Joint Pathology Center
Veterinary Pathology Services

WEDNESDAY SLIDE CONFERENCE 2024-2025

Conference #25 30 April 2025

CASE I:

Signalment:
3-year-old, 9-month pregnant, female, Jersey *(Bos taurus taurus*).

History:
The cow was dried off on June 28, 2022. She had been doing well until August 17, 2022, when she was found recumbent and was diagnosed with possible pink eye. She was treated with aspirin, penicillin, and dexamethasone subconjunctivally. On August 18, 2022, she remained recumbent, began convulsing, and died at 9:30 am. She was submitted for postmortem examination by 11:00 am on the same day.

Gross Pathology:
Fair body condition with mild muscle mass, minimal external adipose stores, and moderate internal adipose stores in all expected locations. Avulsion of the lateral right hind limb dew claw; multifocal 2 to 15 cm diameter area abrasions on the right hip and on the lateral aspect of the right fore limb; and, a 15 x 11 cm area of subcutaneous edema and a 35 x 20 cm area of subcutaneous hemorrhage on the right thorax over the ribs and right shoulder.

Thoracic negative pressure and mild, serosanguineous pleural effusion. Multifocal thoracic cranioventral fibrous adhesions that span between lung, pericardial sac, diaphragm, and body wall. Mild ventrocranial laryngeal edema. Severe, diffuse, frothy, white foam extending from the larynx to the secondary bronchi. Mild to moderate, white frothy fluid oozes from the lungs on the cut section. Multifocal epicardial and left ventricular endocardial petechiae. A focal, 5.5 x 3 cm hemorrhage at the base of the right atrium overlaying adipose tissue.

A focal well-demarcated, 4 x 1 cm subacute healing ulcer on the right lateral aspect of the tongue. Rumen has decreased dry ingesta (dehydrated) with admixed birdshot and rocks. No magnet. There is expected postmortem rumen mucosal sloughing.

The abomasum contains rocks admixed with green organic material and the mucosa has multifocal occasional subacute ulcers. The biliary tract is patent with normal bile. There is a fibrous adhesion of the right liver lobe to the omentum. The liver is moderately congested.

The right caudal mammary quarter has a thick, viscous, white-to-tan discharge without flocculent material, and on section, the mammary gland is pale tan and oozes a cloudy white thick fluid. The supramammary lymph nodes are enlarged and wet.

The subdural space of the brain and the cervical spinal cord has viscous, translucent to yellow serous meningeal fluid and multifocal

hemorrhage. The right ventrocranial aspect of the cerebral frontal lobe and olfactory lobe and bulb are regionally tan to yellow, soft, and friable (encephalomalacia). The area's meninges are thickened by fibrin, edema, and hemorrhage.

The left eye has a regional soft expansion of the conjunctiva (iatrogenic) and is overlaid by at least 3 thin white linear nematodes (favor *Thelazia gulosa*).

FETUS: The left uterine horn has a single female fetus. The fetus is well muscled with abundant adipose stores. The maternal aspect of the chorioallantois is overlaid by multifocal brown, mucoid material. There are multiple (< 5) small (< 0.5 cm), white, discrete, firm, and focal nodules on the amniotic sac. The fetus is 18.4 kg, 72.5 cm from crown to rump, has erupted incisors, and is fully haired with eyelashes (9 month, near term). No thoracic negative pressure and lung sections sink in formalin. The thoracic cavity has mild, serosanguineous fluid. The right lateral and cranial aspect of the liver has a large 10 x 6 cm cyst. When cut, the cyst oozes red-tinged serous fluid with scant fibrin. There is focal hemorrhage of the ruminal serosa and regional suffusive hemorrhage on the right ventricle epicardium.

Laboratory Results:

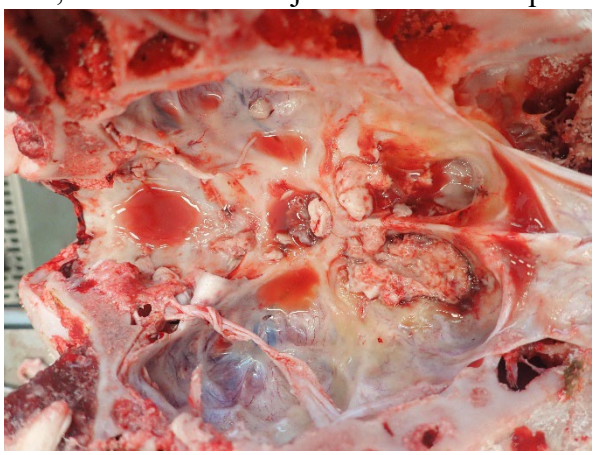
1) A multiplex real-time PCR performed by the USA CDC on fresh brain from the right frontal/olfactory lobe was positive for *Naegleria fowleri* and negative for *Acanthamoeba* spp. and *Balamuthia mandrillaris.*

2) Immunohistochemistry performed by the USA CDC on formalin-fixed paraffin-embedded right frontal/olfactory lobe was immunoreactive for free-living amoeba and *Naegleria*-specific antibodies.

3) Three environment water samples were submitted to Biological Consulting Services of North Florida Inc. for *N. fowleri* analysis. Water from the concrete pond and from the drinking trough of an adjacent pen did not detect *N. fowleri*. Water from the drinking trough of the pen that housed the affected cow was positive for *N. fowleri*.

Microscopic Description:

Brain, right frontal lobe/olfactory lobe: Involving 40% of the section and extending to the leptomeninges, there is locally extensive encephalomalacia with fibrin thrombi, vasculitis, vascular fibrinoid degeneration, neutrophils, cellular debris, hemorrhage, and fibrin. Within these areas, often perivascular admixed with neutrophils, are ovoid to polygonal 8-10 um diameter organisms that have small 1-2 um nuclei that contain a single central nucleolus (karyosome) with a granular amphophilic vacuolated cytoplasm (amoeba trophozoites). Bordering the area of malacia are streams of degenerate neutrophils and fibrin, and within the adjacent intact neuropa



Cranium, ox: The remnant neuroparenchyma of the right frontal/olfactory lobe is soft, friable, tan to light yellow, and has multifocal hemorrhage (encephalomalacia). The adjacent subdura is thickened by fibrin and edema. (Photo courtesy of: Midwestern University, College of Veterinary Medicine, Diagnostic Pathology Center. *https://www.mwuanimalhealth.com/diagnostic-pathology-center.)*

The cow's drinking water trough that tested positive for N. fowleri was heavily fouled by organic debris (Photo courtesy of: Midwestern University, College of Veterinary Medicine, Diagnostic Pathology Center. *https://www.mwuanimalhealth.com/diagnostic-pathology-center.)*

renchyma and leptomeninges, are frequent dense perivascular cuffs of lymphocytes, plasma cells, and histiocytes with variable spongy change, fibrin, vascular fibrinoid degeneration, reactive vascular endothelium, and hemorrhage.

Contributor's Morphologic Diagnosis:

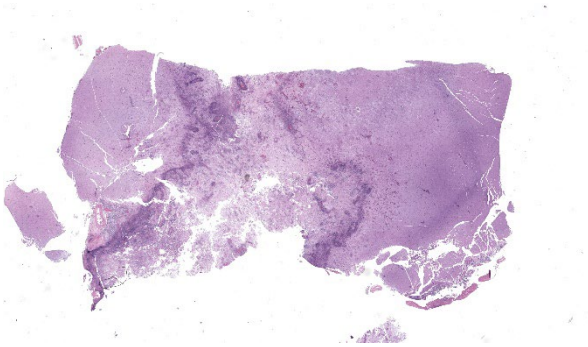
Brain, frontal right lobe/olfactory bulb: Meningoencephalitis, necrotizing, suppurative, mononuclear, multifocal, severe, acute to subacute, with intralesional amoeba trophozoites

Contributor's Comment: The cow's morbidity and mortality were due to necrotizing encephalitis caused by *Naegleria fowleri*, a eukaryotic, amphizoic, thermophilic, and

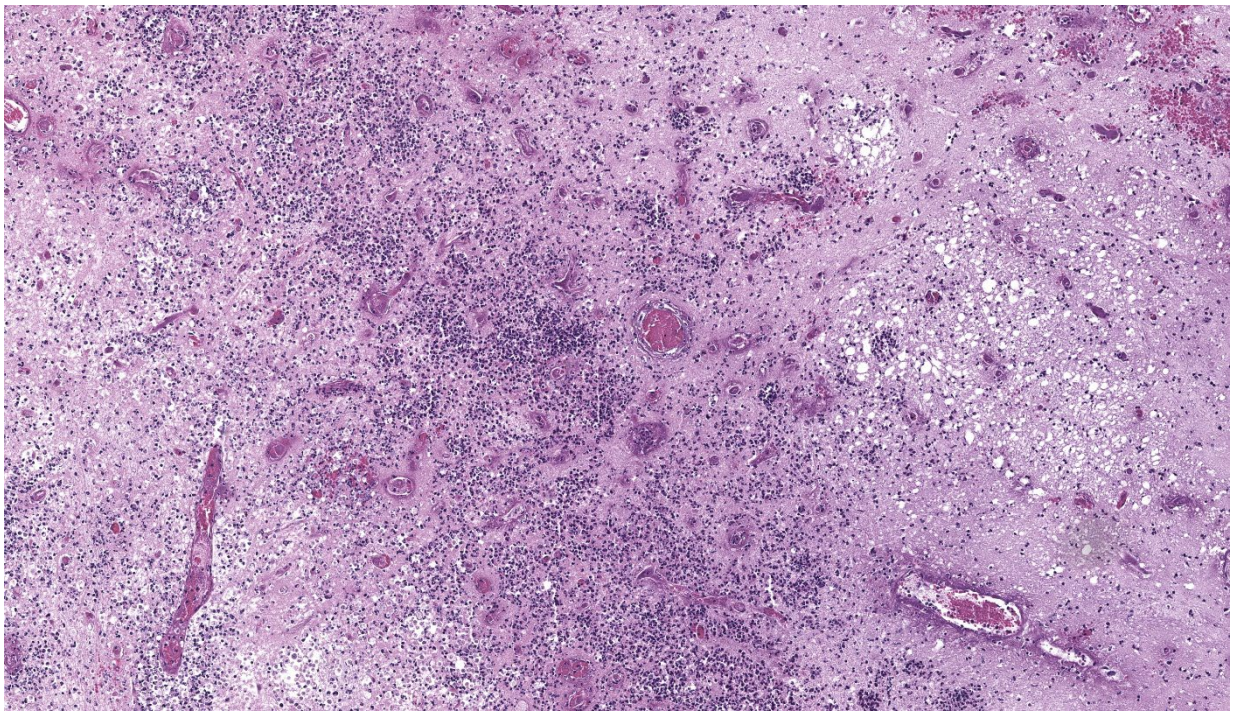
Cerebrum, ox: A large area of necrosis is partially bounded by a dense band of infiltrating neutrophils and cellular debris. (HE, 8X)

free-living amoeba that is ubiquitous in the environment. Multiplex PCR performed on fresh brain from the right frontal and olfactory lobe confirmed *N. fowleri.* Immunohistochemistry performed on a formalin-fixed paraffin-embedded section of the affected brain detected intralesional *N. fowleri*. Analysis of the cow's drinking water visually detected amoeba trophozoites, and PCR confirmed *N. fowleri*, thereby determining the probable environmental source. Although the necrotizing inflammation was most severe in the right frontal and olfactory lobes, histopathology recognized similar lesions with fewer amoeba in the ventral periventricular cerebellum, brainstem, fourth ventricle choroid plexus, and cervical spinal cord. The distribution of these secondary inflammatory nidi suggests the amoebae spread via the cerebrospinal fluid following primary invasion of the right olfactory bulb.

Naegleria fowleri, *Balamuthia mandrillaris, Acanthamoeba* spp., and *Sappinia pedata* are pathogenic free-living amoebae that naturally cause central nervous system (CNS) disease in mammals.[3,6] These ubiquitous amoebae are opportunistic, target immunocompetent and



immunosuppressed hosts, and may occupy soil, air, and water.[3,6] Infections occur in humans and animals; however, *S. pedata* has



Cerebrum, ox: There is necrosis of the neuroparenchyma with abundant perivascular inflammation. (HE, 135X)

occurred in only one human case of encephalitis.[4,6] Unlike other amoeba, *N. fowleri*, the cause of fulminating primary amoebic meningoencephalitis, causes encephalitis following a direct entry into the CNS via the olfactory neuroepithelium, and the resulting lesions lack intralesional cysts.[6]

Naegleria fowleri naturally subsists on phagocytosed bacteria and thrives in unchlorinated warm bodies of water (upwards of 45ºC), including freshwater pools, puddles, lakes, rivers, hot springs, aquaria, sewage, irrigation canals, ponds, irrigation ditches, and thermally polluted effluents of power plants.[1,6] Resistant cysts form during adverse environmental conditions; otherwise, the protozoa is in a transitory flagellate stage or, more frequently, is an infectious amoeboid trophozoite equipped with a vesicular nucleus that has a single central nucleolus (karyosome).[6] Trophozoites reproduce by binary fission and will become cysts if food is lacking or the environment impairs growth.[6] Human and animal infections develop when nasal passages are inadvertently (e.g., during aquatic activities) or purposefully (e.g., nasal flush) exposed to warm unchlorinated or inadequately chlorinated water harboring infectious trophozoites. Trophozoites are first phagocytosed by the sustentacular cells of the olfactory neuroepithelium, then migrate through the cribriform plate, invade the leptomeninges, and finally, access the rostral neuroparenchyma where they can proliferate and potentially spread to other neuroanatomical locations.[6] Generally, onset of disease is rapid, as soon as 24 hours, and death usually occurs within a week.[6] This cow was likely exposed to *N. fowleri* during drinking activities and perhaps inadvertently snorted contaminated water or transferred amoeba to the nostrils during licking, which allowed trophozoites to reach and invade the right cribriform plate and subsequently cause malacia of the right frontal/olfactory lobe. Although the cow's drinking water was purported to be chlorinated, the trough contained warm stagnant water, there was surface scum, and a

thick layer of organic debris lined the bottom-collectively, these factors probably inhibited efficient chloramination and facilitated the survival of *N. fowleri* trophozoites.

Meningoencephalitis due to *N. fowleri* is reported in cattle from Costa Rica, the state of Paraiba, Brazil, California, USA, and now Arizona, USA.[2,4,5] As in this case, the incidence of *N. fowleri* in California cows correlated with warm summer temperatures, acute CNS clinical signs, olfactory and cerebellar necrosuppurative lesions, and the probable exposure to trophozoites in drinking water.[2]

Although uncommon in cattle, amoebic meningoencephalitis caused by *N. fowleri* is an important differential diagnosis of an acutely neurologic cow that is most likely during the summer in a geographic area with high ambient temperatures. Other important and more common differential diagnoses for neurologic disease in cattle include rabies virus, polioencephalomalacia, lead toxicosis, salt toxicity, thrombotic meningoencephalitis, cerebral abscess, and bacterial meningitis.[2]

Contributing Institution:
Midwestern University, College of Veterinary Medicine, Diagnostic Pathology Center

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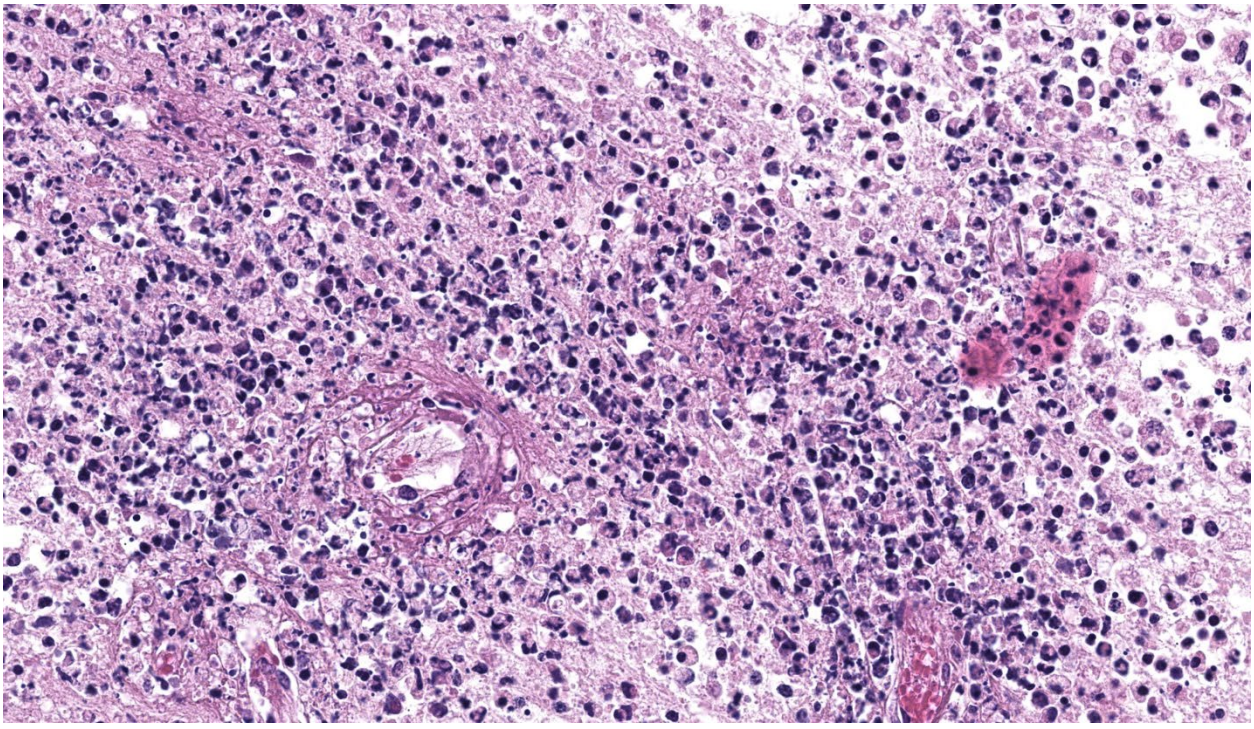
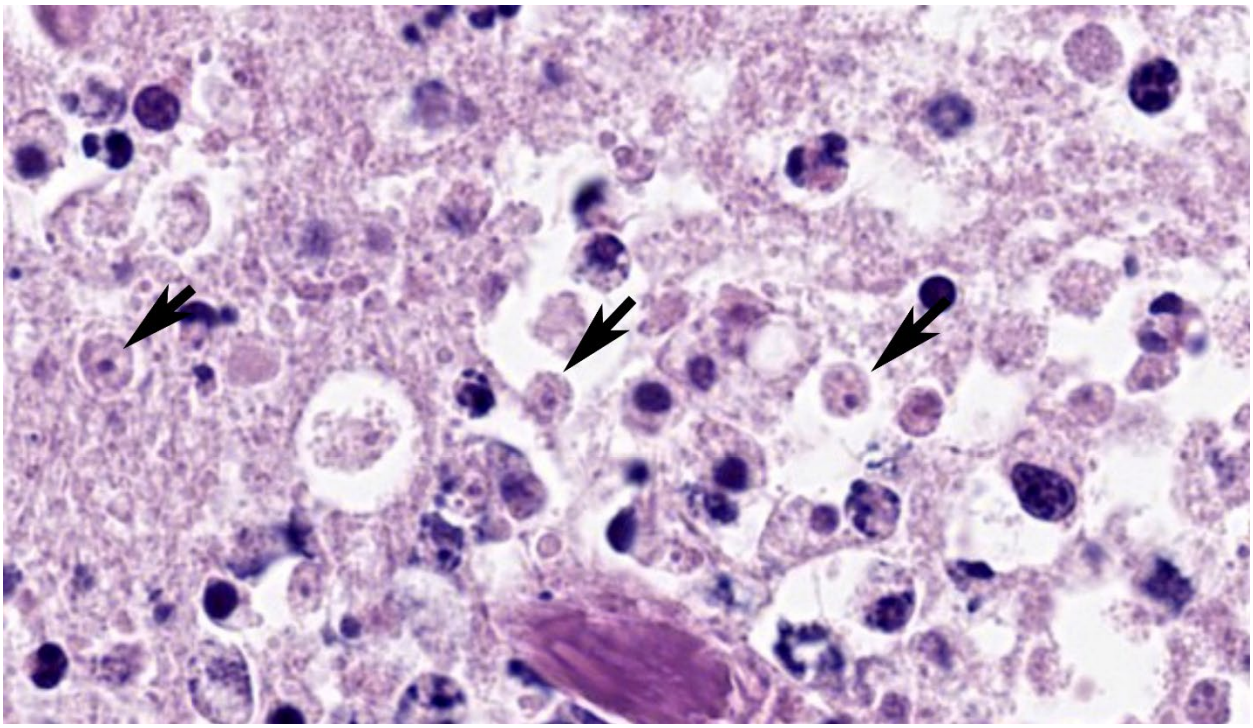
JPC Morphologic Diagnosis: Cerebrum: Meningoencephalitis, necrotizing and suppurative, focally extensive, subacute, severe, with vasculitis, thrombosis, and numerous amoebic trophozoites.

JPC Comment: This week's moderator was Dr. Jey Koehler from Auburn University who selected an array of neuropathology cases to



Cerebrum, ox: Necrotic and thrombosed vessels are surrounded by large numbers of necroitic and few viable neutrophils and abundant cellular debris. There is necrosis of the neuroparenchyma with abundant perivascular inflammation. (HE, 578X)



Cerebrum, ox: Numerous amoebae with prominent karyosomes are scattered throughout the necrotic and inflamed neuropa-renchyma. (HE, 870X)

discuss with conference participants. Her pre-conference lecture on evaluation of the nervous system proved helpful in refining descriptive elements and recognizing important artifacts within the brain and spinal cord – herein we capture some of these pearls of wisdom in our discussion.

This first case leaves little doubt from subgross where the lesion is on the slide, though there are several descriptive features not to miss on higher magnification. The cause of the abundant necrotizing inflammation is characteristic with amoeba having distinct, round central nuclei and round karyosomes that were best appreciated with the iris diaphragm closed down. In comparison to *Balamuthia* and *Acanthamoeba*, we did not note any tissue cysts, though Dr. Koehler posited that *Naegleria* infection is rapidly fatal to most (all?) animals, leaving little time for these to develop.[8] The marked fibrinoid vasculitis and many fibrin thrombi reflect both direct damage to vessels from secreted amoebic proteases and trogocytosis of neural tissue (literally, nibbling of host cells to gain nutrients!)[7] in addition to the indirect ischemic effects. The large presence of neutrophils reflects both amoebic recruitment and response to cellular injury. Dr. Koehler emphasized that remembering the number of neutrophils (granulocytes) within the neuroparenchyma was easy – that number should be zero (or else prompt you to look further for why they are there). For another example of amoebic disease (*Entamoeba*) with necrotizing inflammation in a colobus monkey, see Conference 9, Case 1 from this year.

The contributor provides an interesting take on *Naegleria* that is cemented by a solid gross photo of the waterer for this animal. Absent this highly suggestive image, conference participants also discussed other causes of focal encephalitis which included dehorning injury/trauma, abscessation (e.g. from a

nose ring), bovine herpesviruses, *Histophilus*, and angioinvasive fungi (*Aspergillus)*. We did not identify any other agents present in section, however.

Finally, conference participants enjoyed an enlightening discourse on the nature of necrosis within the brain, encephalitis, and true malacia. We differed from the contributor's interpretation of this case slightly in that we feel that the separation of the neuroparenchyma is largely artifactual (i.e. the process of cutting a soft brain) versus true cavitation due to necrosis. Dr. Koehler emphasized that thin gliovascular strands extending between adjacent vessels within increased clear space histologically are consistent with malacia (see Conference 5, Case 4 of the current year for an excellent example in a SV40-infected macaque) which was not observed here and not consistent with the mechanism of injury expected for *Naegleria*. We briefly debated whether this case represents an encephalitis versus meningoencephalitis given the minimal involvement of the overlying meninges and the notion that observed changes may simply extend outward towards the meninges. We ultimately accepted the contributor's note that this lesion was distributed multifocally and features may have differed in other sections.

References:

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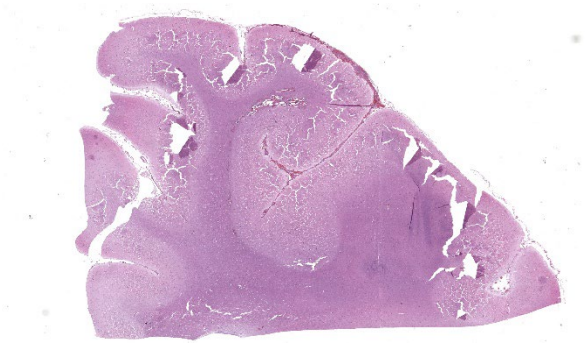
CASE II:

Signalment:
1 year, 2 months old male sitatunga

History:
This sitatunga (*Tragelaphus spekii*) was born at a zoological institution in the mid-Atlantic region. He was apparently healthy at birth, nursed well, and had normal baseline bloodwork. He received routine vaccinations for tetanus at 8 and 12 weeks of age and rabies at 16 weeks. At 3 months of age, he was first reported to have mild, intermittent ataxia in the rear limbs, which continued over the next several months, along with occasional rear limb lameness. There were periods when the ataxia became more severe and the animal became lethargic; at times signs progressed to leg crossing, circling and falling. He was somewhat responsive to treatment with NSAIDs and antibiotics, but intermittent ataxia persisted. Bloodwork was always within normal limits and spinal radiographs were unremarkable. Vitamin E serum levels were slightly low but similar to other animals in the collection that did not have clinical signs. He was treated with injectable vitamin E/Selenium weekly with some improvement in ataxia. At 11 months of age the animal presented with acute worsening of ataxia, with a right head tilt, right circling and collapsing, horizontal nystagmus, and crossing of legs in front and back. Over the next two months he was treated with NSAIDs, vitamin E/selenium and showed mild improvement. On the day prior to necropsy, he acutely became severely ataxic, with crossing of front and rear legs, right head tilt, severe right circling leading to falling, and decreased awareness of surroundings. Euthanasia was elected.



Cerebrum, sitatunga: One section of cerebrum is submitted for examination. At subgross magnification, an area of hemorrhage is present in the meninges (upper left). (HE, 8X)

Gross Pathology:
Post-fixation, on cut section there was an area of hemorrhage within the parenchyma at the level of the right basal ganglia, and multiple dark brown areas within the meninges and extending into the superficial cortex

Laboratory Results:
PCR targeting a portion of the rRNA ITS-2 region of *Parelaphostrongylus spp* was performed on DNA isolated from formalin-fixed brain tissue from this case. The resulting PCR product showed 100% sequence identity to *P. tenuis*

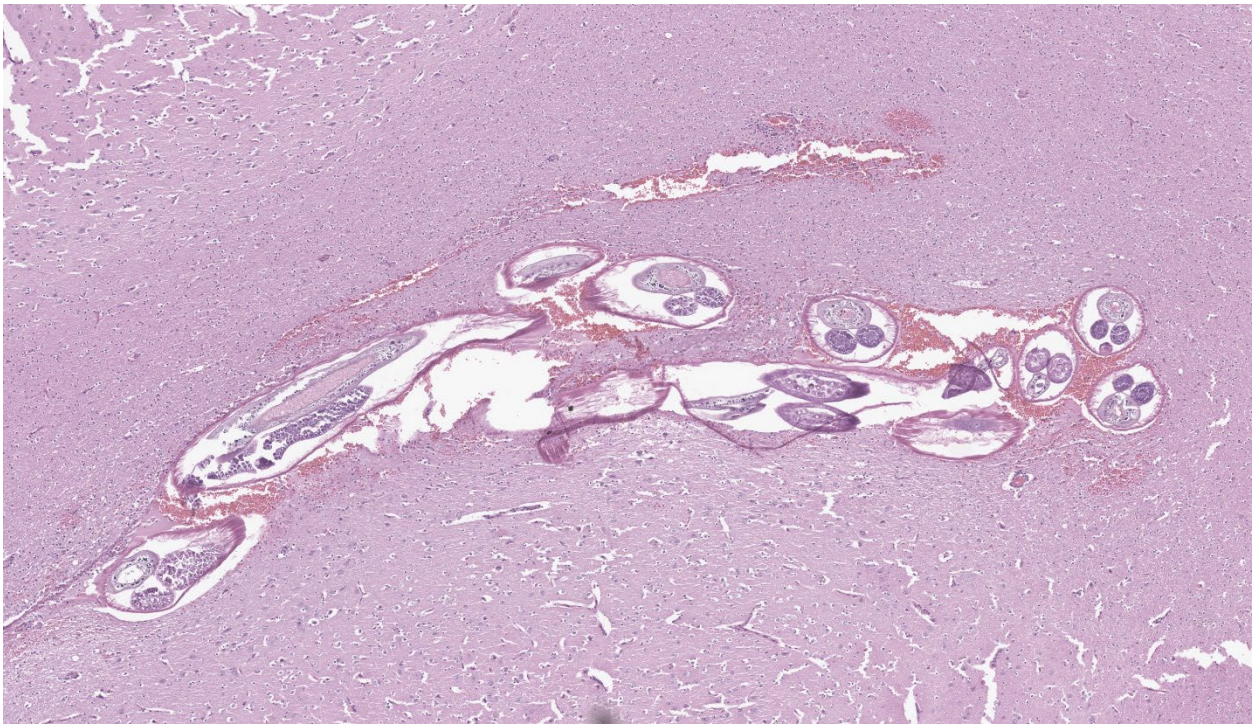
Microscopic Description:
Cerebrum at the level of the basal ganglia: Beneath the meninges and extending into the outer layers of the cerebral cortex is a focally extensive area of hemorrhage, with rarefaction of the neuropil and abundant eosinophils, lymphocytes, histiocytes, and plasma cells. Throughout the parenchyma, there are multiple smaller tracts of hemorrhage, necrosis and loss of neuropil. Within some of these lesions are several, 100-250 um in diameter cross sections of adult nematodes characterized by a thin smooth cuticle, coelomyarian musculature, accessory hypodermal chords, a large intestinal tract with few multinucleate

cells, and a reproductive tract. There is moderate to severe periventricular edema and gliosis, and multifocal lymphoplasmacytic perivascular cuffing.

Contributor's Morphologic Diagnosis:
Brain: meningoencephalitis, lymphohistiocytic and eosinophilic, multifocal, chronic active, severe, with reactive gliosis, hemorrhage, necrosis, and intralesional nematodes

Contributor's Comment: The necrotizing tracts in the brain caused by migrating nematodes are consistent with the clinical signs of progressive ataxia, circling, head tilt, and loss of awareness of surroundings. Histological characteristics of the organism including a thin smooth cuticle, coelomyarian musculature, accessory hypodermal chords, and a large intestinal tract with few multinucleate cells, are consistent with a metastrongyle nematode.[4] PCR and DNA sequencing confirmed identification of *Parelaphostrongylus tenuis*.

P. tenuis, also known as the meningeal worm, is a nematode most commonly found in white-tailed deer which is the definitive host. In this species, adult worms are found within the cranial venous sinuses and the subdural space. Here, adults lay eggs that travel through the venous blood and into the lungs. In the lungs, eggs embryonate into larvae which move into the respiratory tract, then are swallowed and eliminated into the feces. Larvae then penetrate into the foot of terrestrial molluscs. Deer or aberrant hosts become infected by ingesting gastropods which contain infective larvae. After ingestion, larvae migrate to the spinal cord and develop into adults in the dorsal horn of the gray matter. They migrate into the spinal subdural space and into the cranium, through the dura mater and into the venous sinuses.[1]



Cerebrum, sitatunga: At the junction of the white and gray matter, multiple cross- and tangential sections of an adult female metastrongyle are evident within a hemorrhagic migration tract. (HE, 73X)

White-tailed deer commonly harbor meningeal worms, particularly in areas of deciduous forest regions where the habitat is suitable for gastropods. Prevalence in white-tailed deer populations is highly variable and has been reported to be up to 94% in certain areas.[6]

P. tenuis causes little damage to the definitive host, but can cause severe neurologic disease in other animals such as moose, caribou, wapiti, mule deer, fallow deer, elk, llamas, alpacas, wolves, horses, antelope, sika deer, sheep, calves, goat, and guinea pigs.[1-3,5-10] Clinical signs can include ataxia, hypermetria, paresis, paralysis, head tilt, circling, blindness, weight loss, depression, seizures, and death. Treatment of mildly affected animals has been successful with anthelminthics such as ivermectin, steroids, and supportive care. However, prognosis is guarded in animals with severe neurological signs.[6] To our knowledge, this is the first report of *P. tenuis* infection in a sitatunga.

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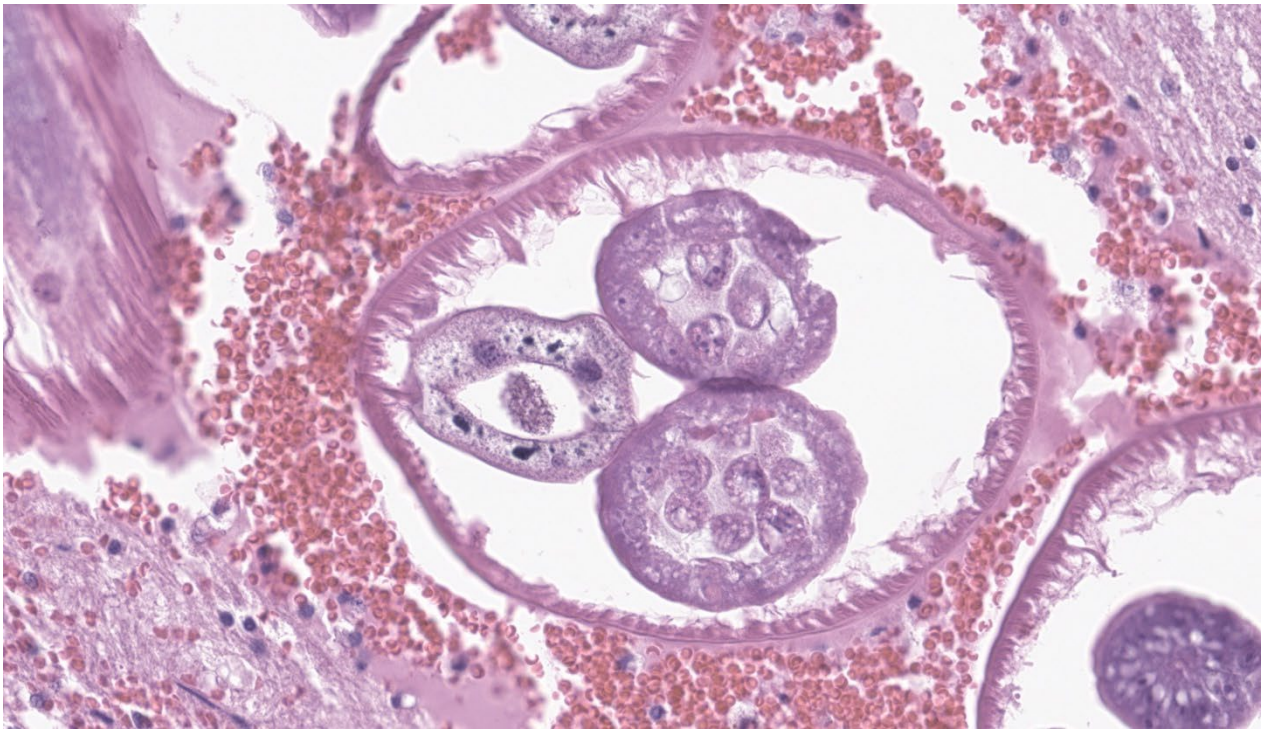
JPC Morphologic Diagnosis: Cerebrum: Meningoencephalitis, necrohemorrhagic, focally extensive, subacute, moderate, with adult metastrongyle nematode.



Cerebrum, sitatunga: A cross section of the nematode exhibits the following: a think cuticle, pseudocoelom, polymyarian, coelomyarian musculature, a large intestine with multiple uninucleate cells, and two ross sections of uterus with luminal ova. (HE, 626X)

JPC Comment: The contributor provides a lovely section of *P. tenuis* that illustrates the characteristic features of this nematode in histologic section. While PCR is an important tool in diagnostic and research settings, it is important to recognize these features and generate a putative 'culprit' as recovery of nucleic acids, particularly from formalin-fixed tissue can present issues with organism identification. In contrast to the first case, the thickening of the meninges is more pronounced here and is accompanied by both rarefaction (small/fine-sized vacuolar change of the parenchyma) and spongiosis (appreciably larger vacuoles) in the immediate vicinity. The linear tract of necrosis and hemorrhage functions almost as a signpost towards the profiles of these nematodes, though absent these arriving at a specific diagnosis would be difficult and we would also have to consider migrating foreign material (e.g. grass awn) as an outside possibility. Dr. Koehler noted that after the animal's death, nematodes may continue to actively traverse the CNS and therefore be missed in histologic section. One interesting feature of this case was that the pigmented intestinal epithelial cells of *P. tenuis* were highlighted with Prussian blue, suggesting that these nematodes accumulate iron through ingestion of tissue and red blood cells. We differed from the contributor's morphologic diagnosis only in severity, though admittedly, this is separate and distinct from clinical effect whereby even mild processes within the brain can have marked effects.

While the periphery of this section does not have many significant changes, it does provide an opportunity to discuss some of the challenges of processing nervous tissues for histologic section as discussed by Dr. Koehler in her preconference. In some cases, autolysis will soften the brain and chattering or tearing of tissue is inevitable. One quick test for autolysis is to examine glial cells in the parenchyma – well-preserved/fixed tissue should have small, round glial cells. The submitted tissue in this case is fixed appropriately, but possibly had minor deviations in temperature, reagent mixture, and/or workflow that led to artifactual separation – the difference may be as small as a few seconds or a few degrees Fahrenheit! We say all of this to emphasize that the production of quality slides is a laborious process and histology technicians all around the world work minor miracles every day to allow us to do the work that we do. We appreciate what the contributor provides here and provide this note as a reference to those starting out on their neuropathology journey.

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CASE III:

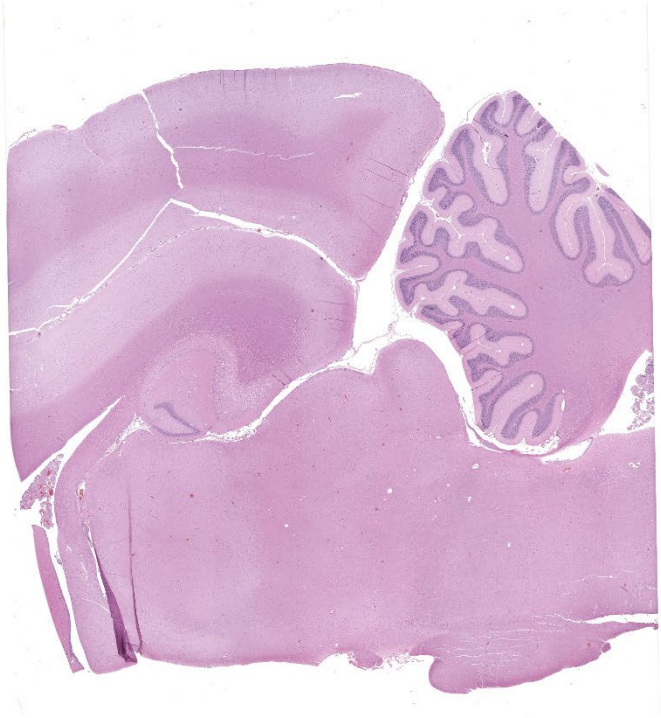
Signalment:
8-year-old spayed female domestic shorthair cat (*Felis catus).*

History:
The patient presented for an approximately 72-hour progressive history of seizures manifesting as lip twitching, masticatory movements, excessive vocalization, blindness, and ptyalism. Interictal behavioral changes of restlessness, loss of environmental awareness and elevated pain as perceived by the owner were also reported. At first presentation (48 hours), a focal, full thickness ulcer was observed on the right cranial tongue. Physical examination was otherwise unremarkable. Complete blood cell count and blood chemistry were also unremarkable and the patient was sent home with robenacoxib and buprenorphine for pain control. At the final presentation (72 hours), the patient was reported to be hyperthermic and extremely agitated. While attempting to place an IV catheter for treatment, the patient underwent acute cardiac arrest.

Gross Pathology:
There were no remarkable gross findings within the formalin fixed brain. The right rostral tongue had a focal, linear, well-demarcated, purple to dark purple ulceration that measured 9 mm x 5 mm x 2 mm. The left lateral aspect of the tongue had a linear, red to dark red focus that measured 5 mm x 2 mm.

Laboratory Results:
Feline Herpes Virus - 1 PCR: Negative.
Snap FeLV/FIV Combo Test: Negative.

Microscopic Description:
Cerebrum, hippocampus: Confined to the hippocampus and most prominent within CA1, scattered neurons are characterized by swelling, vacuolation, prominent nissl substance or are shrunken and angular with hypereosinophilic cytoplasm and fading or pyknotic nuclei. Glial cells are increased in number with frequent reactive astrocytes. Microglial cells frequently flank neuronal debris



A section of diencephalon and anterior cerebellum is submitted for examination. At this magnification, the prominent neurons of the hippocampus are difficult to see (with the exception of those of the dentate gyrus). (HE, 8X)

and are occasionally within degenerate and necrotic neurons (neuronophagia). There is proliferation of small caliber blood vessels lined by hypertrophic endothelium with rare perivascular aggregates of small numbers of mononuclear cells and edema. Neurons occasionally have basophilic glassy, nuclei.

Contributor's Morphologic Diagnosis:
Cerebrum, hippocampus: Neuronal degeneration and necrosis, moderate to marked, regionally extensive and bilateral, acute with neuronophagia, astrocytosis, gliosis, microvascular proliferation, perivascular inflammation.

Other significant histological findings (slides not submitted):
Tongue: Full thickness ulceration, marked, multifocal, acute with necrosuppurative glossitis, muscular necrosis, neuritis and abundant intralesional bacterial colonies.

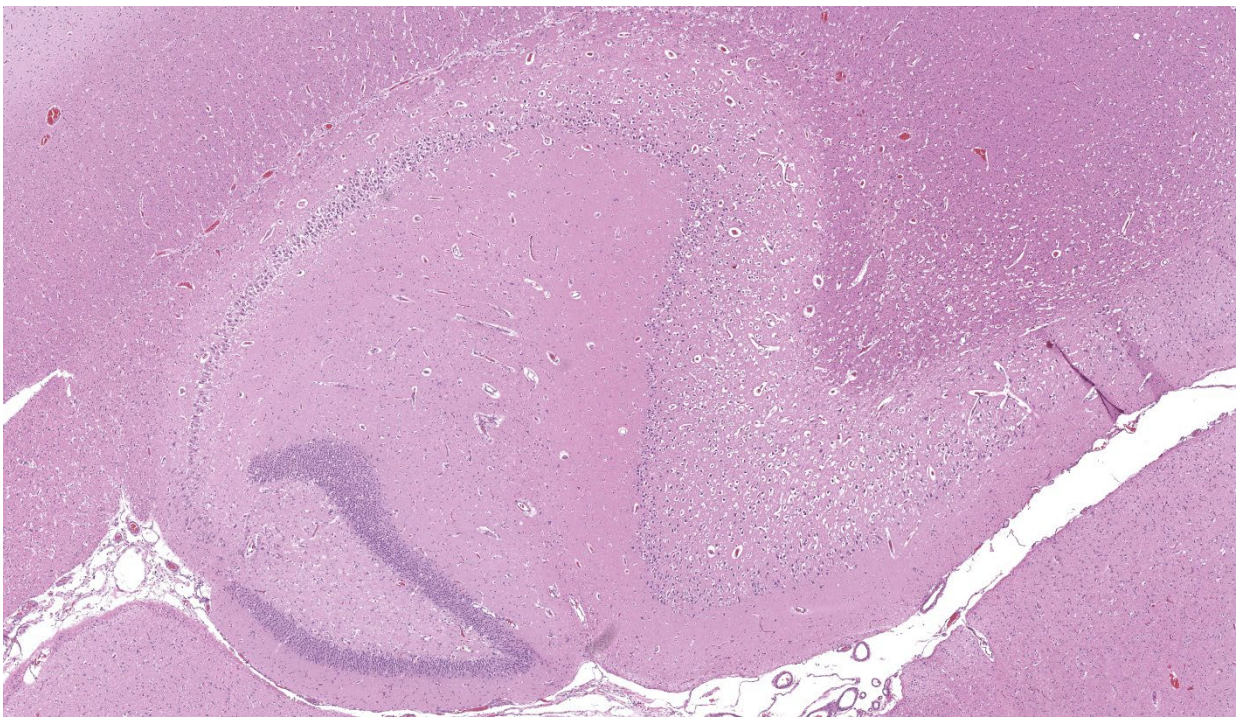
Condition: Feline hippocampal and piriform lobe necrosis (FHN)

Contributor's Comment: A diagnosis of feline hippocampal and piriform necrosis (FHN) was given based on clinical presentation and histopathologic lesions consistent with those described in the literature and previous case reports. FHN is an acute onset neurologic disorder characterized clinically by rapidly progressive, often refractory focal, complex-partial and/or generalized tonic-clonic seizures. Interictal behavioral changes reflective of limbic dysfunction are common: loss of environmental awareness, agitation/aggression, hyperesthesia, ptyalism, pyrexia, urinary retention and hyperexcitability are described.[5,7,8,15] FHN has been reported in several countries: Australia, Austria, England, Finland, Italy, Switzerland, and the

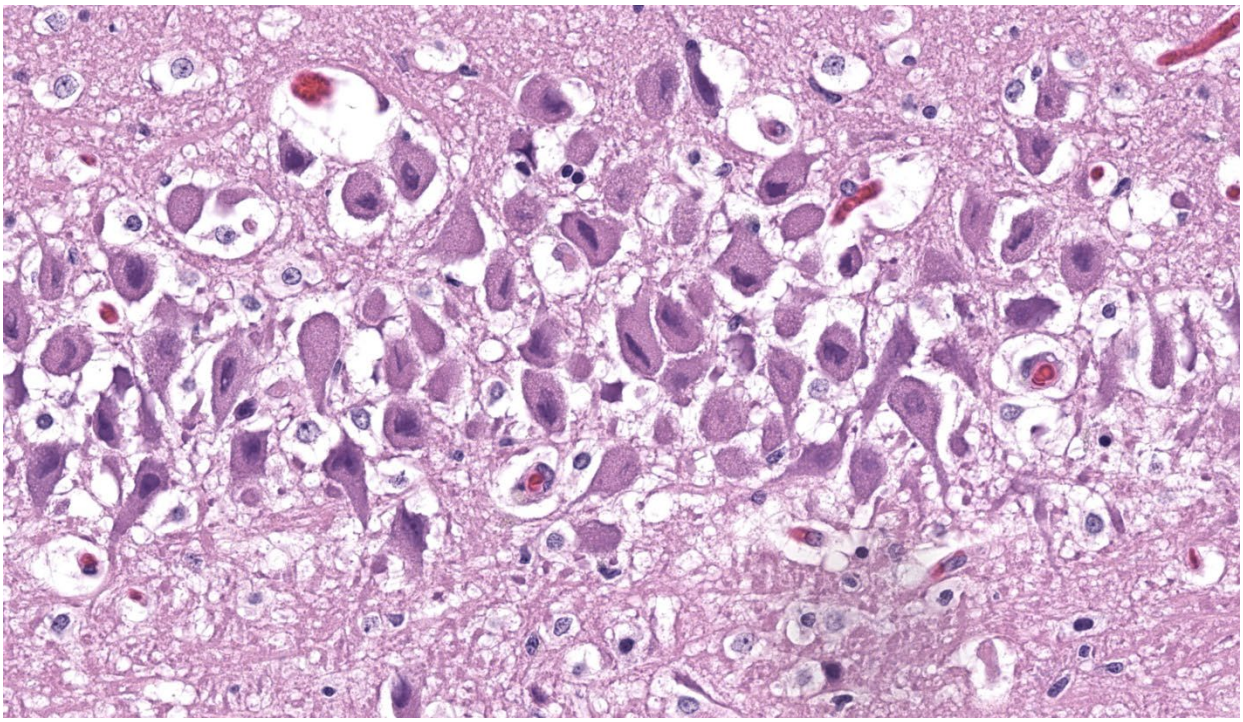
United States.[4,7,9,15,17,19,22] No sex, breed nor age disposition has been identified.

Neurologic examination and laboratory findings are non-specific. Therefore, clinical diagnosis is often by exclusion, coupling clinical presentation with Magnetic Resonance Imaging (MRI) findings (the hippocampus and piriform lobes are T2 and FLAIR hyperintense, T1 hypointense, +/- contrast enhancement).[4,7,9,15,17,19,22] Gross examination of the brain is regularly unremarkable, however, accentuated vascular structures or mild malacic changes in the piriform lobe and hippocampus have been described.[1,7] Definitive diagnosis of FHN is made via histopathology. Microscopically, FHN is characterized by varying degrees of acidophilic neuronal necrosis confined to the hippocampus and piriform lobe structures. The distribution of lesions is bilateral and symmetric, and tend to be most prominent within CA1. Microvascular proliferation, microgliosis/neuronophagia and astrocytosis are also common features. Lymphohistiocytic perivascular inflammation, and central chromatolysis may also be present, though less frequently.[5,7]

Aforementioned, the exact pathogenesis of FHN is yet to be elucidated. Epileptogenic, immune-mediated, infectious, toxic, vascular, structural, degenerative and paraneoplastic processes have all been proposed.[3,4,7,9,10,15,19,20,22] Given the shared clinical presentation and histologic findings of FHN across a potpourri of suggested etiologies, some authors hypothesize that FHN is more suggestive of a pathogenic neurolocalization as opposed to a specific entity.[19] Hippocampal pyramidal neurons are particularly susceptible to endogenous excitotoxicity, so it seems conceivable that alterations in metabolism, function and/or architecture of this neuroanatomical region could uncouple the regulatory mechanisms of neurotransmitter metabolism (hypothesized to be glutamate



Hippocampus, cat. Neurons of the hippocampal regions CA1-CA3 lack significant differential staining, but those of the dentate gyrus stain normally. (HE, 37X)



Hippocampus, cat. Neurons of the hippocampal regions CA1-CA3 are degenerating (with marked cytoplasmic vacuolation and condense nuclei) and few overtly necrotic (hyperchromatic cells with pyknotic nuclei) are present. (HE, 750X)

and/or aspartate),[2,5] leading to regionally extensive edema, ischemia and necrosis.

The scope of comparative pathology of the FHN phenotype is relatively narrow. Bilateral ischemic changes have been reported in dogs with refractory epilepsy and/or prolonged seizures.[11,12] However, the topic represents an exciting area of immunology and neuropathology research. The clinical presentation and histologic findings described in FHN are similar to those described in human Autoimmune Limbic Encephalitis (ALE).[3,10,13,20] Many cases of ALE are defined by aberrant production of antibodies against the neuronal cell membrane antigens.[3,10,13,16,20,21] Antibodies against voltage-gated potassium channel complex (VGKC) extracellular domains of leucine-rich glioma-inactivated 1 (LGI1) and contactin-associated protein-like 2 (CASPR2) are some of the most prevalently isolated, which together have been defined as LG1 encephalitis. Voltage-gated potassium channels (VGKCs) represent a group of signaling proteins capable of modulating a wide variety of synaptic functions, most prominently neuronal excitability and neurotransmitter release. Dysfunction or damage to the VGKC complex carries the potential of hyperexcitability, seizure and resulting excitotoxicity. In veterinary literature, recent studies have demonstrated the presence of anti-LGI1 antibodies in cats with clinical presentations, MRI findings and histologic hippocampal necrosis/sclerosis that parallel human LG1 encephalitis. Clinically, this constellation of findings has been termed feline complex partial seizures with orofacial involvement (FEPSO). FEPSO may represent an immune-mediated etiology of FHN, and carries the potential to serve as a spontaneously occurring animal model of human LG1 encephalitis.[3,10,19]

Unfortunately, feline epilepsy is often enigmatic as many epileptic cats have atypical seizures, genetic markers for feline epilepsy

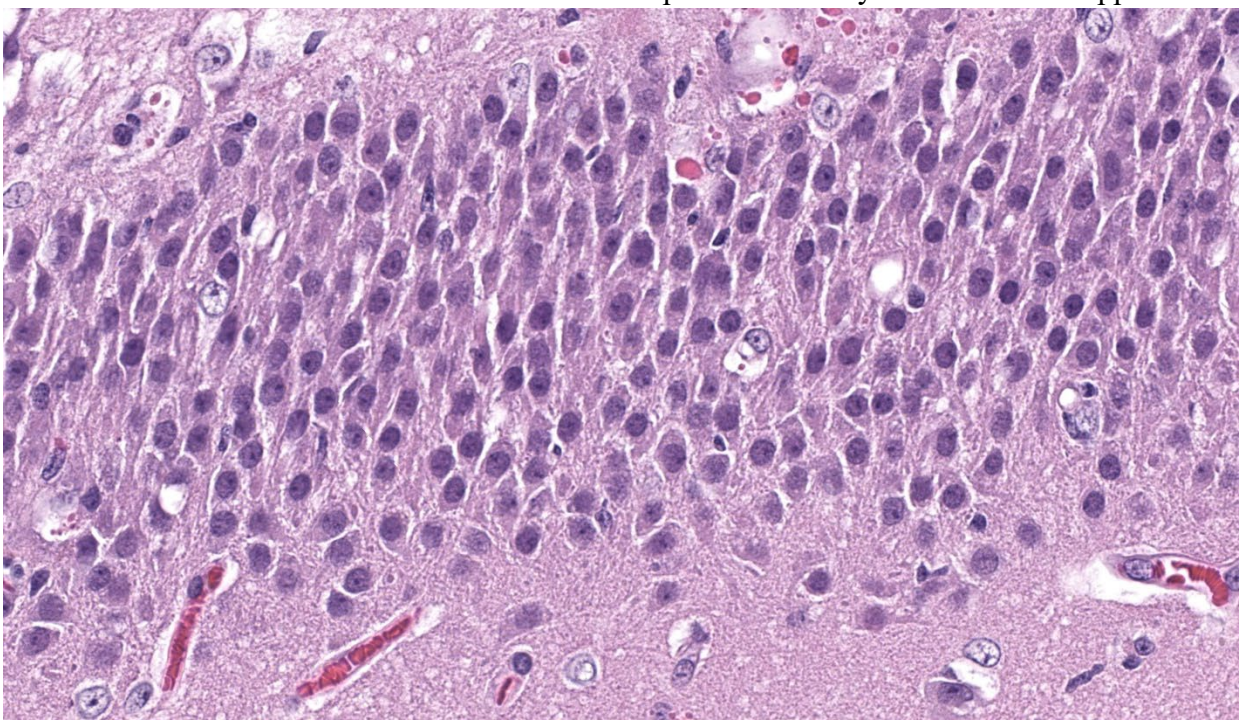
are poorly described, and a complete neurologic work up is often not performed.[17] Therefore, these challenges hinder a more thorough depiction of the processes underlying the FHN phenotype, resulting in ambiguous diagnoses which muddle antemortem characterization and histopathologic correlation (when available). Fortunately, growing awareness of FHN as a component in feline epilepsy will hopefully chaperone further exploration and clarification on the likely heterogeneous FHN phenotype.

In the presented case, several neurons had smudgy to glassy, basophilic appearance prompting PCR for feline herpesvirus-1, which was negative. Thus, the histogenesis remains unclear. FeLV/FIV status for this animal was negative and the cat was up to date on vaccinations and was housed solely indoors, decreasing suspicions for rabies and/or *Toxoplasma* spp. The ulceration observed on the tongue was attributed as a sequelae to an unobserved seizure.

Contributing Institution:
Colorado State University Veterinary Diagnostic Laboratory
Fort Collins, CO
https://vetmedbiosci.colostate.edu/vdl/

JPC Morphologic Diagnosis: Hippocampus: Neuronal degeneration and necrosis, segmental, with reactive astrocytosis and spongiosis.

JPC Comment: Although the lesion in this case is somewhat understated relative to the other slides in this conference, the contributor's summary is anything but, and wonderfully summarizes the current literature on this entity (and we appreciate the callback to previous WSC!). The sagittal sectioning of this brain provides another opportunity to check for autolytic change, using the granular and molecular layer interface as a good anchoring point – these layers should be in apposition



Diencephalon, cat. Neurons of the dentate gyrus for comparison. (HE, 750X)

with little vacuolation and condition of cerebellar neurons should also be evaluated.[23] The slide is well-preserved with little artifact present.

The hippocampal changes in this case are better appreciated with a matched animal control, or at least, review of pertinent veterinary literature[24] to brush up on the various subfields of the cornu ammonis (CA). Neuronal necrosis within CA1 was appreciable as shrunken, eosinophilic cells with pyknotic nuclei, though Dr. Koehler reminded conference participants that the ventral hippocampus can also have darker neurons as an artifact secondary to tissue manipulation and excessive pressure, and that these should be carefully distinguished. Other corroborating evidence such as reactive astrocytes (with increased cytoplasm, peripheralized chromatin, and occasional doublets representing division) also confirmed that changes observed were real. We captured this distinction of 'reactive' in our morphologic diagnosis as we feel that it emphasizes not only the cellular changes of astrocytes, but the increased cell number elicited by this process.

This case also had good examples of simultaneous cytotoxic and vasogenic edema. This is possibly attributed to seizure episodes, though glutamate effects are more localized to CA3 and changes in this cat were attenuated. Likewise, seizure episodes might also generate lesions in other portions of the brain (e.g. head trauma and hemorrhage) which are absent in this section, though the effects of global hypoxia and cytokine generation might explain vascular-centered edema in this brain. We also briefly discussed the smudgy inclusions within neurons noted by the contributor – these likely reflect clumped protein aggregates and cellular dysfunction (unfolded protein response and integrated stress response)) and should not be confused with viral inclusion bodies, to include Negri bodies from rabies virus.[18]

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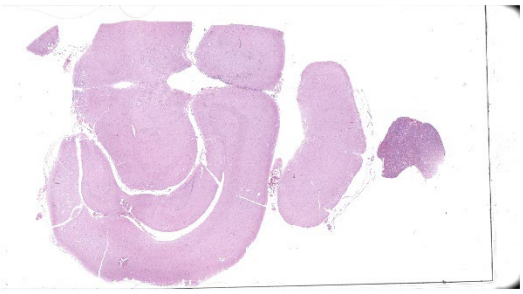
CASE IV:

Signalment:
Adult, female intact, North American beaver (*Castor canadensis*)

History:
The beaver was found in a creek bed and animal control found the beaver lethargic and unresponsive. Following capture, the animal was reported to be "rolling in the crate". The beaver was brought to a local wildlife rehabilitation center where she was reported to be neurologic and ataxic while walking with impaired vision. Euthanasia was elected and the animal submitted for necropsy exam.

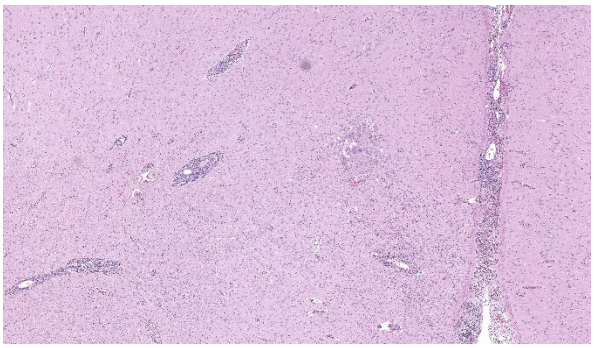


Brain, beaver: One hemisection of diencephalon and one of brainstem and pituitary gland are submitted for examination. At low magnification, perivascular cuffs and areas of pallor are seen in the cerebrum and thalamus. (HE, 6X)

Gross Pathology:
A 7.14 kg intact female beaver (*Castor canadensis*) was submitted for necropsy, 3 days postmortem and in fair postmortem condition. The nutritional state was fair based on small amounts of visceral and subcutaneous adipose tissue, and muscling was adequate. The lungs, heart, liver, kidneys, spleen, and gastrointestinal tract were unremarkable. The stomach contained a moderate amount of pale tan and fibrous digesta. The small intestine contains a moderate amount of tan to grey, mucoid digesta. The large intestine and rectum contain an abundant amount of well-formed feces.

Laboratory Results:
Rabies antigen and highly pathogenic avian influenza PCR of fresh brain was negative. Canine Distemper IHC had variable immunoreactivity in the nucleus of neurons and astrocytes in the brain (interpreted as artifact) and negative by PCR on formalin fixed, paraffin embedded brain and lung.

Microscopic Description:
Brain, cerebrum: Examined are sections of cerebrum, hippocampus, and mid-brain. Predominately affecting the left hemisphere of the cerebrum, numerous eosinophils, macrophages, lymphocytes and plasma cells expand the perivascular and meningeal space. Abundant eosinophils and fewer plasma cells, and increased glial cells are scattered throughout the neuropil of affected areas. Embedded within the neuropil of the white matter are cross and tangential sections of



Cerebrum, beaver: The meninges and Virchow-Robins spaces are expanded by large number of lymphocytes, macrophages and eosinophils, and multifocal migration tracts are present within the parenchyma. (HE, 56X)

larval nematodes. The nematodes are approximately 70 µm in diameter with a 2.5 um thick cuticle and prominent lateral chords and lateral alae. The pseudocoelom contains coelomyarian musculature and digestive tract composed of uninucleate columnar cells. Scant inflammatory cells surround the nematodes. Multifocally within the grey and white matter are foci of necrosis characterized by disruption, loss and vacuolation of the neuropil and presence of macrophages and Langerhans type multinucleated giant cells with fewer lymphocytes and glial cells, and scant plasma cells. Throughout the cerebrum, there are rare necrotic neurons and neurons surrounded by glial cells (satellitosis). The white matter of the midbrain is rarified with bands of eosinophilic, fibrillar material, increased clear space, glial cells and astrocytes. Rare neurons within the adjacent gray matter are variably replaced by homogenous to coarsely stippled basophilic mineral.

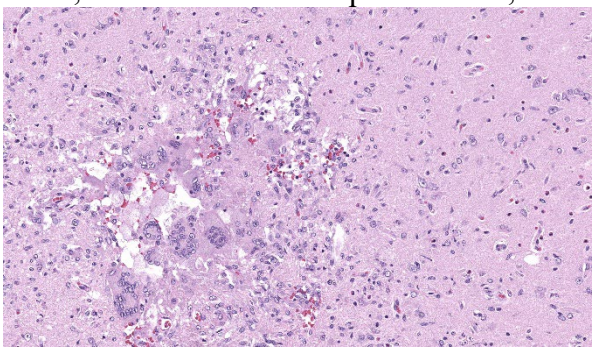
Brain, brain stem: Section contains histologically unremarkable brain stem.

Brain, pituitary, pars distalis: Section contains histologically unremarkable pars distalis.

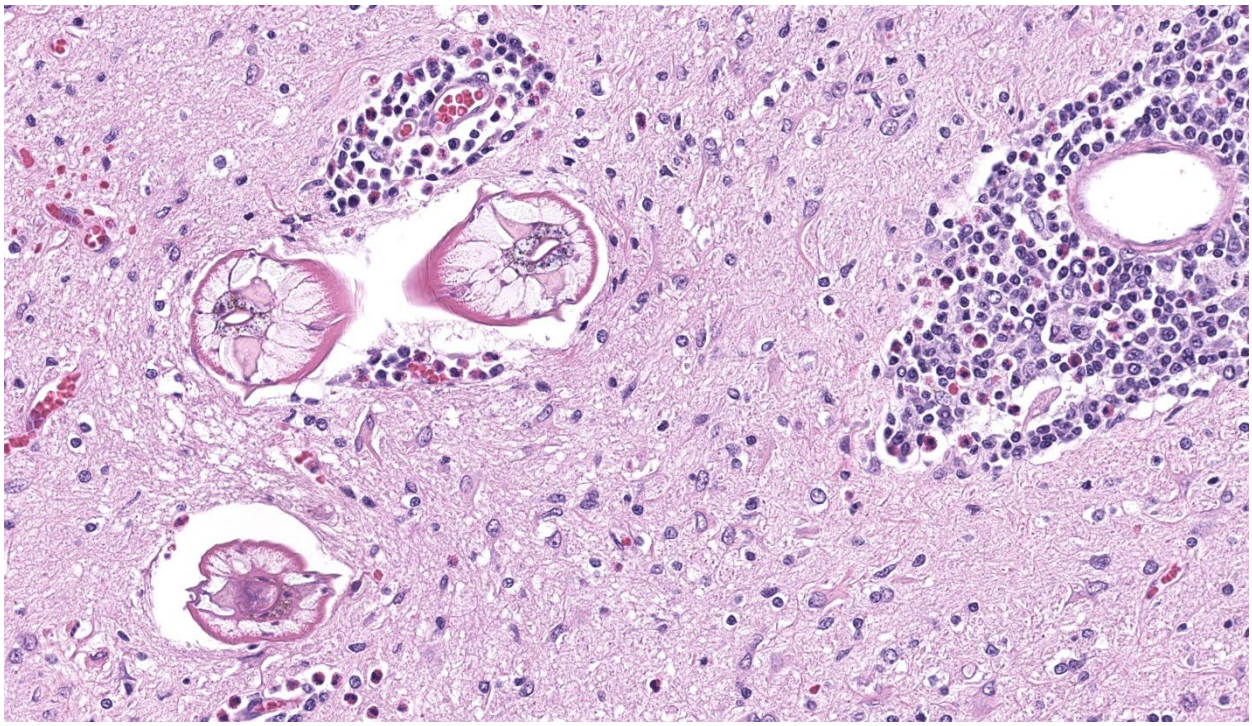
Contributor's Morphologic Diagnosis: Brain, cerebrum: Eosinophilic and necrogranulomatous meningoencephalitis, chronic, severe, with gliosis and nematode larvae

Brain, midbrain: White matter degeneration, chronic, moderate, with astrogliosis and astrocytosis (glial scar)

Contributor's Comment: *Baylisascaris* species are nematodes that share the order Ascaridia with *Toxocara canis* and *Toxocara cati*. The most widespread and ubiquitous *Baylisascaris* is *B. procyonis*. Raccoons (*Procyon lotor*) and dogs (*Canis familiaris*) are the definitive hosts of *B. procyonis,* although numerous species of mammals and birds have been identified as intermediate hosts,[3] including a report in two American beavers (*Castor canadensis*).[2] In raccoons, *B. procyonis* is confined to the intestines and rarely causes disease.[3] In definitive hosts, eggs hatch and develop into adults in the intestine and subsequently females lay eggs that are passed into the environment with feces, continuing the cycle. Consumption of contaminated feces or an infected host may cause reinfection in the definitive host or infection in intermediate hosts. In intermediate hosts, larvae do not develop into adults, but



Cerebrum, beaver: The meninges and Virchow-Robins spaces are expanded by large number of lymphocytes, macrophages and eosinophils, and multifocal migration tracts are present within the parenchyma. (HE, 56X)



Cerebrum, beaver: Adjacent to a vessel cuffed by large number of lymphocyte, macrophages and eosinophils, there are three cross sections of a larval ascarid nematode with a thin cuticle with lateral alae, a pseudocoelom, polymyarian-coelomyarian musculature, prominent lateral chords, and a small intestine lined by multinucleated cells. (HE, 480X)

can migrate to numerous tissues such as the brain (neural larval migrans, NLM), eye (ocular larval migrans, OLM), and viscera (visceral larval migrans, VLM) where they may cause substantial disease and death.[3] The precise pathogenesis of larval migrans is unclear, however, migration through the intestinal epithelium into the portal vasculature or lungs has been proposed.[7]

Compared to *Toxocara* spp., *B. procyonis* is particularly pathogenic due to aggressive tissue migration,[6,9] continued growth and development of larval migrans,[6,9] and release of tissue damaging proteins and host eosinophilic toxins.[4,6,8]. Most often, lesions are nodular foci consisting of larvae encased in granulomas with substantial eosinophilic inflammation. In this case, there was substantial meningoencephalitis and there were granulomas, but larvae were not observed encased in a granuloma (perhaps as a function of cut).It has been reported that encapsulation of larva takes longer in the central nervous system.[7]

B. procyonis is reported to be widespread in raccoons in North America with a prevalence between 37 and 82% of raccoons affected.[6,11] *B. procyonis* has also spread through Europe with the introduction of American raccoons.[12] *B. procyonis* is recognized as zoonotic and it can cause fatal visceral and neural larval migrans in children, though ocular migrans is more common in adults.[3] In a survey of 150 adults from California, as many as 7% of non-symptomatic adults tested seropositive, suggesting that the prevalence in human populations may be higher than previously thought.[13]

At least nine species of *Baylisascaris* have been described (Table 1), with the most notable being *Baylisascaris procyonis* due to its destructive larval migration. It is also the only known species of *Baylisascaris* to infect humans. While reports of larval migrans in

Baylisascaris procyonis are common, in other species confirmed disease in naturally infected paratenic hosts are rare (Table 1). However, all species of *Baylisascaris* are potentially pathogenic, as most species have been shown to experimentally infect and cause disease in rodents.[10]

In this case, the only other histologic findings were a mild eosinophilic and lymphoplasmacytic enterocolitis with a single, intraluminal, unidentified nematode egg in cross section and a focal lymphoplasmacytic interstitial nephritis with minimal eosinophils. Parasites are common in wildlife species, and the eosinophilic enterocolitis and intraluminal parasitic egg is consistent with a parasitic enteropathy. The clinical significance of these findings is unknown.

Table 1. *Baylisascaris* species and definitive hosts with reported larval migrans in natural infected paratenic hosts.

Baylisascaris spp.	**Definitive host(s)**	**Natural Paratenic Host**
Baylisascaris columnaris	Skunks	Primates[15]
Baylisascaris devosi	Fishers, martens, wolverines	No reports
Baylisascaris laevis	Marmots, ground squirrels	No reports
Baylisascaris melis	Badgers	No reports
Baylisascaris potosis	Kinkajou	No reports
Baylisascaris procyonis	Raccoon, dogs	Humans,[14] mammals, and birds[1]
Baylisascaris schroederi	Giant Panda	No reports
Baylisascaris transfuga	Bears	Moose[5]
Baylisascaris venezuelensis	Spectacled bear	No reports

Contributing Institution:
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Department of Microbiology, Immunology, and Pathology
https://vetmedbiosci.colostate.edu/vdl/

JPC Morphologic Diagnosis: Transverse cerebrum at the level of the thalamus: Meningoencephalitis, necrotizing, eosinophilic, and granulomatous, subacute, multifocal and asymmetric, marked, with gliosis and larval ascarids.

JPC Comment: The final case of this conference provides both overlapping and differing features in comparison to the *P. tenuis* meningoencephalitis observed in Case 2 in a sitatunga. Cross-sections of larval *Baylisascaris* were focal in the sections we reviewed, though the expansion of the leptomeninges and reactive astrocytes with distinct processes are a solid indication of a more clinically severe process that led to the decline of this animal. While both cases were necrotizing, there is a sizable eosinophil contingent as well as the presence of multinucleated giant cell macrophages which are conspicuous here. We considered the chronicity of this case at length – did the presence of multinucleated giant cells not indicate a transition to chronic inflammation? The presence of inflammatory cells within the neuroparenchyma (reminder from Case 1 discussion: the number of eosinophils in the brain is should still be zero) is an indicator of the breach of the blood-brain barrier, and the entry of large histiocytes should theoretically take longer given their size and circulating number. Dr.

Koehler stood fast on subacute chronicity, noting that the large numbers of eosinophils and macrophages can appear relatively quickly within the brain (within 72 hours) and that meningeal fibrosis was a better arbiter of the actual transition to chronic inflammation – this was not a feature of this case at all. Conversely, the large numbers of intact eosinophils argued against a longer time course as lifespan within tissue is several days on average and overall numbers should decline with time. Accordingly, the features of this case certainly straddle the line of acute and chronic, though the clinical history of 'Justin Beaver' (this animal's actual given name) leaves much information to our imagination and allows both camps to feel vindicated in their interpretation. Finally, we extend a special thank you to the contributor for their excellent summary (Table 1) of *Baylisascaris* across species and hope others will find it useful.

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