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Conference Moderator: Dr. Jim Raymond, Diplomate ACVP
Pathology Associates International
Charles River Laboratories
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CASE I – 03B5515 (AFIP 2941535)

Signalment: An adult American alligator (*Alligator mississippiensis*).

History: Between September and December of 2003, American alligators from several alligator farms in Louisiana died suddenly or showed various neurological signs including circling, ataxia, head and muscle tremor, and head tilt.

Gross Pathology: With the exception of gas-filled, empty gastrointestinal tracts and a diffuse thin pseudo-membrane on the colonic mucosa, no significant gross findings were noted.

Laboratory Results: All brain specimens taken from 13 alligators that showed the clinical signs were positive for West Nile virus (WNV) by RT-PCR. Viral isolation was successful from 10 out of the 13 brain specimens. Real-time PCR revealed a high viral load in a fecal sample. Immunohistochemistry for WNV showed strong immunoreactivity on the sections of brain, liver, pancreas, and small and large intestines.

Contributor's Morphologic Diagnosis: Colon: Colitis, heterophilic and granulomatous, multifocal, acute, moderate.

Contributor's Comment: The colonic mucosa is multifocally attenuated and fused with irregular paucity of colonic glands. The lamina propria is expanded with infiltration of moderate numbers of lymphocytes, plasma cells, and macrophages as well as heterophils. The inflammation often extends to the submucosa. The individual glandular epithelial cells are occasionally necrotic with pyknosis. Heterophilic exocytosis is evident. Some colonic glands are dilated with mucus and exfoliated degenerate epithelial cells. The submucosal lymphoid follicles are

hyperplastic with heterophilic infiltration. There is a luminal core composed of a large amount of mucus admixed with exfoliated degenerate epithelial cells, heterophils, various bacteria, and a small amount of fibrin. Some tissue sections contain severe heterophilic infiltration surrounding bacterial colonies in the submucosal lymphoid follicle.

Other major microscopic findings were heterophilic meningoencephalitis, necrotizing and heterophilic hepatitis, heterophilic and histiocytic splenitis, and necrotizing, heterophilic pancreatitis, and generalized heterophilic lymphoid folliculitis.

Since it first emerged in 1999, West Nile virus (WNV) infection has been established as a seasonal epidemic in North America. WNV generally circulates between mosquitoes and birds. The infected birds commonly have a high level viremia and serve as reservoir hosts. WNV infection has been reported in various species but primarily in warm-blooded animals. Recently, epizootic WNV infections in American alligators have been described from the states of Florida (2002) and Georgia (2003). Although the role of alligators in the transmission cycle of WNV infection is still largely unknown, there are concerns that these reptiles may be important regionally because they can develop high viremia and shed the virus in their feces. Immunohistochemistry for WNV confirmed that the viral antigens were located within the macrophages, intravascular monocytes, and intestinal epithelial cells in the colon. It is believed to be that alligators are initially infected by mosquito bites on the oral mucosa and then epizootics occur rapidly by orofecal transmission. In this case, the virus was detected from a fecal sample. In the report of the cases from Florida, the authors speculated that WNV in the horsemeat fed to the alligators might be the direct source of the infection among the alligators. However, it is considered unlikely because horses are the dead-end hosts of WNV infection with low numbers of viruses in the body after a short period of viremia. There have been 3 human cases of WNV infection, among workers on an alligator farm in Louisiana.

AFIP Diagnosis: Colon: Colitis, histiocytic and heterophilic, subacute, diffuse, moderate, American alligator (*Alligator mississippiensis*), reptile.

Conference Comment: West Nile virus (WNV) was first isolated from a woman in 1937 in the West Nile district of Uganda. Since then it has been reported in western Asia, the Middle East, Europe, southern Russia, and in 1999 in the United States. WNV is a member of the genus *Flavivirus*, family Flaviviridae, and is known to cause encephalitis in a wide variety of species, including humans, birds, horses, other mammals and reptiles.[3] Natural infections have been reported in bats, a chipmunk, a skunk, a domestic rabbit, reindeer[5] and several species of

squirrels.[4] Mice and rhesus monkeys have been infected experimentally. Interestingly, dogs, rabbits, guinea pigs, hedgehogs, and sheep do not develop encephalitis after experimental inoculation with WNV.[5]

As mentioned by the contributor, mosquito vectors transmit the virus among reservoir bird populations, and susceptible mammalian species are infected incidentally. A wide variety of native and exotic birds are susceptible, although infection typically does not cause clinical signs in most birds. However, it does result in unusually high mortality in crows. Gross lesions in birds include meningeal hemorrhage, multifocal pale myocardial foci, splenomegaly, mucosal hemorrhage in the small intestine, and white foci in the kidneys. In birds, the most severe histological lesion is hemorrhage in the cerebellar folia, with degeneration and necrosis of the cerebellar molecular layer and Purkinje cells.[4] Other lesions include lymphoplasmacytic meningoencephalitis, necrotizing myocarditis, and lymphoplasmacytic enterocolitis. Subacute inflammation may be seen in the spleen, kidneys, liver, adrenal glands, or pancreas.[6] In horses, WNV exhibits a pronounced, if not exclusive, CNS tropism. As with WNV infection in humans and squirrels, the brainstem is the most severely affected area in horses.[4] Horses typically have polioencephalomyelitis, with prevalent involvement of the lower brain stem and ventral horns of the thoracolumbar spinal cord.[7] WNV infections in humans are usually mild, with affected individuals exhibiting non-specific flu-like symptoms. Less than 15% of infected humans develop more severe forms of the disease, such as meningoencephalitis, hepatitis, pancreatitis, or myocarditis. Fatalities are more common in humans over the age of 50 and often a result of severe central nervous system disease.[8]

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CASE II – SA787-04 (AFIP 2937490)

Signalment: Twenty-day-old Ross broiler chicken (*Gallus domesticus*).

History: A large number (exact number unknown) of chickens died with symptoms of paralysis and incoordination. Parent flock young (less than 30 months old).

Gross Pathology: Negative, except for dehydration and nephrosis.

Laboratory Results: Serum from the affected chicks as well as from the parent flock tested negative for the presence of antibodies against Avian Encephalomyelitis virus (AEV) using the Enzyme Linked Immunosorbent Assay (ELISA) test.

Contributor's Morphologic Diagnoses: Multiple tissues presented for examination, including cerebrum, cerebellum, medulla oblongata (some sections), proventriculus, ventriculus (some sections) and pancreas.
1. Brain: Encephalitis, lymphocytic, subacute, multifocal to coalescing, severe with neuronal degeneration and necrosis, gliosis and perivascular lymphocytic infiltration. Neuronal degeneration and necrosis are characterized by chromatolysis and eosinophilic discoloration of some nuclei, which was particularly severe in the Purkinje cells of the cerebellum.
2. Proventriculus and ventriculus (some sections): Lymphocytic infiltration, multifocal, mucosal, submucosal and intermuscular, mild to moderate.
3. Pancreas: Lymphocytic infiltration, interstitial, multifocal, mild to moderate.

Contributor's Comment: The history of a high morbidity and a high mortality in young 20-day-old chickens, with neurological signs of paralysis and incoordination as well as severe neural lesions characterized by lymphocytic encephalitis with marked neuronal degeneration and necrosis, are consistent with the lesions described in the central nervous system of birds due to avian encephalomyelitis

virus (AEV), a Picornavirus. The lymphocytic infiltrations in the proventriculus, ventriculus and pancreas provide further support for the diagnosis.[1]

The high mortality and severity of the lesions was probably the result of a high susceptibility in the affected chicks and their parents as supported by the negative ELISA test results.[1]

The most sensitive method, and the method of choice, for the detection of AEV appears to be the inoculation of serologically negative chickens at 2 weeks of age with infected brain tissue culture cells. These chickens should be observed for typical symptoms and positive serological reactions with the ELISA or immunodiffusion (ID) tests. In addition, brain, proventriculus and pancreas can be examined by indirect immunofluorescence and for the presence of typical histopathological changes.[1]

Picornavirus particles in crystalline array of 22-25 nm in diameter have been identified within the cytoplasm of Purkinje cells from infected chickens.[2,3] The AEV, a single-stranded RNA virus, has the capacity to induce nuclear DNA fragmentation with apoptosis in embryonal nerve cells through its structural VP3 – and non-structural 2C proteins.[4,5]

Avian encephalomyelitis (AE) should be differentiated from a number of diseases with similar clinical signs in young chicks such as Newcastle disease, equine encephalomyelitis virus infection, as well as from certain nutritional imbalances such as rickets, encephalomalacia and riboflavin deficiency. Newcastle disease in 1-3 week-old chicks can be distinguished from AE by peripheral chromatolysis in neurons; in contrast, AE results in central chromatolysis within neurons and multifocal infiltrations of lymphocytes within the proventriculus and the pancreas.[1] Rickets, encephalomalacia and riboflavin deficiency cause very dissimilar lesions which cannot be confused with AE.[1]

Although AE occurs almost worldwide, the virus has a limited host range, and the incidence is very low due to vaccination and relatively high levels of immunity in commercial chicken and turkey production systems. Fatal natural infections have been reported in pheasants and quail[1] and also recently in pigeons in Turkey with typical symptoms and lesions.[6] Experimental infections of guinea fowl and ducklings have also been reported.[1]

Avian encephalomyelitis virus is most closely related to the human hepatitis A virus.[7] All isolates of AEV are serologically similar, but two distinct pathotypes of the virus exist. The natural field strains are enterotropic, and infection occurs via the oral route with fecal excretion of the virus. These strains have a low pathogenicity and only cause neurological signs in vertical or horizontal infection of

susceptible chicks at a young age. Embryo-adapted strains represent the second group of pathotypes which are highly neurotropic by intracerebral inoculation and parenteral infection. These require high doses for oral infection and do not spread horizontally.[1]

AFIP Diagnoses: 1. Brain: Encephalitis, lymphoplasmacytic, multifocal, mild, with gliosis, and neuronal degeneration and necrosis, domestic chicken, avian.
2. Pancreas: Lymphoid infiltrates, multifocal, moderate.

Conference Comment: Avian encephalomyelitis virus (AEV) is a non-enveloped icosahedral single-stranded RNA virus of the Picornaviridae family and is pathogenic to young chickens, pheasants, quails, and turkeys, resulting in reduced hatching, ataxia, and tremors in 1-7 day old chicks.[5] Transmission may be vertical, fecal-oral, or via fomites. The only gross lesions associated with avian encephalomyelitis (AE) are areas of pallor in the tunica muscularis of the ventriculus. Histological lesions occur in the central nervous system (not the peripheral nervous system) and some viscera. Lesions in the CNS include diffuse nonsuppurative encephalomyelitis, Purkinje cell degeneration and gliosis in the molecular layer, and central chromatolysis, especially of large neurons in the midbrain. Dense aggregates of lymphocytes in the muscular wall of the proventriculus are pathognomic.[1] Similar lesions occur in the ventriculus muscle, myocardium, and pancreas. Although lymphoid nodules are normally found in the pancreas, in animals with AE, these nodules will be increased in number two to three fold.[1] Some common Picornaviruses include the following:[8]

Virus	Primary species affected	Disease
Aphthovirus		
FMD viruses	Ruminants, swine	Foot-and-mouth disease
Enterovirus		
Swine vesicular disease virus	Swine	Swine vesicular disease
Porcine enterovirus-1	Swine	Polioencephalomyelitis
Avian enteroviruses	Chickens	Avian encephalomyelitis
	Ducks , turkeys	Hepatitis
Coxsackieviruses	Humans	Aseptic meningitis, myocarditis, poliomyelitis
Cardiovirus		
Encephalomyocarditis virus	Swine, elephants	Encephalomyocarditis
Theiler's murine encephalomyelitis virus	Mice	Murine polioencephalomyelitis

Rhinovirus

Bovine rhinovirus	Cattle	Mild rhinitis
Human rhinovirus	Humans	Common cold

Hepatovirus

Simian hepatitis A virus	Monkeys	Hepatitis
Human hepatitis A virus	Humans	Hepatitis

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CASE III – PA 4121 (AFIP 2943312)

Signalment: 8 year old, male castrate Pug dog.

History: This dog presented with a progressive history of weight loss and poor doing. Diarrhea developed later in the clinical course. Despite aggressive clinical supportive measures, the animal continued to deteriorate and was euthanized.

Gross Pathology: The kidneys were bilaterally enlarged, pale, firm and somewhat gritty on cut surface. No additional gross findings were specified.

Laboratory Results: Proteinuria was reported without additional specification/quantification.

Contributor's Morphologic Diagnoses: 1. Glomerular amyloidosis, global and diffuse, marked, with additional mild, patchy, interstitial (peri-tubular) amyloid deposits.
2. Tubular proteinosis, patchy to diffuse, moderate.
3. Interstitial nephritis, lymphoplasmacytic, patchy, mild.
4. Interstitial fibrosis, patchy, mild-moderate.
5. Tubular mineralization, multifocal, mild-moderate.
6. Vascular thrombosis, multifocal (some sections).

Contributor's Comment: The pale, amorphous, eosinophilic material effacing the architecture of most glomeruli was confirmed as amyloid via strong positivity under fluorescence with Thioflavin T staining.

Amyloidosis is well described in the canine. Although familial renal amyloidosis is reported in several breeds (Shar Pei, Beagle), concurrent neoplasia or chronic inflammatory disease is detected in over half of affected animals. Dogs often present with progressive protein-losing nephropathy and frequently demonstrate the nephrotic syndrome, including ascites, peripheral edema and hypercholesterolemia. A thromboembolic phenomenon is seen in up to 40% of affected dogs, and this lesion is seen in some of the submitted sections. Amyloid was not noted in a limited number of other organs submitted with this case, nor was an underlying chronic inflammatory or neoplastic disorder recognized.

The primary clinical differentials in dogs that present with renal associated protein loss include primary congenital glomerulopathy, described in the Samoyed, Bull Terrier and English Cocker Spaniel, immune-mediated glomerulonephritis, also known to have breed predilection, including Bernese Mountain Dogs and Soft-coated Wheaten Terriers and occasional functional renal tubular transport disorders.

The prognosis for dogs with renal amyloidosis is quite guarded, and most dogs die or are euthanized shortly after diagnosis.

AFIP Diagnoses: 1. Kidney: Amyloidosis, glomerular, diffuse, global, severe and interstitial, multifocal, mild, with tubular proteinosis, Pug, canine.
2. Kidney: Nephritis, interstitial, lymphoplasmacytic, chronic, multifocal, moderate.
3. Kidney, large pelvic vein: Thrombus, organizing, with mineralization.

Conference Comment: Amyloid, an insoluble fibrillar protein with a beta-pleated sheet conformation, is deposited between cells in various tissues. With progressive accumulation it encroaches on and produces pressure atrophy of adjacent cells. On standard tissue sections stained with H&E, amyloid appears as an amorphous, eosinophilic, hyaline, extracellular substance. It is congophilic, with apple green birefringence when polarized.[5]

There are three main types of amyloid protein: amyloid light chain (AL); amyloid-associated (AA); and beta-amyloid (Aß). AL protein is derived from plasma cells and contains immunoglobulin light chains, which may be complete immunoglobulin light chains, the NH_2-terminal fragments, or both. It is commonly seen in association with immunocyte dyscrasias, particularly multiple myeloma. AA protein is derived from serum amyloid-associated (SAA) protein that is synthesized in the liver, and is associated with chronic inflammatory conditions. Aß amyloid is found in the cerebral plaques of human patients with Alzheimer disease. Amyloidosis, a heterogeneous group of disease processes that result in the deposition of amyloid, may be classified as localized or systemic (generalized). Examples of localized amyloidosis include cerebral plaques in Alzheimer disease, islet associated amyloid polypeptide (IAPP) with type II diabetes, and some prion diseases. Systemic or generalized amyloidosis can be further classified as primary or secondary. Primary amyloidosis is associated with immunocyte dyscrasias, while secondary amyloidosis occurs as a complication of an underlying chronic inflammatory disease. [5]

Regardless of the inciting cause or type of amyloid, amyloidosis results from the abnormal folding of proteins, which are deposited as fibrils in extracellular tissue and disrupt normal tissue function. In this case, glomerular filtration was almost certainly severely compromised and resulted in proteinuria. Glomerular amyloid deposition initially causes selective loss of albumin, but as the disease progresses, large protein molecules (globulins) also may be lost. If protein loss is severe, then hypoproteinemia and edema develop.[6] As a result of the protein-losing nephropathy, animals can become deficient in antithrombin III, resulting in an

increased tendency for thrombosis,[7] which may have been the cause of the thrombus formation in this case.

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CASE IV – KL-8 M3 (AFIP 2936433)

Signalment: 2-year-old, male North American opossum (*Didelphis virginiana*)

History: Wild opossum rescued by a rehabilitation program. The opossum presented with dyspnea and pleural and abdominal effusions. He died post-thoracocentesis.

Gross Pathology: Heart, lungs, adrenal gland and portions of kidney and liver were submitted in 10% neutral buffered formalin. Gross lesions were restricted to the lungs and liver. All lung lobes were collapsed, firm and rubbery. On cut section, there were multifocal to coalescing, pale tan to reddish-brown, 3 mm diameter, perivascular and peribronchial nodules (Figure 1). On cut sections of the liver, an enhanced reticular pattern was apparent, somewhat resembling a nutmeg liver (Figure 2).

Contributor's Morphologic Diagnosis: Lung, granulomatous pneumonia and catarrhal bronchitis, chronic, multifocal, marked with intralesional *Didelphostrongylus hayesi*, pulmonary smooth muscle hyperplasia and widespread atelectasis.

Contributor's Comment: The majority of the pulmonary parenchyma is atelectatic. Within alveoli, bronchioles and bronchi are numerous transverse and longitudinal sections of nematodes characterized by a cuticle, coelom, gastrointestinal tract with intraepithelial black pigment, and reproductive tract with ova, sperm and developing larvae. Associated with scattered free larvae in alveolar spaces are variable numbers of multinucleated giant cells, lymphocytes, plasma cells and fewer eosinophils. Numerous bronchial lumina contain large amounts of mucus admixed with free larvae. There are increased goblet cells distended with mucus lining most bronchial lumina. These bronchi are also associated with increased peribronchial mucous glands and prominent lymphoid nodules. Marked smooth muscle hyperplasia involving terminal bronchioles, alveolar ducts and less frequently, arterioles is apparent. Interstitial spaces around blood vessels are distended by proteinaceous fluid (edema). There are multiple foci of heterotopic bone in the pulmonary parenchyma, and mesothelial hyperplasia is present on all pleural surfaces. Some sections contain subpleural aggregates of lipid-laden macrophages with acicular (cholesterol) clefts. Additional histologic findings included chronic, multifocal, marked centrilobular hepatocellular degeneration and coagulation necrosis with fibrosis.

Didelphostrongylus hayesi, named in honor of Professor Frank A. Hayes who made great contributions to the study of North American wildlife diseases, is a common metastrongyloid lungworm in opossums.[1] In one retrospective study, pulmonary parasites were documented in 18/27 (67%) opossum necropsies with 13/18 (72%) being *D. hayesi*.[2] In another, *D. hayesi* larvae were found in 13/20 (65%) resident and 10/13 (77%) newly arrived opossums in an opossum care program.[3] Finally, *D. hayesi* was documented in 11/20 (55%) opossum necropsies, and contributed to the cause of death in 8/11 (73%) of these cases.[4] The parasite has an indirect lifecycle similar to other metastrongyloid nematodes, with the intermediate hosts being the terrestrial snails *Triodopsis albolabris* and *Mesodon perigraptus*.[1]

Histopathologic findings reported with *D. hayesi* infection are as seen in this case.[2-6] Pulmonary inflammation is associated with free larvae rather than intact adult nematodes. A feature of *D. hayesi* infected lungs is bronchiolar and alveolar ductular smooth muscle hyperplasia, which is reminiscent of the marked pulmonary arteriolar smooth muscle hyperplasia seen in *Aelurostrongylus abstrusus* infected cats. The hepatic lesions in this opossum and reported in others were consistent with right-sided heart failure secondary to verminous pneumonia-induced pulmonary

hypertension.[4] Foci of heterotopic bone have also been reported in the lungs of unparasitized opossums and are considered to be incidental findings.[5]

Although a complete blood cell count and differential were not performed in this case, opossums with *D. hayesi* display a regenerative erythrogram characterized by nucleated red blood cells and polychromasia.[4,6] Similar findings are reported in cats with *A. abstrusus*. However, it is unknown whether this is due to hypoxia or a direct stimulus from the lungworms.[6] In spite of the heavy parasitic burden in these opossums, a peripheral eosinophilia has not been reported.[4]

Evidence of endogenous lipid pneumonia was present in some slides. This lesion was present in 19/27 (70%) opossums from Louisiana, with 13/19 (68%) of these animals having pulmonary parasites.[2] In addition to *D. hayesi*, the pulmonary parasites included *Capillaria* sp. and *Besnoitia darlingi*. It is hypothesized that these parasites induce pulmonary irritation which results in type II pneumocyte hyperplasia and surfactant overproduction with subsequent accumulation in alveolar macrophages.

AFIP Diagnosis: Lung: Bronchopneumonia, histiocytic, multifocal, mild, with many adult and larval metastrongyles, bronchiolar mucus cell hyperplasia with abundant catarrhal exudate, atelectasis, and bronchiolar and arteriolar smooth muscle hypertrophy, North American opossum (*Didelphis virginiana*), marsupial.

Conference Comment: The contributor provides a thorough overview of *Didelphostrongylus hayesi* infection in opossum. Conference attendees discussed lung parasites in other species as listed below:[7]

Species/Parasite	Location	Lesion/Comment
Canine		
Filaroides osleri	Tracheal bifurcation	Luminal nodules
Filaroides hirthi	Bronchioles, alveoli	Subpleural nodules
Paragonimus kellicotti	Bronchioles	Subpleural nodules
Angiostrongylus vasorum	Vasculature	Chronic arteritis
Dirofilaria immitis	Vasculature	Chronic arteritis
Crenosoma vulpis	Sm. bronchi/bronchioles	Catarrhal bronchitis
Feline		
Aelurostrongylus abstrusus	Bronchioles, alveoli	Subpleural nodules
Paragonimus kellicotti	Bronchioles	Subpleural nodules
Dirofilaria immitis	Vasculature	Chronic arteritis
Syngamus laryngeus	Larynx	"gapeworm"

Equine		
Dictyocaulus arnfieldi	Bronchi	Eosinophilic bronchitis
Parascaris equorum	Interstitium	Migrating larval stages
Bovine		
Syngamus laryngeus	Larynx	Asia and S. America
Dictyocaulus viviparous	Intrapulmonary bronchi	Bronchitis, BALT hyperplasia, edema
Ascaris suum	Bronchioles, alveoli	Interstitial pneumonia
Ovine/caprine		
Dictyocaulus filaria	Small bronchi	Catarrhal bronchitis; BALT hyperplasia
Muellerius capillaries	Subpleural alveoli	Pulmonary nodules
Protostrongylus rufescens	Bronchioles	Pulmonary nodules
Porcine		
Metastrongylus apri	Bronchioles	Catarrhal bronchitis
Ascaris suum	Subpleural alveoli	Subpleural hemorrhage

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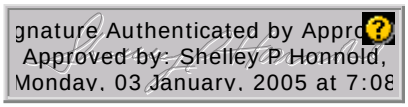

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