

The Armed Forces Institute of Pathology
Department of Veterinary Pathology
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Conference Moderator: MAJ Greg Saturday, Diplomate ACVP
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Armed Forces Institute of Pathology
Washington, DC 20306

CASE I – 04-01930 (AFIP 2948759)

Signalment: 2-year-old Baladi (native Egyptian breed) mare.

History: Baladi horses are used as dancing and parade horses. Two days post-dancing parade; this mare had acute progressive muscle stiffness and considerable distress with transient pyrexia. Shortly before euthanasia she had very stiff thigh muscles and occasional lateral recumbence.

Gross Pathology: The paraspinal lumbosacral muscles and the thigh muscles of both legs, especially the gluteal muscles, were moist, mildly swollen, and had massive patchy to regionally extensive pale streaks.

Contributor's Morphologic Diagnosis: Skeletal muscles: Acute degenerative and necrotizing myopathy with intermyofibrillar edema, moderate, multifocal.

Contributor's Comment: The current gross and histologic lesions are typical of equine recurrent exertional rhabdomyolysis (ERER). Polysaccharide storage disease was ruled out by negative PAS (periodic acid-Schiff) stain. ERER, or myoglobinuria, belongs to a group of muscle diseases called exertional myopathies. Exertional myopathies also include capture myopathy and porcine stress syndrome (malignant hyperthermia), characterized by a common initiating factor of intensive or exhaustive muscle activity.¹ ERER is characterized clinically by sudden onset of stiff gait, reluctance to move, and swelling of affected muscles groups especially gluteal muscles.¹ Diagnosis is based on clinical signs in association with an increase in serum creatinine kinase (CK), aspartate amino-transferase (AST), and in severe cases myoglobinuria. The exact etiology and pathogenesis of ERER are still unknown. Recently, a heritable defect in muscle cell calcium regulation of muscle

excitation-contraction coupling was suggested as the primary factor for this disease.² Few reported cases of ERER have an underlying polysaccharide storage myopathy; however, the extent of PSM in the majority of ERER is unknown.³

AFIP Diagnosis: Skeletal muscle: Degeneration and necrosis, acute, multifocal, moderate, Baladi horse, equine.

Conference Comment: Conference attendees discussed the differential diagnosis of the gross lesion, pale streaks in striated muscle. Differentials include: exertional rhabdomyolysis, equine polysaccharide storage myopathy (EPSSM), nutritional myopathy (Vitamin E/Selenium deficiency), ischemic myopathy due to anesthesia, plant toxicity (*Cassia occidentalis*, coffee weed), ionophore toxicity (monensin), clostridial myositis (malignant edema, or botulism), malignant hyperthermia-like syndrome, protozoal myopathy (*Sarcocystis* spp.), and Streptococcus-associated myopathy.

In this case, the top three differentials are equine recurrent exertional rhabdomyolysis (ERER), EPSSM, and nutritional myopathy. EPSSM is an inherited polysaccharide storage disease of quarter horses, warmbloods, and draft-related breeds. Histologically this disease can be diagnosed by the accumulation of periodic acid-Schiff (PAS)-positive and amylase resistant material in affected muscles. ERER is a group of myopathies which include EPSSM and other often unidentified causes of rhabdomyolysis. ERER is also known as tying up, azoturia, or Monday morning disease. There is some evidence to suggest that ERER in Thoroughbreds is due to abnormal calcium homeostasis within skeletal muscle. Vitamin E and selenium deficiency most commonly occurs in foals and young adult horses. In foals, the most severely affected muscles are those that have the highest workload (cervical muscles, proximal limb muscles, tongue, and masticatory muscles). In young adult horses, the most severely affected muscles are often the temporal and masseter muscles. Histologically, the lesions in the affected muscles are those of a multifocal, multiphasic segmental necrosis.³

Comparatively, wildlife, especially deer, can exhibit capture myopathy, which is identical to exertional rhabdomyolysis. Cattle, sheep, racing greyhounds, and sled dogs can exhibit exertional rhabdomyolysis. And pigs, dogs, and humans can have malignant hyperthermia, which is a hereditary molecular defect in the ryanodine receptor which is involved with calcium regulation in muscle.³

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CASE II – S 2/04 (AFIP 2942015)

Signalment: 15-years-old male, Lady Amherst's Pheasant (*Chrysolophus amherstiae*).

History: This animal was kept in a zoological garden and was found dead in its aviary.

Gross Pathology: The pheasant was emaciated. The cecal wall was multifocally thickened with numerous, up to 3 mm large, round, subserosal and intramural white nodules. In the lumen there were several, up to 1.5 cm long, nematodes.

Laboratory Results: Bacteriology revealed *Salmonella enteritidis* in all parenchyma and intestine.

Contributor's Morphologic Diagnosis: Cecum, submucosa: Typhlitis, granulomatous and fibroplastic with intralesional larval and adult ascarid nematodes, etiology consistent with *Heterakis* spp.

Contributor's Comment: Infections with *Heterakis* spp. occur worldwide and affect ducks, chickens, quails, grouse and especially pheasants. Besides *H. dispar*, *H. gallinarum* and *H. isolonche* are the species most commonly found in pheasants.¹ These nematodes are morphologically characterized by prominent cuticular alae, large lateral chords, polymyarian-coelomyarian musculature, and triradiate intestine with uninucleate columnar intestinal cells. The exact identification of the species can be made by measuring the length and estimating the shape of the spicules and oesophagus.² *H. isolonche* has a direct life cycle, lives within the cecal submucosa and induces nodular granulomas with considerable mesenchymal proliferation or even leiomyomas.^{2,3} Defecated non-embryonated eggs gain their infectivity outside

the host. After hatching in the small intestine, the larvae reach the cecal submucosa and develop into adult worms.

AFIP Diagnosis: Cecum: Typhlitis, nodular and granulomatous, multifocal, moderate, with marked mesenchymal infiltration and intralesional adult and larval nematodes, etiology consistent with *Heterakis* spp., Lady Amherst's pheasant (*Chrysolophus amherstiae*), avian.

Conference Comment: Conference attendees discussed the histogenesis of the cecal nodules. Some reports classify them as granulomas, while others describe them as fibrous hyperplastic tissue or even leiomyomas.¹ The spindle cells forming the nodules in this case are not producing collagen as identified with Masson's trichrome stain, nor are they immunohistochemically positive for smooth muscle actin. Therefore, these cells may be of histiocytic origin; however, further immunohistochemistry would be necessary to determine the definitive histogenesis.

Heterakis spp. are known to cause nodular typhlitis in a number of avian species, including chickens, turkeys, ducks, geese, grouse, guinea fowl, partridges, pheasants, and quail. However, the chief economic importance of *Heterakis gallinarum*, the cecal worm, lies in its role as a carrier of *Histomonas meleagridis*.⁵

Histomoniasis is a parasitic disorder of the ceca and liver of many gallinaceous birds. Grossly, the disease is characterized by well-demarcated necrotic foci surrounded by a raised hyperemic ring in the liver and necroulcerative lesions in the ceca that often lead to the development of cecal cores composed of necrotic debris. Microscopically, histomonads are pale, lightly stained, 15-20 μ m, oval bodies within lacunae in the lamina propria and muscularis mucosa and are admixed with lymphocytes, macrophages, and heterophils. Histomonad invasion with necrosis may extend well into the muscular tunics, nearly to the serosa. With time, large numbers of giant cells form nodules that may be seen grossly as granulomas bulging from the serosal aspect of the cecum.⁵

The life cycle of *H. meleagridis* is complex with histomonads being found in the intestinal epithelial cells of *H. gallinarium*. *Histomonas meleagridis* infected *Heterakis gallinarium* eggs are passed in the feces of susceptible avian species. The eggs then embryonate and may either be swallowed by a susceptible host (direct transmission) or they may be ingested by the earthworm (indirect transmission). In the earthworm, eggs hatch and larvae may live for months. The earthworm is then eaten by a susceptible host, resulting in infection with both *Heterakis gallinarium* and *Histomonas meleagridis*.⁵

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CASE III – NADC MVP-1 2004 (AFIP 2936146)

Signalment: Full term fetus, white-tailed deer (*Odocoileus virginianus*).

History: Twin full-term fawns were born to a 2.5 year-old white-tailed deer. One fawn was stillborn while the other appeared healthy.

Gross Pathology: The stillborn fawn had marked abdominal distention due to marked bilateral nephromegaly. Kidneys maintained their reniform shape but were enlarged (8.8 x 6.0 cm), pale, tan and smooth. The capsule was thin, tightly adherent and translucent, through which could be seen numerous fluid-filled cysts. On cut section, there were numerous 1-5 mm, round to fusiform cysts that contained clear fluid. The ureters and bladder were grossly normal. On cut surface of the liver, the intrahepatic bile ducts were variably ectatic with irregular outlines and intraluminal bile. Gross lesions were not seen in other organs.

Contributor's Morphologic Diagnosis: Kidney, glomeruli, tubules and collecting ducts: Ectasia and cysts, diffuse, severe, white-tailed deer (*Odocoileus virginianus*).

Contributor's Comment: Microscopically, there is severe dilatation of all renal tubules. The corticomedullary junction is obscured. Dilated tubules are lined by low cuboidal to flattened squamous epithelium. Most dilated tubules are empty, but some contained a flocculent eosinophilic material. The number of glomeruli is greatly reduced; those present are small and located within a dilated Bowman's capsule. The liver (not submitted) is characterized by marked biliary hyperplasia. Bile ducts are dilated to 1 to 5 mm in diameter, irregular in contour and contain intraluminal inspissated bile.

In humans, polycystic kidney disease (PKD) is characterized by progressive enlargement of the kidneys due to numerous expansile cysts and ultimately leads to renal failure. In humans, PKD is heritable and recognized in at least 2 genetically distinguishable forms; autosomal recessive PKD (ARPKD) or autosomal dominant PKD (ADPKD). The autosomal dominant form is often associated with a variety of extrarenal manifestations and usually leads to death from renal failure in late adulthood. The autosomal recessive form is rare, often diagnosed in early infancy by massive nephromegaly, and is rapidly progressive.¹ Syndromes resembling both the recessive and dominant forms of human PKD have been recognized in animals including cats,^{2,3} with Persian cats appearing disproportionately affected,⁴ dogs,^{5,6} mice,⁷ pigs, raccoons⁸ and ruminants such as cattle,⁹ goats,^{10,11} sheep¹² and Springbok (*Antidorcas marsupialis*).¹³ PKD has not been reported previously in any member of the family Cervidae.

In domestic animals, PKD is most often consistent with the human ARPKD in that disease manifests as stillbirths or death within the first few weeks of life, although manifestations consistent with the ADPKD have also been described. Reported extrarenal manifestations of PKD in animals include biliary and pancreatic cysts.^{3,5,6,10-12}

Many humans with ARPKD have been found to have mutations in the gene, polycystic kidney and hepatic disease 1 (PKHD1). This gene is predicted to code for a protein that is known as fibrocystin or polyductin.^{14,15} The protein is expressed on adult and fetal kidney, liver and pancreas and may be a receptor protein that plays a role in collecting duct and bile duct differentiation. The basic defect in ARPKD may, therefore, be a failure of terminal differentiation in collecting and bile ducts.¹⁵ PKHD1 gene products are members of a novel class of proteins that share structural features with hepatocyte growth factor receptor and plexins, members of a class of proteins involved in the regulation of cell proliferation, cellular adhesion and repulsion.^{14,15} Genetic factors may be involved in congenital PKD of Cairn Terriers, springbok and Persian cats as the condition has been described in groups of related animals.

AFIP Diagnosis: Kidneys, glomeruli and tubules: Cystic change, diffuse, severe, white-tailed deer (*Odocoileus virginianus*), cervid.

Conference Comment: The contributor provides a thorough overview of polycystic kidney disease in humans and animals. As mentioned by the contributor, animals with polycystic kidney disease (PKD) often have biliary cysts and pancreatic cysts in addition to the renal changes. Extrarenal cysts are not found in conditions leading to congenital or acquired renal cysts.

Congenital renal cysts can occur in cases of renal dysplasia or can occur as a primary entity. There may be only one cyst or there may be many cysts that often distort the contour of the kidney. Some cysts may cause no alteration in renal function, and are therefore considered incidental findings. Cysts may arise anywhere along the nephron and can be located in either the cortex or the medulla and may range in size from barely visible to several centimeters in diameter.¹⁶

Acquired renal cysts can occur as a result of renal interstitial fibrosis, as in chronic renal disease, or they may occur in renal diseases that cause intratubular obstruction. These cysts are usually small, only 1-2 mm in diameter, and occur primarily in the renal cortex. In all cases with renal cysts, the cysts must be differentiated from hydronephrosis.¹⁶

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CASE IV – Case #2 (AFIP 2946684)

Signalment: Young female striped skunk (*Mephitis mephitis*) of unknown age with an approximate weight of 4 pounds (1.8 Kg).

History: The skunk had a history of seizures and accumulation of ocular/periocular crusty debris. The skunk was found in a populated area where dogs and cats resided, and was transferred to a wildlife rehabilitation center where it subsequently died. The carcass was refrigerated until a necropsy was performed. Selected tissues were collected and preserved in a 10% buffered neutral formaldehyde solution for histopathologic examination. Small fragments of lung and gastric mucosa were collected and preserved in a 3% buffered glutaraldehyde solution for examination by transmission electron microscopy.

Gross Pathology: The stomach and duodenum had numerous white nematode parasites that measured approximately 2.5 mm long. The uterus contained six fetuses each measuring approximately 1.5 cm in length.

Laboratory Results:

1. Canine Distemper Virus (CDV) and Rabies Virus fluorescent antibody tests – positive CDV antigen immunoreactivity in the lungs, tongue, and brain. Negative for Rabies Virus antigen immunoreactivity. Viruses were not isolated from the lungs, brain, or tongue.
2. Histopathology (Tissues not submitted for review) –
 - a. Lung: Interstitial pneumonia with bronchial epithelial inclusion bodies.
 - b. Brain: Meningoencephalitis, lymphocytic.
 - c. Bronchial lymph node: Histiocytosis and follicular lymphoid hyperplasia
 - d. Liver: Congestion and hepatocellular vacuolar degeneration with biliary epithelial inclusion bodies.
 - e. Spleen: Lymphoid depletion
 - f. Epithelium (multiple sites): Inclusion bodies

Contributor's Morphologic Diagnosis: Ciliated columnar epithelium (bronchus): Intracytoplasmic and intranuclear viral inclusions consistent with CDV.

Contributor's Comment: The transmission electron photomicrograph of bronchial epithelium contained ciliated columnar epithelial cells with intracytoplasmic and intranuclear viral inclusion bodies consistent with CDV. Intracytoplasmic inclusion bodies were consistent with accumulated viral nucleocapsids and were characterized most frequently by amorphous aggregates of moderately electron dense granular material, and less frequently by amorphous aggregates of tubular-like structures. The nuclei of most cells were of decreased electron density due to dispersion of the chromatin pattern. One cell had intranuclear inclusions characterized by parallel, stacked arrays of electron dense, tubular to filamentous material. Other findings in the bronchial epithelial cells consisted of vacuolar epithelial cell degeneration characterized by mild dilatation of the smooth endoplasmic reticulum and the perinuclear cisterna, loss of apical microvilli, low numbers of secondary lysosomes, and cellular debris in the luminal surface. Examination of fine mitochondrial detail was not possible due to mild autolysis.

CDV is grouped in the family *Paramyxoviridae*, genus *Morbillivirus*, and is related to Measles Virus, Peste de Petits Ruminants Virus, and Rinderpest Virus.¹ It is an RNA virus that displays spherical to filamentous morphology ultrastructurally. It is reported that there is a single serotype of CDV; however, more than one genotype is known to exist. CDV isolates vary in biologic activity and tissue tropism.

CDV is transmitted primarily by contact with respiratory, ocular, or oral fluids.¹ CDV may also be transmitted less frequently by contact with infected shed skin cells, feces, and urine, and by the transplacental route. Transmission is likely enhanced by increased density and contact between susceptible animal populations, animal behaviors conducive to transmission, increasing dose of virus, and immunosuppression.¹ Other factors that influence susceptibility to CDV are age, species of host, virus strain, and environmental conditions. A strong antibody response to infection by the virus is reportedly protective, while weak antibody responses are associated with illness.

CDV may infect and cause clinical disease in a wide variety of carnivores including canids, felids, mustelids, procyonids and others.¹ Striped skunks are reportedly less susceptible to disease caused by CDV, but may suffer from the disease nonetheless. CDV-infected wild and domestic carnivores present a significant risk to zoological collections with susceptible species. The incubation period reportedly varies from one week to > 1 month, and clinical disease may last approximately 1-6 weeks. Infection may be fatal, particularly in highly susceptible species such as domestic ferrets (*Mustela putorius furo*). Clinical signs associated with CDV infection include depression, mucopurulent oculonasal discharge, fever, cough, anorexia, vomiting, diarrhea, and central nervous system (CNS) dysfunction.¹⁻⁴ Clinical signs consistent with CNS dysfunction in CDV-infected animals include seizures, convulsions, paresis, paralysis, and other clinical signs. CDV-infected mustelids, such as striped skunks, may have symptoms similar to those described above.¹

Macroscopic lesions include oculonasal discharge, diarrhea, hyperkeratosis (in prolonged infections primarily), poor body condition, and pulmonary changes consistent with pneumonia.¹ Other less frequently seen macroscopic findings may occur and in some cases lesions may not be evident. Commonly seen microscopic findings include interstitial and/or bronchopneumonia, and lymphoid depletion in the spleen, lymph nodes, and thymus.¹ Formation of intracytoplasmic and intranuclear eosinophilic inclusions are a characteristic microscopic feature and can be seen in epithelial and neural cells of infected animals. In the present case, inclusions were seen in multiple epithelial tissues by light microscopy. CDV-induced primary lesions may also be seen in other tissues including tissues of the CNS, stomach, and intestines.¹⁻⁴ Concurrent opportunistic infections may occur in CDV-infected animals secondary to immunosuppression, and may obscure CDV-induced lesions.^{1,5} This skunk had microscopic lesions consistent with CDV.

Laboratory tests, other than light microscopic examination, utilized to diagnose CDV-infection include transmission electron microscopy, fluorescent antibody testing (FAT)/immunohistochemistry, PCR assays, nucleic acid hybridization, virus isolation, determination of antibody titers, and cytologic examination of tissue

samples or blood smears.^{1,6-15} In the present case the ultrastructural characteristics of the viral particles and the FAT results were consistent with CDV.

The most important differential diagnosis in a suspected CDV-infected carnivore, particularly those with CNS dysfunction, is Rabies Virus.¹ In the present case Rabies was considered an important differential diagnosis and specific testing indicated that the skunk was not infected with Rabies Virus. Infection with other microbiologic agents or exposure to toxins are differential diagnoses that must also be considered.¹



AFIP Diagnosis: Ciliated respiratory epithelium: Degeneration and necrosis, with intracytoplasmic and intranuclear viral inclusions, striped skunk (*Mephitis mephitis*), mustelid.

Conference Comment: The contributor provides a thorough overview of Canine Distemper Virus (CDV) including species affected, clinical signs, transmission, microscopic and ultrastructural findings, diagnostic tests, and etiologic differentials.

For most pathologists, describing ultrastructural changes and interpreting electron micrographs can be challenging. However, when examining electron micrographs one must only consider three cellular alterations: degeneration, necrosis, and something added or taken away. Then one must systematically evaluate and describe the cells present and their organelles in order to identify the cells/tissue and the process. When describing electron micrographs it is important to start with a brief description of the normal features which allow one to identify the cells and or tissue. Such features may include: number and arrangement of cells, plasma membrane, surface decorations, cellular junctions, cytosol, endoplasmic reticulum (smooth and rough), lysosomes, mitochondria, nuclei, and other intra- and extracellular features. Below are two helpful charts to assist in evaluating electron micrographs.^{16,17}

Organelle	Normal features and changes to note on EM
Plasma membrane	Cilia, villi; loss of surface specialization; cytoplasmic blebs; types and locations of intercellular junctions
Cytosol	Rarefaction (swelling); presence of myelin figures; inclusions
ER (smooth and rough) SER / RER	Relative amounts of SER and RER; swelling/dilation; detachment of ribosomes; increased amounts of SER
Mitochondria	Relative number and location; low amplitude / high amplitude swelling; matrix flocculent densities; calcification; vacuolization; rupture
Lysosome	Relative number; swelling; rupture
Nucleus	Clumped, dispersed, or marginalized chromatin; heterochromatin, euchromatin; pyknosis, karyorrhexis, karyolysis; viral inclusions
Other	Intranuclear or intracytoplasmic inclusions; bacteria; parasites; fungi; algae

Organelle	Reversible Changes	Irreversible Changes
Plasma membrane	Blebbing, blunting, distortion; loosening of intercellular attachments	Disruption of cellular membranes;
Mitochondria	Swelling, rarefaction, small amorphous densities	Marked dilation; large amorphous densities
ER	Dilation, detachment of ribosomes	
Nucleus	Chromatin clumping	Pyknosis, karyorrhexis, karyolysis
Other	Cellular swelling; creation of myelin figures	Increased cellular swelling; swelling and disruption of lysosomes; increased numbers of myelin figures

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