these areas using the glial fibrillary acidic protein (GFAP) stain.

Storage diseases comprise a heterogeneous group of conditions that result from the accumulation of material within the cell, which is unable to be metabolized or further broken down, either due to resistance to cellular processing or excessive

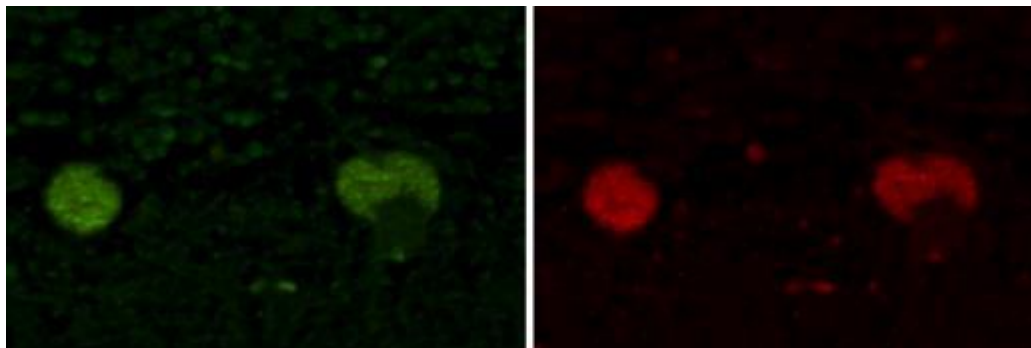
accumulation that exceed the cell's capacity to process it. Many of the storage diseases involve lysosomes, and in animals nearly all of the inherited storage diseases are lysosomal in nature. They often affect neurons due to the long-lived nature of these cells, which provides a longer period over which material can be accumulated as compared to cells with short turnover times.



Cerebellum, dog.. Intracytoplasmic granules (right) is positive on periodic acid-Schiff (A), Sudan black (B), and Luxol fast blue (C). (Image courtesy of Department of Veterinary Pathology, Freie Universität Berlin, Germany, <http://www.vetmed.fu-berlin.de/en/einrichtungen/institute/we12/index.html>)

Defects in lysosomal processing may involve defects in a specific enzyme or lysosomal hydrolase due to a genetic defect, and can include defects in post-translational processing, production, or trafficking. Non-inherited mechanisms of storage disease include ingestion of an exogenous toxin which inhibits a lysosomal enzyme, with the result being similar to those involving genetic

defects. This is the case with ingestion of “locoweed” which produces the phytotoxin swainsonine. Resistance of the accumulating material to cellular



Cerebellum, dog: Intracytoplasmic granules exhibit autofluorescence. (Image courtesy of Department of Veterinary Pathology, Freie Universität Berlin, Germany, <http://www.vetmed.fu-berlin.de/en/einrichtungen/institute/we12/index.html>)

Breed	Reference	Gene	Onset	Age
American Bulldog	4,34	CTSD	Early	1 – 3 Years
American Staffordshire Terrier	1	ARSG	Late	1.5 – 9 Years
Australian Cattle Dog	28		Early	12 Month
Australian Shepherd	17,23	CLN6	Early	18 – 21 Month
Border Collie	19	CLN5	Early	15 Month
Chihuahua	21		Early	1 – 2 Years
Chinese Crested dog	12	MFSD8	Early	19 Month
Cocker Spaniel	20		Late	1.5 – 6 Years
Dachshund	3,27	TPP1 (CLN2)	Early	6 – 12 Month
Dachshund	26	CLN1	Early	9 Month
Dachshund	32		Late	4.5 – 7 Years
Dalmatian	9,10		Early	6 – 12 Month
English Setter	18	CLN8	Early	1 – 1.5 Years
Labrador Retriever	25		Late	7 Years
Miniature Schnauzer	15,24		Late	2 – 4 Years
Mixed breed (Australian Shepherd / Blue Heeler)	11	CLN8	Early	8 Month
Polski Owczarek Nizinny (PON)	22		Early-late	0.5 – 4.5 Years
Retriever	30		Late	3 Years
Saluki	2		Early	12 Month
Tibetan Terrier	6,35	ATP13A2	Late	4 – 8 Years
Welsh Corgi	14		Late	6 – 8 Years

Table 1: Dog breeds with neuronal lipofuscinosis and, if known, the affected gene (ARSG: Arylsulfatase G, ATP13A2: ATPase type 13A2, CTSD: Cathepsin D, CLN: Ceroid-lipofuscinosis neuronal, MFSD8: Major facilitator superfamily domain containing 8, TPPI: tripeptidyl peptidase 1)

processing may also be due to specific alterations in the substrate, either exogenous or endogenous, and not due to a processing enzyme defect per se. The detailed mechanisms involved in cellular dysfunction and death, secondary to the accumulation of undigested material, in most cases are unclear.⁵

In the veterinary literature neuronal ceroid-lipofuscinoses (NCL) is best characterized in sheep and dogs, and as described in the above chart, the condition in dogs is generally classified by age of onset and course of disease.²¹ The actual defect resulting in abnormal accumulations may not only involve lysosomal enzymes, but also

mitochondrial defects or other defects in protein processing involving the endoplasmic reticulum. The variation in gene mutations and resulting defects likely play a role in the variation in clinical presentations and histologic findings. The storage material seen within the Purkinje cell cytoplasm can be present in multiple organs, but is particularly damaging in neurons, and may be seen in the cerebral cortical and retinal neurons in addition to Purkinje cells. Severe blindness may be the primary clinical presentation in which case retinal atrophy would likely be the primary lesion, whereas other animals will present with gait abnormalities, aggression, seizures or dementia with loss of Purkinje cells and/or

neurons within other regions of the brain (hippocampus, cerebrum, brainstem).⁵ Lipofuscin accumulates in many cells throughout the body as part of the normal aging process, and in the retina is normally only seen in the retina pigment epithelium. Autofluorescent material within other retinal cells, including ganglion and Mueller cells, is diagnostic for neuronal ceroid lipofuscinosis.¹¹

Contributing Institution:

Department of Veterinary Pathology, Freie Universität Berlin, Germany,
<http://www.vetmed.fu-berlin.de/en/einrichtungen/institute/we12/index.html>

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CASE II: 49052 (JPC 4048842).

Signalment: 5-year-old, 9.3 kg, tricolor, female, intact Beagle mix (*Canis familiaris*)

History: The patient presented to the Neurology Service with a 3-week history of peracute onset paraplegia. There was no known trauma and no therapy was undertaken. At the time of presentation, the dog was paraplegic with pain sensation and severe extensor rigidity of the hind limbs. She had an MRI performed which showed a locally extensive intramedullary myelopathy from the level of L2 extending caudally. There was minimal to no contrast enhancement with T2 hyperintensity of the gray matter (irregularly shaped and undulating) from L2 to the conus medullaris. Due to poor prognosis for return to function, the owner elected euthanasia.

Gross Pathology: Nervous: The brain and spinal cord are removed and fixed whole in formalin. The brain is externally grossly normal. The lumbar spinal cord exhibits moderate, locally extensive swelling, such that the diameter of the majority of the segment approaches that of the intumescence. The fixed spinal cord is dissected. A locally extensive segment of the lumbar spinal cord from L2 to L7 exhibits severe cavitation of the grey matter and diffuse swelling (myelomalacia and edema). Extensive grey matter cavitation is also noted on longitudinal sections.



MRI Longitudinal section of the spinal cord, T2W image. A well-margined, irregular, undulating T2 hyperintensity is present from L2-3 to the conus medullaris. (Photo courtesy of: Animal Medical Center, 510 East 62nd St. New York, NY 10065 <http://www.amcnv.org/>)

MRI report: Fairly well margined, irregularly shaped and undulating T2 hyperintensity is within the spinal cord from the level of L2-3 caudally to the conus medullaris (T2W, Figure 1). This area remains heterogeneously hyperintense on flair images and is hypointense on T1 weighted images without evidence of contrast enhancement. There is no evidence of signal voids on the FFE sequences. The spinal cord is increased in diameter over this region. The disc spaces are essentially normal with only a minimal amount of narrowing to the nucleus pulposus of 4-5.

Diagnosis: Locally extensive intramedullary myelopathy, from L2 caudally.

Comments: Consideration is given to noncontrast enhancing neoplasia. Another perhaps less likely differential could include intramedullary cyst formation. The persistent hyperintensity on flair images makes a cyst alone unlikely.



Cross sections (A) and Longitudinal sections (B) of the fixed spinal cord, showing severe grey matter cavitation and overall edema. (Photo courtesy of: Animal Medical Center, 510 East 62nd St. New York, NY 10065 <http://www.amcnv.org/>)

Histopathologic Description: Three cross sections and two longitudinal sections of lumbar spinal cord are examined. In all sections, multifocal to coalescing, asymmetric and symmetric regions of predominantly grey matter undergo necrosis, characterized by sharply defined parenchymal loss and replacement by myriad Gitter cells with formation of cavitated, cystic spaces (infarction). Infarcted regions measure up to 5 x 6 mm and comprise approximately 50 – 75% of the spinal cord parenchyma. Within and at the periphery of these regions of necrosis, within the regional grey and white matter and less frequently the leptomeninges, multiple arterioles contain amorphous amphophilic hyaline material which partially or fully occludes the lumen

(fibrocartilaginous emboli). Multifocally, emboli are covered by endothelial cells (organization). Few neurons in the surrounding grey matter exhibit cell swelling with cytoplasmic pallor, dispersed or absent Nissl substance and nuclear fading (chromatolysis). Predominantly ventral, but also lateral and dorsal funiculi contain multifocal dilated myelin sheaths with digestion chamber formation and Gitter cell infiltration. Axons are multifocally enlarged (swollen) and eosinophilic (spheroids), (Wallerian degeneration). In the regional parenchyma, increased populations of glial cells are also present, including microglia, which exhibit rod morphology, and astroglia with gemistocytic astrocytosis. Ventral spinal nerves are hypercellular with myelin sheath dilation, myelin loss, macrophage infiltration and Schwann cell proliferation (Büngner's bands). Spinal nerves also contain scattered inflammatory populations including lymphocytes and plasma cells. Emboli stain magenta with PAS and blue with Alcian blue.

Contributor's Morphologic Diagnosis:

Lumbar spinal cord (L2-L7): Poliomyelomalacia, severe, locally extensive with intralesional fibrocartilaginous emboli, Gitter cell infiltration and cavitation (infarction), consistent with fibrocartilaginous embolic myelopathy (FCEM)

Lumbar spinal cord (L2-L7): Myelin vacuolation, ventral, lateral and dorsal funiculi myelin vacuolation with Gitter cell infiltration, axonal spheroid formation, (Wallerian degeneration) and gliosis with gemistocytic astrocytosis

Lumbar spinal cord (L2-L7): Myelin vacuolation and loss, spinal nerves with Schwann cell proliferation (Büngner's bands,

Wallerian degeneration) and neuritis, multifocal lymphoplasmacytic, mild

Contributor's Comment: Fibrocartilagenous embolic myelopathy (FCEM) is defined by the presence of occlusive, intravascular material histologically and histochemically similar to the nucleus pulposus of the intervertebral disc resulting in ischemic necrosis of the spinal cord.^{2,3} FCEM is most commonly reported in large and giant breed dogs, however, small breed dogs can also be affected.²⁻⁶ Some studies have found that approximately 80% of dogs with FCEM had a body weight greater than 20 kg.⁴ Male predominance has been found in some studies, whereas others find no sexual predilection. Ages can range from 2 months to 11 years, with a median of 5-6 years in the majority of studies.³ In many cases, clinical signs are associated with exercise or trauma.^{2,3} Neurologic signs are typically peracute in onset (less than 6 hours), as in this case, and are often asymmetric, nonprogressive and nonpainful after the first 24 hours.^{3,5} Maximal neurologic deterioration occurs within the first 6 to 24 hours and is followed by gradual improvement or stabilization of signs.³ Progression beyond 24 hours may be secondary to additional embolizations or secondary spinal cord injury. The distribution of lesions is in the location of the infarction. The most commonly affected spinal cord segments have been reported to occur in the regions of L4-S3 and C6-T2 in dogs with a histologic diagnosis of FCEM and L4-S3 and T3-L3 in dogs with an antemortem diagnosis.^{2,3} Relative sparing of the thoracic spinal cord may be due to protective effects of the intercapital ligament overlying the intervertebral discs or the fewer and smaller radicular arteries and anastomotic surface vessels.²

The embolizing material has been identified as fibrocartilage histologically and is histochemically identical to the nucleus pulposus of the intervertebral disc. There are multiple hypotheses to explain how the fibrocartilagenous material enters the spinal vessels.³ The pathophysiology of this process is controversial and the exact mechanism is poorly understood.⁴

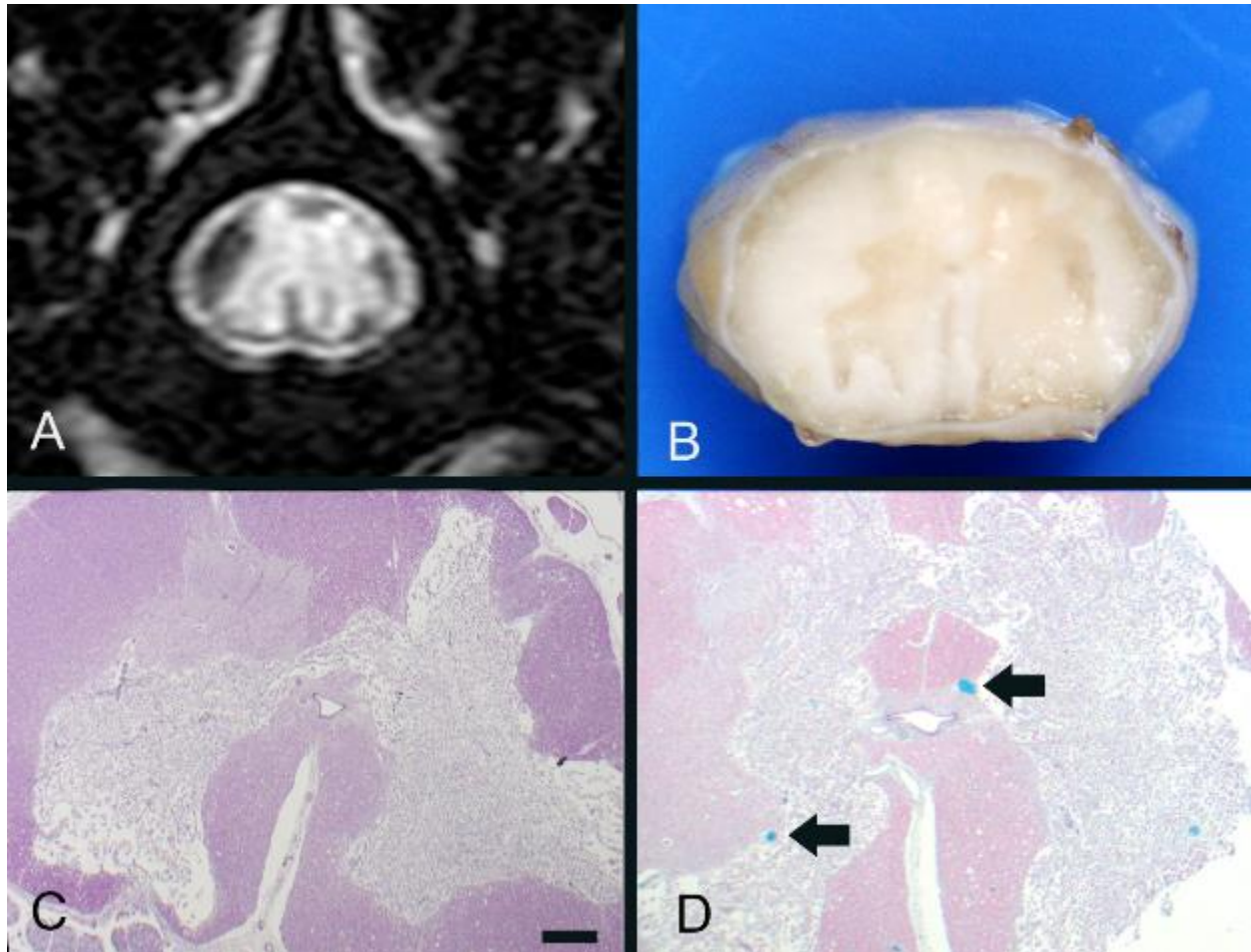
- 1) Direct penetration of nucleus pulposus fragments into spinal cord or vertebral vessels. Penetration into thin walled veins is considered more likely, however, injection entrance or arteriovenous anastomoses could explain the presence of emboli in arteries. In large breed and non-chondrodystrophoid dogs, the nucleus pulposus remains soft for a longer period of time, which may predispose to mechanical vascular injection with type II disc disease.^{2,4,6}
- 2) Chronic inflammatory neovascularization of the degenerated intervertebral disc, with penetration of nucleus pulposus fibrocartilage into the newly formed vessels after a sudden rise of intervertebral disc pressure.³
- 3) Remnant embryonic vessels within the nucleus pulposus, which is normally avascular in adults.³
- 4) Mechanical herniation into the vertebral bone marrow sinusoidal venous channels with retrograde entrance into the basivertebral vein and internal vertebral venous plexus. In humans, this hypothesis is supported by the presence of Schmorl's nodules (masses of fibrocartilage within the vertebral body cancellous bone), however, these are extremely rare in dogs.³

- 5) Fibrocartilage may arise from vertebral growth-plate cartilage in immature dogs or metaplasia of the vascular endothelium, which ruptures into the lumen and embolizes within the spinal cord intrinsic vasculature.³

Other types of material which can occlude vessels include thrombi, bacterial, parasitic, neoplastic or fat emboli. FCEM should be differentiated from noncompressive nucleus pulposus extrusion, in which nondegenerated nucleus pulposus extrudes during strenuous exercise or trauma, causes a spinal cord contusion and dissipates within the epidural

space. Other differential diagnoses are compressive intervertebral disc extrusion, infectious and immune mediated myelitis, neoplasia and intra- and extramedullary hemorrhages.³

Definitive diagnosis of FCEM can only be obtained with histologic examination of the affected spinal cord segments, which demonstrates fibrocartilaginous material in spinal vessels within or near an area of focal myelomalacia.³⁻⁵ The infarcted region is most severe at the center of the lesion and tends to taper off in adjacent cranial and caudal segments.⁵ The distribution reflects the supply of the occluded vessels, and is



Cross section of lumbar spinal cord. MRI image (A), fixed spinal cord, L4 (B), H&E low magnification view of L4, 20x, bar is 500 μ m (C), and Alcian Blue (D). Well delineated grey matter necrosis with replacement by Gitter cells (infarction) is observed. (Photo courtesy of: Animal Medical Center, 510 East 62nd St. New York, NY 10065 <http://www.amcn.org/>)

typically asymmetric. As in this case, grey matter is generally more severely affected than white matter, and lesion margins are typically well delineated.^{3,4} At gross examination, the spinal cord is commonly swollen and may appear grey or hemorrhagic.⁵ Severely malacic regions can be replaced by large sheets of macrophages embedded within a vascular network,⁴ or with cavitation. Infarction within a spinal funiculus will result in focal axonal swelling and spongy ballooning of myelin at its margins. If the ventral horn grey matter is infarcted, Wallerian degeneration develops in its neuronal projections in the ventral funiculus and in the ventral spinal roots.^{4,5}

Fibrocartilagenous material can be observed in both arteries and veins. In some cases, it can be difficult to identify the type of vessel occluded due to attenuation of the wall by the embolism. Emboli are amphophilic in H&E sections, magenta with PAS (Figure 4C) and blue with Alcian blue stains (Figures 3D, 4D). Attempts at organization are manifest as endothelial coverage, also observed in these sections.⁵

In order to produce infarction of the spinal cord parenchyma, multiple intramedullary tributaries must be occluded.⁵ The ventral spinal artery (VSA) extends along the ventral median fissure for the entire length of the

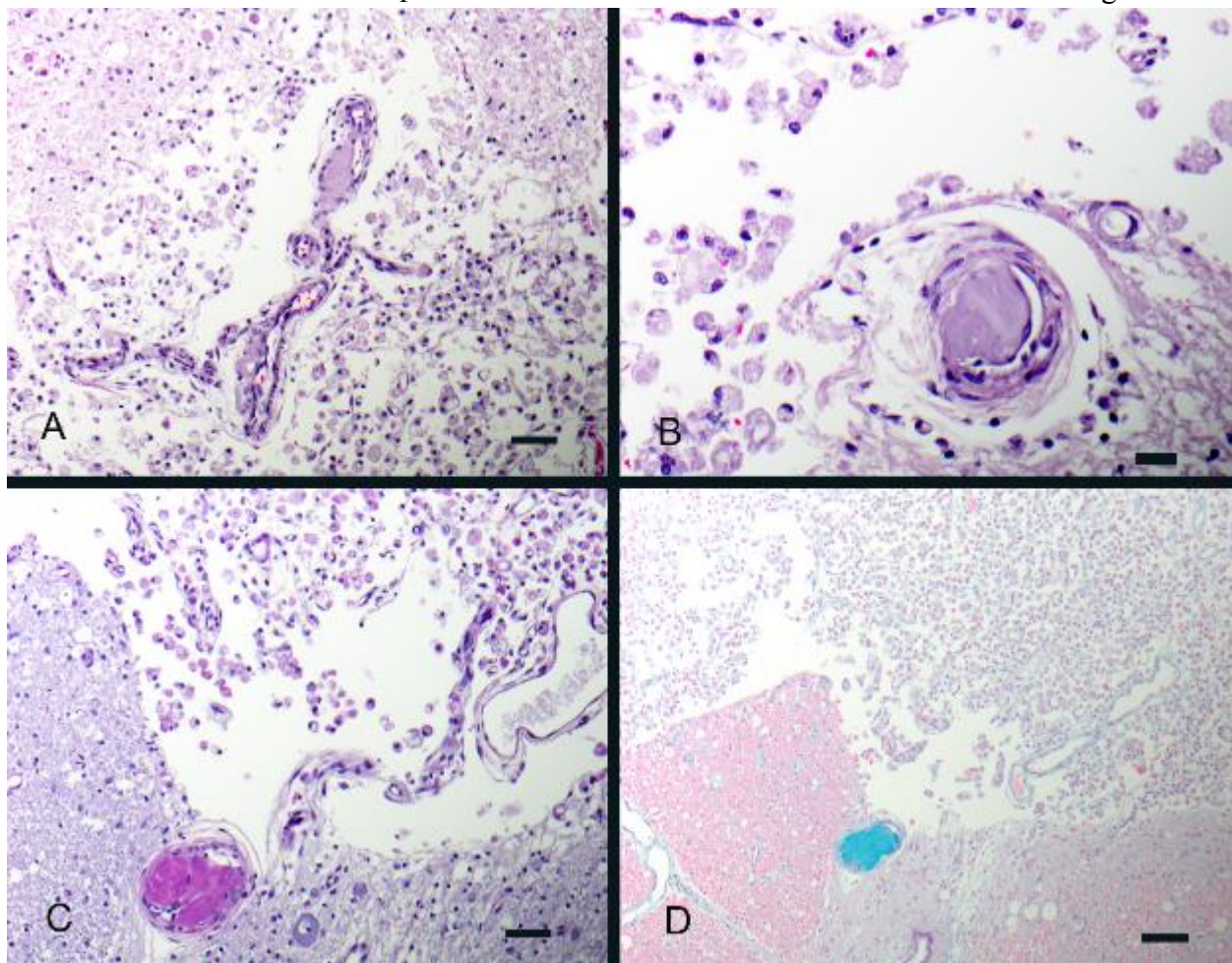
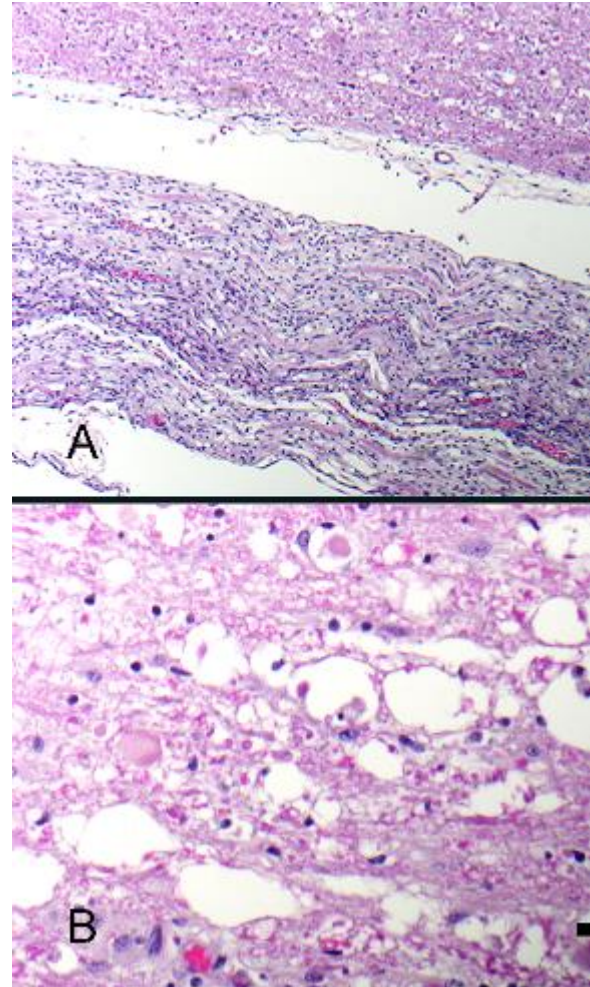


Figure 4. Cross section of lumbar spinal cord. MRI image (A), fixed spinal cord, L4 (B), H&E low magnification view of L4, 20x, bar is 500 μ m (C), and Alcian Blue (D). Well delineated grey matter necrosis with replacement by Gitter cells (infarction) is observed. (Photo courtesy of: Animal Medical Center, 510 East 62nd St. New York, NY 10065 <http://www.amcnv.org/>)

spinal cord, and is the largest in diameter in the cervical and lumbar regions.³ The VSA gives rise to the central arteries, which supply most of the grey matter and part of the lateral and ventral white matter of the spinal cord, with asymmetric distribution at several spinal cord segments.³ The dorsal spinal arteries are also continuous throughout the spinal cord, have the largest diameter in the cervical and lumbar regions and supply the dorsal white and grey matter. The anastomotic plexus on the surface of the spinal cord gives rise to radial arteries that enter the spinal cord and supply the lateral and ventral white matter.³ In our case, the central arteries were most frequently occluded vessels, resulting in severe ischemic necrosis of predominantly the grey matter.

Prognosis is dependent upon severity and extent of the ischemic injury. One study found that 84% of dogs had either complete clinical recovery or partial recovery with return to normal function as a pet. The lesion length-vertebral length ratio has been associated with outcome. This is the ratio between the length of the intramedullary hyperintensity on mid-sagittal T2 weighed images and the length of the vertebral body (C6 in dogs with cervical lesions or L2 in dogs with thoracolumbar lesions). Dogs with a lesion-length vertebral length ratio (LL:VL) greater than 2.0 or a percent cross sectional area of the lesion of 67% or greater were significantly more likely to have an unsuccessful outcome than those with lower values.³ In this case, the LL:VL was 7 (11.12/1.6) and the percent cross sectional area of the lesion was 75%. Lower motor neuron signs have been correlated with a poor prognosis, but distinction between upper and lower motor neuron signs was not found to be statistically significant in one case series, in which extension of the lesion appeared to be a more important prognostic factor than localization.⁴ Absence of deep pain

perception was significantly associated with dogs that were later euthanized, and was determined by some authors to be the most important negative prognostic factor observed.⁴ This change is likely associated with severe, bilateral grey and white matter damage. Additional negative prognostic factors were involvement of intumescences and symmetrical clinical signs. Immediate



Spinal nerves are hypercellular with myelin loss and Schwann cell proliferation (Büngner's bands), (100x, bar is 100um, A). The spinal cord surrounding the infarcted regions undergoes myelin vacuolation with digestion chamber formation, Gitter cell infiltration, gliosis and axonal swelling (spheroids, Wallerian degeneration), (400x, bar is 500um, B). (Photo courtesy of: Animal Medical Center, 510 East 62nd St. New York, NY 10065 <http://www.amcnv.org/>)

physiotherapy and hydrotherapy had a major positive influence on the recovery rate.⁴

Figure 5: Spinal nerves are hypercellular with myelin loss and Schwann cell proliferation (Büngner's bands), (100x, bar is 100um, A). The spinal cord surrounding the infarcted regions undergoes myelin vacuolation with digestion chamber formation, Gitter cell infiltration, gliosis and axonal swelling (spheroids, Wallerian degeneration), (400x, bar is 500um, B).

JPC Diagnosis: Spinal cord: Poliomyelomalacia, extensive, multifocal, marked with cavitation, spinal nerve demyelination and intravascular fibrocartilagenous emboli.

Conference Comment: The conference histologic description was similar to the contributor's very thorough description. For complete histologic examination of the spinal cord, the moderator discussed the benefits of examining both transverse and longitudinal sections. Ascending and descending tracts are readily visualized with transverse sections but axonal changes are difficult to evaluate. In contrast, axonal changes are much easier to appreciate with longitudinal sections, but invariably not all tracts will be seen. Therefore, the conference moderator highly recommended that conference participants evaluate an oblique and a transverse section and considered such evaluation as the optimal method to evaluate spinal cord segments. In addition to the aforementioned thorough histologic description, histologic evidence of chronicity in this case was discussed including the degree of cavitation and re-endothelialization around emboli.

The contributor provides an excellent review of FCEM in dogs. In addition to being reported in dogs, FCEM (though much less

common) has also been reported in other species including horses, pigs, turkeys and cats. Of note, FCEM usually occurs in middle aged to older cats, with equal representation between males and females, and most commonly occurring at the C6-T2 spinal cord segments.² Interestingly, Horner's syndrome has also been associated with FCEM in cats when the lesion is localized to the T1-T3 spinal cord segments.¹

Contributing Institution:

Animal Medical Center
<http://www.amcny.org/>

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CASE III: 13-526 (JPC 4048788).

Signalment: Adult, 8-year-old, female spayed, DLH cat (*Felis catus*)

History: Presented to an emergency clinic with acute onset of blindness and inappetence. Owner had noted subtle change in behavior the previous day and believed the cat had been drinking and urinating more in the past 2 weeks. Physical examination: mentally dull and anxious, severely hypertensive (230 mmHg systolic on Doppler). Ophthalmic examination: no menace response, palpebral reflex present, sluggish bilateral pupillary light reflex, equivocal dazzle reflex. Hospitalized to treat (amlodipine besylate) and monitor hypertension. Tonic-clonic seizure developed 4 hours later, resolved with diazepam, but the cat remained stuporous and showed anisocoria. Euthanasia was elected.

Gross Pathology: Gross findings were very nonspecific. Tissues throughout the body were hyperemic with marked congestion seen in large abdominal veins (caudal vena cava, renal veins). Renal capsular surfaces were irregularly depressed overlying wedge-shaped pale areas extending to the corticomedullary junction (chronic infarcts).

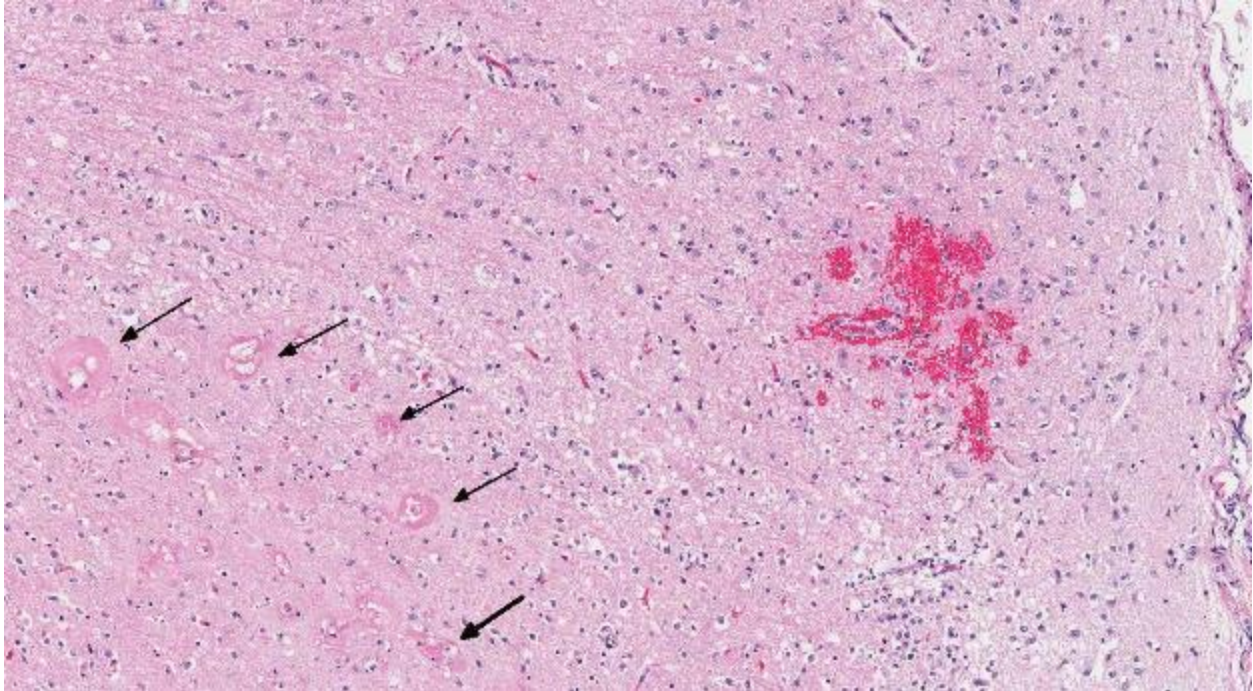
Laboratory Results:

Clinical pathology: Hematology: low platelets with clumping observed; Serum biochemistry: mild hyperglycemia (stress), mild hyponatremia (pressure naturiesis); Urinalysis: glucosuria, negative for protein, USG 1.010 (isosthenuria consistent with pressure diuresis).



Cerebrum, cat. There is mild pallor in the parietal lobe (lower right), barely visible on low magnification. (HE, 5X)

Histopathologic Description: Brain: There is a large poorly demarcated wide area of pallor within each dorsal parietal lobe extending from deep white matter and encompassing full thickness of the associated overlying grey matter. Pallor is caused by marked separation and accentuation of the linear myelin sheaths in white matter and marked vacuolation (spongiform change) in the overlying grey matter. Severe neuronal degeneration, necrosis and loss is seen with shrunken, eosinophilic and angular neurons, scattered nuclear debris (karyorrhexis) and heavy complement of glial cells, gitter cells and reactive astrocytes. Occasionally, glial cells replace neurons. There are a few microhemorrhages within the area of edema and necrosis in the grey matter. Vessels within the area of pallor show severe effacement of architecture by amorphous eosinophilic material and small amount of nuclear debris (fibrinoid change). These vessels are surrounded by large clear vacuoles (perivascular edema). Blood vessels with intact walls are often lined by hypertrophic (reactive) endothelial cells and surrounded by low numbers of neutrophils, macrophages, lymphocytes and plasma cells. Multifocally throughout the section, Virchow-Robin space is markedly expanded by clear space transected by fine eosinophilic strands (edema). Leptomeninges overlying the affected gyrus are mildly expanded by edema and low numbers of mixed



Cerebrum, cat. Walls of arterioles within the affected parietal lobe are necrotic, and diffusely expanded by pale by extruded protein (fibrinoid necrosis). (HE, 96X)

inflammatory cells, mostly mononuclear with occasional neutrophils. Pial arteriolar walls often contain amorphous eosinophilic droplets or circumferentially (protein leakage).

Contributor’s Morphologic Diagnosis:

Brain, cerebrum, parietal lobes, bilateral, edema with neuronal degeneration, necrosis and loss, locally extensive, acute, severe associated with arteriolar fibrinoid change, acute, severe.

Contributor’s Comment:

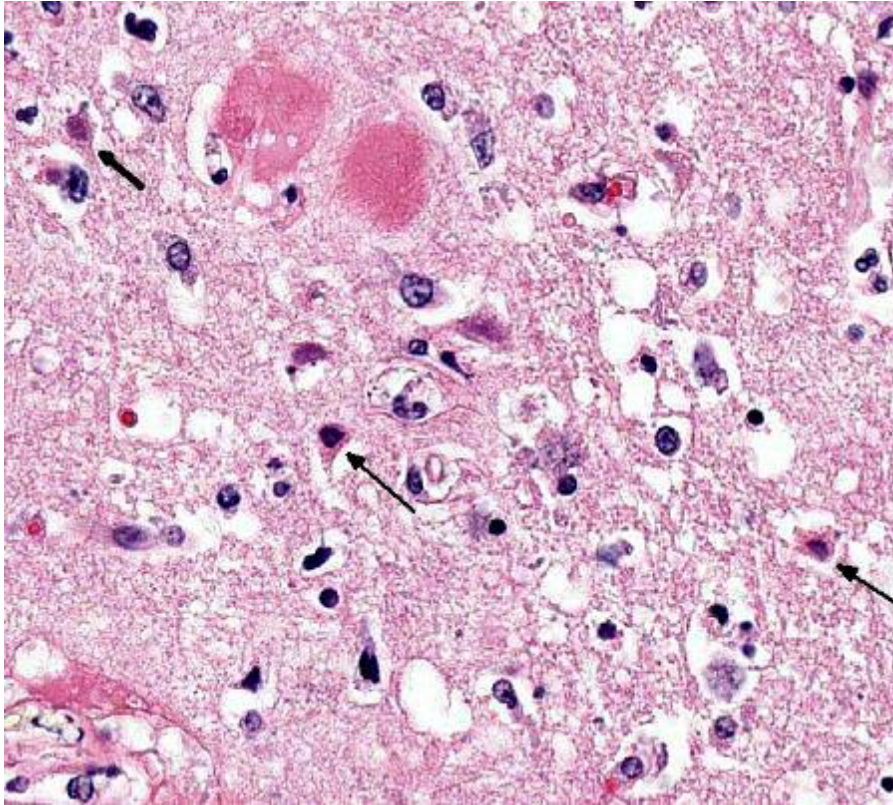
Systemic hypertension as a clinically important condition in domestic cats was initially described in 1986.⁴ It has been defined as a sustained increase in systolic blood pressure ≥ 160 -170 mmHg.² Three clinical categories are recognized and defined as:

- Stress-induced (“white coat”) hypertension: transitory artifactual increase (median rise of 17.6 ± 5.9

mmHg) secondary to activation of the sympathetic nervous system in the classical “fight or flight” response;

- Secondary hypertension: most common and associated with systemic diseases or treatments including chronic renal disease, hyperthyroidism, primary hyperaldosteronism, pheochromocytoma, diabetes mellitus and erythropoietin treatment; and
- Idiopathic (primary or essential) hypertension: about 20% of hypertension in cats occurs in the absence of other demonstrable disease conditions.

Target organ damage (TOD) is a risk in the face of uncontrolled hypertension with the heart, brain, eyes and kidneys being at greatest risk. The cat of this report showed



Cerebrum, cat. In the affected area, neurons are necrotic as a result of ischemia (arrows). (HE, 284X)

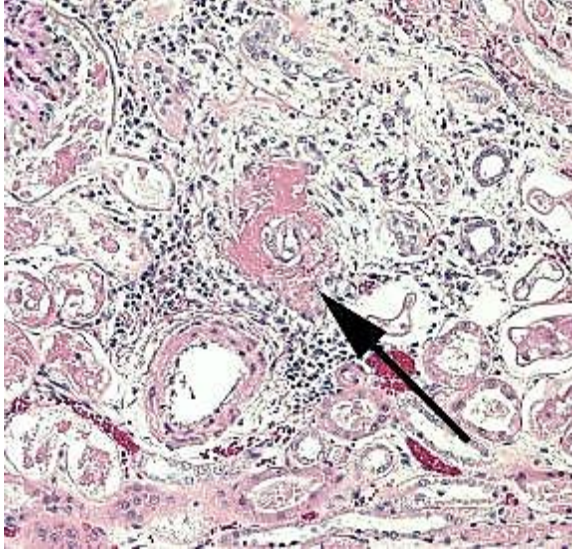
TOD in the brain as described above. Changes in the eyes and kidneys were also focused largely on vascular structures, specifically arterioles, with similar effacement by amorphous eosinophilic material with small amounts of nuclear debris, commonly known as fibrinoid change or necrosis. This cat presented with acute onset of blindness and an anxious demeanor with rapid deterioration to seizing and stupor. This is a classical presentation for target organ damage in a hypertensive cat with the first noted sign often being acute blindness associated with catastrophic effusive retinal detachment (Fig. 2). Sudden onset of intracranial neurological signs is also common. Renal and cardiac changes are generally more insidious. Accelerated progression of chronic kidney disease and development of congestive heart failure associated with left ventricular hypertrophy,

respectively, are reported.³ Pathogenesis of the insidious conditions is poorly understood, particularly regarding cause and effect.

The risk of target organ damage rises as the blood pressure rises.^{4,5} Risk is minimal at <150mmHg, mild at 150-159mmHg, moderate at 160-179mmHg and severe at >180mmHg. This cat had a recorded pressure of 230mmHg at presentation. The vascular lesions in the brain, eyes and kidneys are acute suggesting a relatively short course of hypertension in this cat. There is no evidence to suggest hyperplastic

vascular changes that would be seen as a response to sustained hypertension. It has been suggested that vascular remodeling can occur within 14 days of onset of hypertension.¹

Hypertension in this cat was considered idiopathic despite being younger than reported age of >12 years for development of idiopathic hypertension.⁵ Complete histological evaluation did not show pathology consistent with any of the conditions associated with secondary hypertension. Secondary hypertension is most commonly seen in cats with chronic kidney disease (CKD) or with hyperthyroidism. Many cats with systemic hypertension show some degree of CKD. It is often unclear whether the hypertension initiates renal damage or systemic hypertension develops as a consequence of reduced renal function.



Kidney, cat: There is fibrinoid necrosis of renal arterioles and ischemic damage of surrounding parenchyma. (Photo courtesy of: University of Calgary Faculty of Veterinary Medicine, 3280 Hospital Dr. NW Calgary, AB Canada, T2N 4Z6 <http://vet.ucalgary.ca/>)

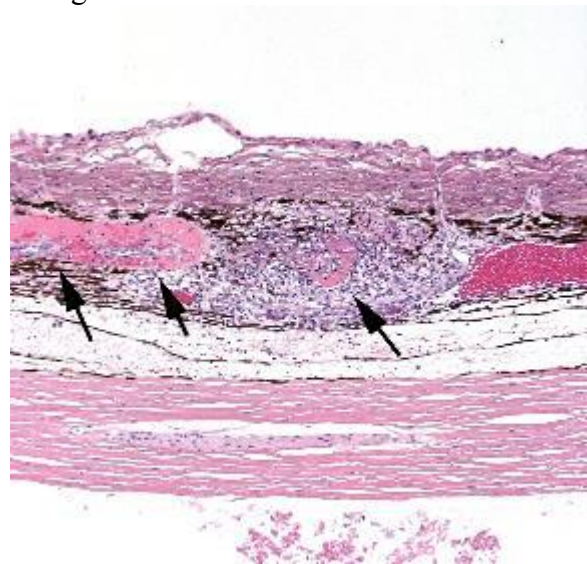
Hyperthyroidism has been considered a risk factor for systemic hypertension with recent information suggesting this risk may be overstated.³

JPC Diagnosis: Cerebrum: Fibrinoid vascular necrosis, multifocal, moderate with neuronal necrosis and edema.

Conference Comment: This was a challenging case for most conference participants with many focusing the majority of their description on the vascular changes. Most participants described an asymmetric fibrinoid vasculitis and listed various etiologic differential diagnosis, such as feline ischemic encephalopathy, FIP, FeLV as well as hypertension. The moderator and many conference attendees stated they had not previously seen a CNS case similar to this, with the unique asymmetric fibrinoid change within vessels, and some speculated that an infarction may result in a similar lesion, although the contributor provided a convincing workup and description of a

hypertension induced lesion / TOD. The lesion was described as focally extensive within the white matter, but also extending into the grey matter with areas of spongiosis, hemorrhage and neuronal necrosis. The affected vessels were described as having indistinct vessel walls and endothelium, largely obscured by dense eosinophilic debris with expansion of Virchow-Robin space by edema, similar to the contributor's description above. Low numbers of mitoses were described within vessel endothelium.

The moderator discussed duration of injury as determined by relative populations of glial cells. It generally takes approximately 4-5 days to see a prominent astrocyte response; in this case there is a mild increase in the number of astrocytes, and a much more prominent increase in the number of microglial cells. Microglial cells respond more rapidly to CNS injury, generally increasing in number within 24 hours, and consequently there was speculation this lesion was approximately 2-3 days duration, which corresponds to the contributor's comment above regarding the acute nature of changes in the br



Eye, cat: There is fibrinoid necrosis of retinal vessels and marked perivascular inflammation. (Photo courtesy of: University of Calgary Faculty of Veterinary Medicine, 3280 Hospital Dr. NW Calgary, AB Canada, T2N 4Z6 <http://vet.ucalgary.ca/>)

Autoregulation of cerebral blood flow normally prevents excesses of pressure and flow within the brain that can result in excess pressure related damage; however, there are upper limits on this autoregulatory mechanism. When this mechanism fails in cases of prolonged and/or excessive systemic blood pressure, vessels become distended and endothelial tight junctions open, resulting in extravascular leakage of fluid, and edema is the end result. Depending on the severity, cerebral edema may be visible grossly along with widening and flattening of the cerebral gyri, and caudal herniation of the cerebellum through the foramen magnum due to increased intracranial pressure.

Histologically, as seen in this case, vacuolation of the neuropil is present, and may be predominantly in the white matter. Vascular lesions can include arteriolar hyalinosis, which may reflect endothelial damage, and leakage of fibrin and other plasma components into the vessel wall and extravascular space; this change may occur prior to onset of fibrinoid vascular necrosis. Hyperplastic arteriosclerosis, microhemorrhages and perivascular cuffing by inflammatory cells may also be seen depending on degree and duration of hypertension.^{1,4}

Contributing Institution:

University of Calgary Faculty of Veterinary Medicine
3280 Hospital Dr. NW
Calgary, AB Canada
T2N 4Z6
<http://vet.ucalgary.ca/>

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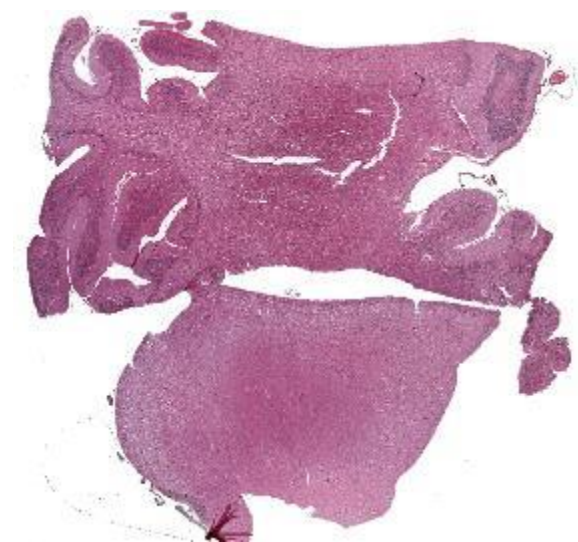
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CASE IV: 15 0160-21 (JPC 4067774).

Signalment: Bovine, Charolais (*Bos taurus*), male, 3 years old

History: This three-year-old, charolais bull was presented for a two-month history of chronic posterior paresia. Clinical examination showed right hock stiffness with right leg mobility reduction.



Cerebellum, brainstem, ox: No abnormalities are visible at subgross examination. (HE, 4X)

Gross Pathology: No lesions were observed on macroscopic examination

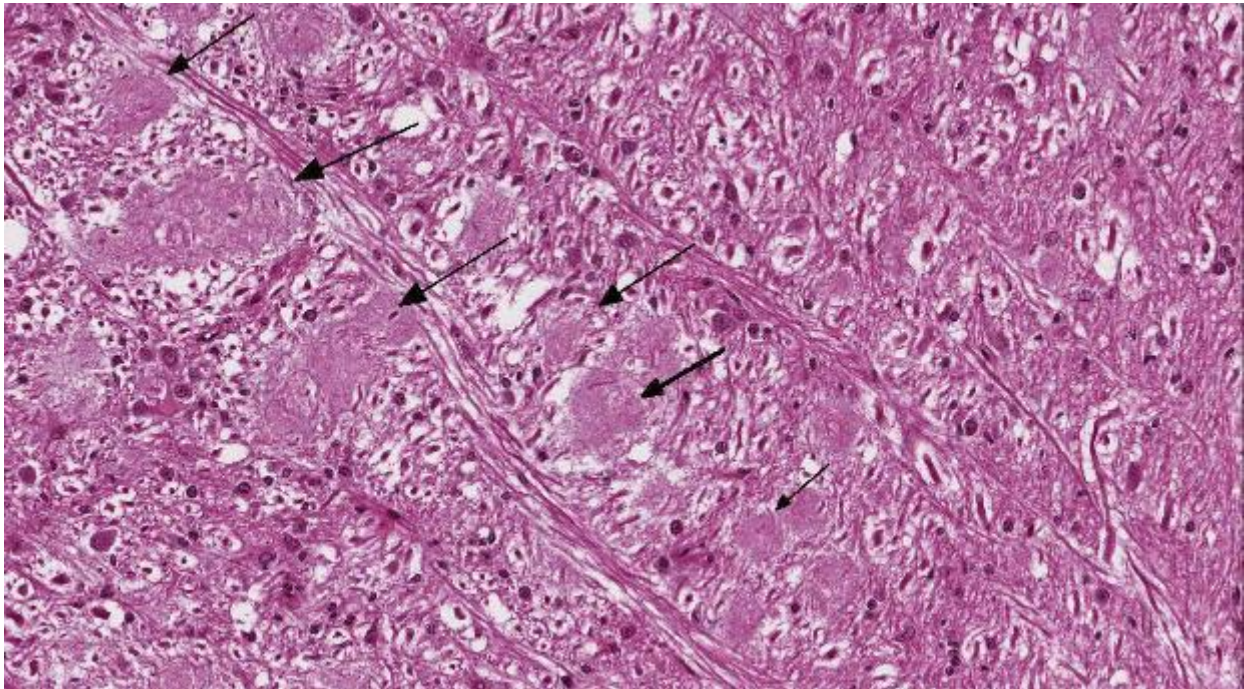
Laboratory Results: No biochemical abnormalities ante mortem were found. Cerebrospinal fluid cytological examination was normal.

Histopathologic Description: Brain, cerebellum: Multifocally in the white matter can be found numerous 20-100 μm diameter eosinophilic, acellular, granular to fibrillar, round to ovoid-shaped plaques, haphazardly distributed. The rest of the white matter contains multifocal, intra- and intercellular, optically empty, vacuolation (spongiosis). A mild, non-suppurative, inflammatory reaction can be found within and around the pathological areas, characterized by discrete lymphocytic perivascular cuffing and mild gliosis with increased number of oligodendrocytes and hyperacidophilic astrocytes (reactive astrocytes).

Kluver and Barerra stains showed the material was bright blue (consistent with myelin). No PAS positive material was observed.

Contributor's Morphologic Diagnosis: Brain, cerebellum, white matter, eosinophilic plaques, multifocal, severe with mild spongiosis and discrete gliosis in a Charolais bull, characteristic of progressive ataxia of Charolais cattle.

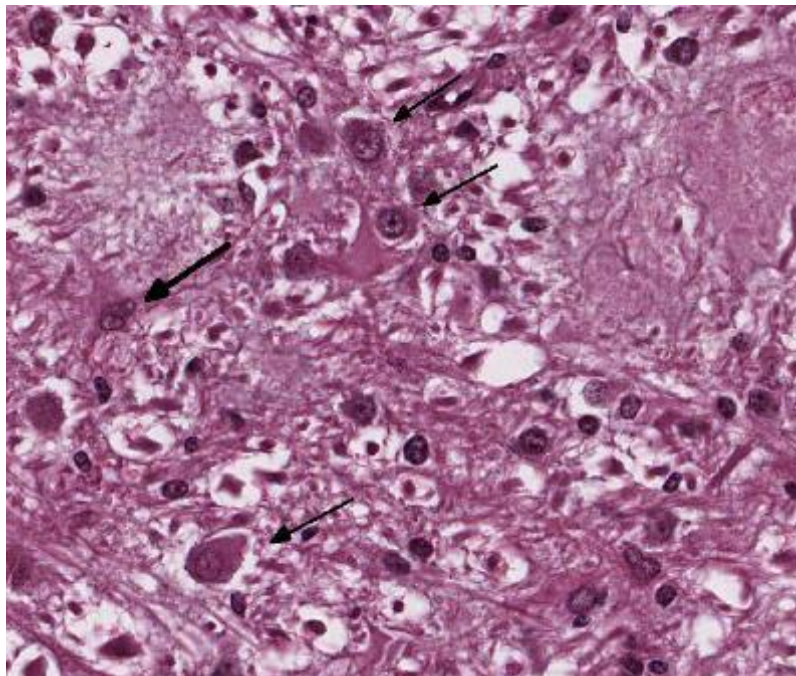
Contributor's Comment: Progressive ataxia is a condition seen in purebred and crossbred Charolais cattle. It is a genetic disease suspected to be of autosomal recessive transmission.^{2,6} The chromosomal locus containing the gene coding the basic myelin protein is likely to be involved in this condition.¹ However studies are still ongoing to identify the causal mutation. It is a slowly progressive disease affecting Charolais cattle from 6 months to two years or more. Clinically, the animal will generally present



There are numerous round densely packed plaques of fibrils arranged in columns throughout the brainstem and cerebellum white matter. (HE, 284X)

a progressive hindlimb stiffness evolving into incoordination and dysuria. All other neurological functions are not thought to be affected.^{2,6} The pathogenesis of the disease is an oligodendroglial dysmyelinogenesis. It is thought that the defect of production and maintenance of myelin sheaths in white matter, leading to widening of the node of Ranvier and subsequent poor saltatory nerve impulse conduction causing the nervous symptoms observed.

Ultrastructurally, the disease is characterized by hypertrophic and hyperplastic oligodendrocytes emitting numerous and disorganized small processes around the node of Ranvier, leading to myelin sheaths malformation in the white matter. The histological examination displays haphazard, multifocal, pale, eosinophilic, granular to fibrillar, 20-100 μm plaques which are pathognomonic for this disease, along with mild oligodendroglial hyperplasia, discrete



Brainstem, ox: Markedly hypertrophic oligodendroglial cells (arrows) are present adjacent to plaques. The plaques are composed of tangled processes of these cells. (HE, 320X).

astrocytosis, lymphocytic infiltration and cuffing.^{2,4,5,6}

This condition has not been described in man. However, a similar condition has been reported in two bull-mastiff dogs.³ In this case, the lesions are characterized by an oligodendroglial dysplasia forming small eosinophilic plaques of 20 μm around axons. Identically to the bovine species, there were only rare and small GFAP positive processes, excluding an astrocytic origin for those plaques.

JPC Diagnosis: Cerebrum and cerebellum, white matter: Dysmyelinogenesis, multifocal, moderate, with fibrillary plaques and oligodendroglial hypertrophy.

Conference Comment: The conference description was very similar to the contributor's description above. Participants discussed the appearance of the fibrillary plaques as having a distinctive structure, often forming columns in certain regions of the section, and being absent of nuclei. The formation and origin of the plaques was discussed as originating from processes of hypertrophied oligodendrocytes, and not from the accumulation of abnormal myelin. This is a unique entity in that there are few known genetic diseases which affect oligodendrocytes. There is some slide variation, but lesion characteristics appear similar in all sections.

This condition is reported in both sexes of Charolais cattle, and has also been reported in three-quarter crossbred as well as purebred animals. Gross lesions are absent, but the microscopic

lesions are unique and distinctive. Axons are found to traverse the plaques with mostly normal myelin and no sign of degradation or phagocytosis of the myelin. Evidence of axonal degeneration, when found, is mild. As mentioned above, ultrastructural examination suggests the abnormality lies within the paranodal region of axons. Younger plaques are characterized by axons wrapped with hypertrophied oligodendrocyte processes, in a thin myelin sheath, near the nodes of Ranvier. In older plaques the axons may be demyelinated and surrounded by more abundant oligodendrocyte processes. The defect lies in the inability of oligodendrocytes to maintain the paranodal myelin structure with resultant oligodendrocyte hypertrophy.²

There are two types of oligodendrocytes within the CNS, interfascicular oligodendrocytes and satellite cells. The interfascicular oligodendrocytes are responsible for myelination of axons and normally they appear as small cells with hyperchromatic nuclei; special - staining techniques, such as myelin basic protein, are normally required to visualize their processes. The nuclei of oligodendrocytes are often seen aligned in rows parallel to myelinated axons, where they maintain the internodal segments of the myelin sheath.⁷

Contributing Institution: Unité d'Histologie, Embryologie et Anatomie pathologique, Département des Sciences Biologiques et Pharmaceutiques.
Ecole Nationale Vétérinaire d'Alfort,
FRANCE
www.vet-alfort.fr

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