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CASE I – MVP1-03 (AFIP 2888424)

Signalment: 7 month old, male reindeer (*Rangifer tarandus*).

History: One of a group of 20 males (7-8 months of age) moved from Michigan to Ames, IA. Diarrhea was noted in 5 of 20 reindeer. Diarrhea persisted for 5-7 days. This animal, in which diarrhea was not observed, was found dead.

Gross Pathology: Variably sized ulcers (3-10 mm) were present on the nares, tongue, larynx, and rumen. Through the cecum and proximal colon were segmental areas of necrosis and hemorrhage with ulcerated areas covered by a fibrinonecrotic membrane. Ileocolic and cecocolic lymph nodes were markedly enlarged, edematous and hemorrhagic. Numerous petechiae were noted in both renal cortices. Although diarrhea had not been reported prior to death, the perineal area was stained with liquid fecal material.

Laboratory Results: Bacteriologic culture of cecum and cecocolic lymph node: *E. coli* (non-toxigenic), *Clostridium perfringens* type A.
PCR for Ovine Herpesvirus-2 (kidney): positive
PCR for BVD virus (cecocolic lymph node): negative

Contributor's Morphologic Diagnosis: Kidney: Vasculitis and perivasculitis, lymphocytic, multifocal, moderate with periglomerular interstitial nephritis and multifocal tubular mineralization, reindeer (*Rangifer tarandus*).

Contributor's Comment: The histologic lesions are consistent with malignant catarrhal fever (MCF). There are multifocal infiltrates of lymphocytes within the renal interstitium centered on vessels and glomeruli. Fibrinoid degeneration is present around vessels where lymphocytic vasculitis and perivasculitis are present. Thickening and hyalinization of Bowman's capsule is seen in some affected glomeruli. There are multiple mineralized tubules scattered throughout the cortex and medulla. Other organs with ulcerative lesions (not included) had vasculitis, perivasculitis and thrombosis in vessels of the submucosa subjacent to ulcerative lesions.

Malignant catarrhal fever is the clinical manifestation of the infection of certain ruminant species with one of a group of pathogenic gammaherpesviruses known as MCF viruses. Most domestic cattle and numerous exotic species of ruminants are susceptible to clinical disease that may be sporadic or occasionally epidemic in nature. Clinical disease can range from peracute to chronic and has been reported in various species of Cervidae including, white-tailed deer, black-tailed deer, mule deer, reindeer, muntjac deer, sika deer, Shira's moose, Pere David's deer, swamp deer, rusa deer, and red deer[1-8]. The disease is characterized primarily by lymphoproliferation, mucosal inflammation and vasculitis. Historically, 2 MCF viruses have been associated with clinical disease, one endemic in wildebeest, known as alcephaline herpesvirus-1 (AlHV-1), and the other endemic in sheep, ovine herpesvirus-2 (OvHV-2) known as sheep-associated MCF (SA-MCF). Only AlHV-1 has been propagated in vitro and partially characterized. OvHV-2 is the major MCF virus worldwide. Recently, however, 2 additional members of the MCF virus group have been associated with clinical disease. An MCF virus of unknown origin that causes clinical disease in white-tailed deer [9], and an MCF virus endemic in goats, provisionally known as caprine herpesvirus-2 (CpHV-2) that has been associated with chronic alopecia in sika and white-tailed deer [1,10]. The literature on MCF contains descriptions of various manifestations of disease with diverse lesion types and organ involvement. The variable nature of disease expression is thought to result from the possession of multiple regulatory genes in gammaherpesviruses acquired during evolution. Cell type as well as host species may alter the expression of these genes [1].

In the present case lesions were consistent with MCF and OvHV-2 was identified by PCR from formalin fixed sections of kidney submitted for analysis. There was no known association with sheep at the farm of origin; however, upon receipt in Ames, IA the reindeer were housed within 50 yards of several pens of adult sheep. PCR analysis of whole blood buffy coat samples from the remaining 19 reindeer did not demonstrate the presence of OvHV-2 DNA.

AFIP Diagnoses:
1. Kidney: Nephritis, lymphocytic and lymphofollicular, perivascular and periglomerular, multifocal, moderate, with periglomerular and interstitial fibrosis, reindeer (*Rangifer tarandus*), cervid.
2. Kidney, cortex: Necrosis, tubular, acute, multifocal.

Conference Comment: This case was reviewed in consultation with the Department of Nephropathology at the Armed Forces Institute of Pathology. There is hyaline change within multiple blood vessels, and perivascular inflammation. However, conference attendees and the nephropathologists did not identify vasculitis in the slides evaluated.

There is acute tubular necrosis (ATN) with retention of the basement membrane, distinct from the autolysis present. Conference attendees discussed differential diagnosis for acute tubular necrosis, including oak bud and aminoglycoside toxicity, but the cause of ATN is not evident in this case.

Conference attendees discussed the presence of small lymphocytes around vessels, rather than lymphoblasts typically present in malignant catarrhal fever. The classic lesions reported in malignant catarrhal fever are lymphoproliferation, mucosal disease, and vasculitis.[1] Typical gross lesions include oral and gastrointestinal mucosal erosions, lymphadenopathy, corneal opacity, mucopurulent nasal discharge, crusted muzzle, and cutaneous ulceration and necrosis. Compared to cattle, MCF in cervids is usually an acute disease with animals showing few clinical signs before death. Lesions are often hemorrhagic, and involve the viscera of the gastrointestinal tract.[11,12]

Differential diagnosis for diseases that cause ulceration and necrosis of the oral and gastrointestinal mucosa in ruminants include bluetongue (Orbivirus), epizootic hemorrhagic disease in deer (Orbivirus), bovine virus diarrhea-mucosal disease (Pestivirus), rinderpest (Morbillivirus), and vesicular diseases. Important vesicular diseases to consider are foot and mouth disease (Aphthovirus) and vesicular stomatitis (Vesiculovirus), which are grossly indistinguishable from one another.[11]

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CASE II - MK03-4768 (AFIP 2892675)

Signalment: Owl monkey (*Aotus nancymae)*, adult female, wild caught, weighing 0.63 kg.

History: The animal had a 2-month history of weight loss and had received nutritional supplements. The animal presented with labored breathing and edema of the lower body. Based on poor prognosis, euthanasia was elected.

Gross Pathology: The animal is well hydrated with scant body fat stores and is thinly muscled. There is diffuse subcutaneous edema. There is serous effusion in the thoracic cavity and a small amount of serous effusion in the pericardial sac. The heart is rounded. Weights are as follows: total heart = 6.715 gm; right ventricle = 1.327 gm; left ventricle and septum = 4.27 gm. The right ventricle free wall measures 1.5 mm in width, the left ventricle 8 mm and the septum 5 mm. Kidneys are mildly pale and slightly enlarged. Lungs are edematous and tan.

Laboratory Results: None reported.

Contributor's Morphologic Diagnoses:
1. Heart: Hypertrophic cardiomyopathy characterized by myofiber loss and fibrosis, multifocal, moderate.
2. Arterioles, heart, intestines and multiple other organs: Degeneration and fibrinoid change, multifocal, moderate to severe.

Contributor's Comment: The animal's poor condition was due to cardiomyopathy and congestive heart failure. The arteriolar changes, present in multiple organs, are consistent with underlying hypertension. The cardiomyopathy is likely secondary to the hypertension. Hypertension is classically subdivided into primary and secondary. Primary hypertension is attributed to either renal retention of excess sodium with vasoconstriction or increased peripheral resistance. In the former, genetic factors result in decreased sodium excretion by the kidneys, which cause an increase in fluid volume and cardiac output. To prevent overperfusion of tissues from an elevated cardiac output, autoregulation leads to increased vasoconstriction and along with it elevated blood pressure. In non-renal associated hypertension, peripheral resistance is the primary cause. This results from vasoconstrictive influences such as catecholamines or structural changes in the vessel wall leading to a thickened wall and narrowed lumen[1]. Secondary hypertension results from renal, endocrine, vascular or neurogenic disturbances. In these cases, hypertension is secondary to a specific disorder of a particular organ or blood vessel, such as the kidney, adrenal gland, or aortic artery.

The gross and histopathological lesions seen in this case are consistent with those seen in previously studied captive owl monkeys and resemble those in humans with hypertrophic cardiac disease and hypertension[2]. Whether primary or secondary, hypertension frequently results in generalized vascular disease that can lead to end-organ damage. In arterioles, the chronic hemodynamic stresses result in hyaline arteriolosclerosis in which there is hyaline thickening of the wall due to accumulation of serum proteins in the subendothelial space and media[3]. The change is accompanied by a reduction in the lumen diameter. These changes were prominent in the intestine in this case and also evident in the heart, kidney, spleen, lymph nodes and stomach. Hypertension increases the workload of the heart and leads to left ventricular hypertrophy. When the heart can no longer compensate for the pressure increase, congestive heart failure will occur. Grossly, this monkey's heart was enlarged with its total weight exceeding 1% of body weight. The left ventricle was hypertrophied and measured 8 mm in width while the right ventricle measured 1.5 mm. Microscopically, there are areas of myofiber loss and fibrosis. The diffuse subcutaneous edema and serous effusion in the thoracic cavity and pericardial sac are due to congestive heart failure. Hypertension can cause renal disease, nephrosclerosis, characterized by sclerosed glomeruli and atrophied tubules. However, these changes may also be explained by infectious disease, parasites, environment and dietary factors[2]. Idiopathic renal disease is commonly encountered in *Aotus* monkeys, but its association with hypertension is not clear.

The vascular changes seen in this case suggest that the monkey suffered from hypertension. However, based on practical difficulties in handling these small nocturnal New World primates, hypertension is difficult to document clinically, and there are no established normative values for these species[2]. Capture of an unsedated monkey will, in itself, alter blood pressure, as will any method of sedation. Implanted telemetry devices are required to record blood pressure accurately.

While we cannot exclude the possibility that the cardiomyopathy in this case is due to familial hypertrophic cardiomyopathy, or cardiomyopathic diseases unrelated to hypertension, we believe a more likely explanation is that the stress of captivity induced hypertension, through a mechanism involving catecholamine release. In an unpublished study performed at the Oregon Primate Center, owl monkeys were implanted with telemetry devices and the blood pressures were continuously monitored. Even the simple entry of a caretaker into the room caused the owl monkeys' blood pressure to elevate and remain elevated, to a far greater degree than observed in rhesus monkeys exposed to similar stimuli (O. Smith, personal communication, 1994). Rozanski et al., in a study of cynomolgus monkeys, showed that some monkeys exhibited exaggerated heart rate and blood pressure responses when presented with engaging, challenging, or aversive stimuli[4]. Gozalo found no direct correlation between severity of heart lesions in *aotus* monkeys and time in captivity. However, those animals in quarantine for 4 months or less showed a lower incidence of hypertrophic cardiac disease than those animals that died after more than six months in captivity, suggesting either an age or captivity related effect[2]. Stress, secondary to the threat of capture or the entry of a caretaker into the room, causes release of catecholamines and cortisol, and stimulates the sympathetic nervous system. This results in vasoconstriction, increased heart rate, elevated blood pressure, and subsequent endothelial cell injury and accompanying mural changes[4].

AFIP Diagnoses:
1. Heart, myocardium: Myofiber degeneration and loss, multifocal, mild to moderate, with fibrosis, owl monkey (*Aotus nancymae*), nonhuman primate.
2. Heart and colon, arterioles: Hyaline degeneration, multifocal, moderate.

Conference Comment: The contributor gives a comprehensive overview of hypertrophic cardiomyopathy (HCM) and hypertension in owl monkeys.

Among the domestic species, hypertrophic cardiomyopathy occurs frequently in cats. The cause of feline HCM is unknown, but heritability has been suggested in Persian and Maine coon cats. Grossly there is symmetric hypertrophy of the ventricles, especially of the left ventricle. This must be differentiated from the concentric cardiac hypertrophy that commonly occurs with hyperthyroidism. Microscopically, HCM is characterized by myofiber hypertrophy, myofiber disarray, myofiber loss, and replacement by fibrosis. In hyperthyroidism, the myofibers are enlarged, but not in disarray in most cases. A common sequelae to HCM in cats is atrial thrombosis with thromboembolic hind limb ischemia (saddle thrombus).[5,6]

Although dilated cardiomyopathy is more common in dogs, HCM does occur and may be associated with carnitine deficiency. Hypertrophic cardiomyopathy is reported to have a familial tendency in the Doberman Pinscher and Cocker Spaniel.[5]

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CASE III – 98-305 (AFIP 2784507)

Signalment: 128 days old, male, C57Bl/6 mouse, *Mus musculus*.

History: This mouse was from a group of mice that were experimentally immune suppressed. This mouse showed signs that preceded the death of similarly treated mice. Since the immune suppression had not been lethal in previous experiments the mouse was euthanized and selected tissues were submitted for histopathology.

Gross Pathology: None reported.

Laboratory Results: None reported.

Contributor's Morphologic Diagnoses: Moderate multifocal splenic necrosis - syncytial giant cell formation.

Contributor's Comment: The lesions are consistent with mouse hepatitis virus infection as seen in immunodeficient mice. Mice that are immune suppressed may not produce antibodies adequate for serologic identification of MHV infection, and the syncytial cells must be distinguished from megakaryocytes commonly found within the spleen of mice.

There was also mild chronic capsulitis of the spleen and hepatic necrosis with syncytial cells visible within the liver (not present on the slides submitted). The diagnostic aspects of MHV infection have been clearly illustrated and succinctly reviewed[1]. The slide was submitted to illustrate the differences between the characteristic syncytial cells associated with MHV infection and megakaryocytes within spleen.

MHV infection may still complicate research using mice because of the variation of sources of mice (many genetically manipulated stocks are not commercially available), the limitations of mouse containment and diagnostic funds, the need to balance the access of the investigators to the mice, the effects of experimental reagents (many are derived from mice) and other interactions of experimental systems and the use of mice.

AFIP Diagnoses:
1. Spleen: Syncytial cells, numerous, viable and necrotic, C57Bl/6 mouse, rodent.
2. Spleen: Plasmacytosis, diffuse, marked.

Conference Comment: Conference attendees discussed the presence of high numbers of plasma cells that efface the T cells of the periarteriolar lymphoid sheath (PALS). Attendees considered whether the plasmacytosis could be associated with the MHV infection, but decided a separate, unknown etiology was more likely.

The typical microscopic findings in the spleen of mice infected with MHV are necrotizing splenitis and syncytial cell formation. This case demonstrates both viable and necrotic syncytial cells. Other lesions of MHV include necrotizing hepatitis, necrotizing encephalitis and meningitis, necrosis of lymphoid tissues, and virus-induced syncytia in target organs. Mouse hepatitis virus infection of neonatal mice results in necrotizing enterocolitis with high mortality. Before MHV was identified as the cause of this syndrome, it was known as lethal intestinal virus of infant mice (LIVIM).[1]

Infection and clinical disease vary with age and immune status of the mouse, virus strain, and the associated tissue tropism. Mice of any age are susceptible, but clinical disease generally occurs in immunocompromised mice, or those less than two weeks of age.[1] It is reported that co-infection with *Helicobacter hepaticus* decreases the severity of lesions during the acute phase of the disease, but increases the severity of hepatitis and meningitis in chronic disease.[2]

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CASE IV - N98-21 (AFIP 2893183)

Signalment: Sixteen years of age, male, Chimpanzee, *Pan troglodytes*.

History: This adult male *Pan troglodytes*, a first-generation captive-born, was born in March 1982 in Texas. He had not been part of any infectious disease studies, however he was part of a maxillary sinus augmentation study in 1996. His clinical history was uneventful until the age of 15. Chronic low-grade anemia was noted eight months prior to death, and a liver biopsy at that time revealed severe, diffuse amyloidosis (Congo-red stain positive, Masson's trichrome stain negative). One week prior to death, an abscess in the area of the right knee was lanced, debrided, and antibiotic therapy was initiated.

Gross Pathology: A complete necropsy was performed and on gross postmortem examination, a 20 x 20 x 10 cm necrosuppurative lesion was present in the subcutaneous tissues around the right knee, extending into the underlying skeletal muscle. The heart and kidneys were pale tan. The pericardial sac contained an excess of pericardial fluid with fibrin. The liver was diffusely pale and enlarged. On the left side of the liver, away from the gallbladder, was a round, white, lobulated 10 cm-in-diameter mass.

Tissues were fixed in 10% neutral buffered formalin, embedded in paraffin, and 5-um sections were mounted and stained with hematoxylin and eosin. Selected liver sections were stained with Congo red. Immunohistochemical staining of liver from chimpanzee 4X0392 for carcinoembryonic antigen (CEA), alpha fetoprotein (AFP), cytokeratins 8/18, and cytokeratin 7 were performed by the Armed Forces Institute of Pathology.

Histologically, the hepatic mass was unencapsulated and highly infiltrative, composed of anaplastic hepatocytes arranged into branching cords one to three cell layers thick. Large areas of necrosis and hemorrhage were present. Sinusoids contained necrotic cellular debris and small numbers of lymphocytes, and occasional sinusoids were greatly dilated. The hepatocytes within the mass formed rare glandular structures. The cells were polygonal and exhibited marked anisocytosis, anisokaryosis, and pleomorphism. They typically contained large amounts of eosinophilic granular cytoplasm and many had multiple small, round, clear, intracytoplasmic vacuoles (lipid). The nuclei were irregularly ovoid, with coarsely clumped chromatin and one to three nucleoli. Numerous multinucleated cells were present. The mitotic rate was high, with approximately eight mitotic figures per 40x field and frequent abnormal mitoses. Immunohistochemical staining revealed strong diffuse staining of neoplastic cells for cytokeratins 8/18, scattered positive staining for cytokeratin 7, strong canalicular staining with CAE, and negative staining for AFP.

Sinusoids in the surrounding hepatic parenchyma were diffusely and markedly expanded by eosinophilic, amorphous, Congo red-positive material (amyloid). Multifocal small to moderately-sized accumulations of amyloid were also identified in the spleen and smaller amounts of amyloid were present in the heart, lung, and kidney. Within the kidney, moderate, diffuse, global, membranoproliferative glomerulonephritis and mild, multifocal, tubular necrosis were present. The lumen of the large intestine contained small numbers of nematodes, morphologically consistent with *Enterobius vermicularis,* and small numbers of *Balantidium coli*. The cause of death was determined to be systemic amyloidosis.

Laboratory Results: Blood work revealed a marked leukocytosis, mild anemia, mild hypoalbuminemia, mild hyponatremia, and mild increases in serum alanine aminotransferase (ALT) and aspartate aminotransferase.

Contributor's Morphologic Diagnosis: Hepatocellular carcinoma, liver, chimpanzee.

Contributor's Comment: Hepatobiliary tumors have been experimentally induced in nonhuman primates by a variety of chemical compounds. Spontaneous hepatobiliary neoplasms, however, have been only sporadically reported. Hepatic neoplasia is rare in chimpanzees. Only four hepatic neoplasms have been reported in chimpanzees, three of which were associated with viral etiologies[1,2,3].

Forty-four percent (30 of 68) of the tumors reported in the literature have been described as benign, with the majority of those being hepatocellular adenomas. Of the malignant tumors described in nonhuman primates, 58% (22 of 38) have been HCCs, previously termed hepatomas. HCC has been reported in prosimians, New World monkeys, Old World monkeys, and apes. Of the reported HCCs with histologic descriptions, the majority had a trabecular pattern, and tumors were evenly divided between low grade and high grade forms. Metastasis was reported in 8 of 22 tumors, with the lung being the most common metastatic site. HCCs appear to be much less common in nonhuman primates than in man, in which the majority of cases are associated with HBV infection, HCV infection, and/or alcoholism.

In humans, HCC is the most common primary malignant hepatic neoplasm and one of the most common of all malignancies. Four grades (I to IV) and several histologic growth patterns are recognized, including trabecular, pseudoglandular, compact, cirrhosis, fibrolamellar, and mixed. The HCC found in chimpanzee 4X0392 had a predominantly trabecular pattern with only rare formation of pseudoglandular structures. The high degree of nuclear atypia, high mitotic rate, multinucleated cells, and areas of necrosis are indicative of a high grade (grade IV) neoplasm. Other features described in human tumors that were not evident in this case include Mallory bodies, non-Mallory cytoplasmic globules, fibrinogen inclusions, and large amounts of intracytoplasmic glycogen.

In addition to having some typical microscopic characteristics of HCC, the carcinoembryonic antigen (CAE) immunohistochemistry staining pattern of this hepatic mass indicated HCC. Antibodies to CAE cross-react with biliary glycoprotein I in the bile canaliculi. A canalicular staining pattern with anti-CAE is considered useful in differentiating HCC from other malignancies. This tumor also stained positive for cytokeratins 7, 8 and 18. Cytokeratins 8 and 18 are commonly demonstrated in both normal and neoplastic hepatocytes, while cytokeratin 7 is a biliary-type keratin found in a subset of HCCs [2]. The neoplastic cells, however, did not stain for the tumor marker AFP, which is normally produced by liver cells during development of the embryo and is the dominant serum protein in early embryonic life. This protein can reappear in the adult serum during certain pathologic states, including neoplasms such as hepatoblastomas, hemangioendotheliomas, and HCC. The level produced by hepatomas, teratocarcinoma, and embryonal cell carcinomas, when present, can be used for monitoring of responses to treatment of these tumors. Human HCC patients often have elevated serum AFP, but the neoplastic cells are usually negative for this protein. However, the absence of AFP is not diagnostic[2].

The cause of death of chimpanzee 4X0392 was determined to be systemic amyloidosis, which is a recognized disease in adult chimpanzees. Systemic amyloidosis in chimpanzees is a chronic, progressive, and fatal disease. The amyloid is of the secondary or reactive type and the liver is the predominant organ affected, with amyloid accumulation leading to elevated liver enzymes and eventual liver failure.

Proliferative liver lesions are of special significance in the chimpanzee, a species that is currently an important model of human viral hepatitis. Our understanding of the role of viruses in hepatic carcinogenesis is far from complete, and the chimpanzee model may allow better understanding of these processes. Only a few hepatic tumors have been described in the chimpanzee, and more cases must be studied before meaningful correlations with human tumors can be made.

AFIP Diagnosis: Liver: Hepatocellular carcinoma, chimpanzee, nonhuman primate.

Conference Comment: The contributor gives an excellent review of hepatic neoplasia in nonhuman primates and hepatocellular carcinomas in humans. As the contributor notes, the study of viral hepatitis is currently an important area of research. Woodchucks (*Marmota marmax*) and a variety of ground squirrels have been identified as developing hepatic disease in association with hepadnavirus infection and have been suggested as animal models.[4]

Woodchuck hepatitis virus (WHV) causes hepatitis and is associated with the development of hepatocellular carcinoma in this species. The woodchuck is a useful animal model for studying viral hepatitis and hepatocarcinogenicity, and for the development of antiviral drugs for treatment of chronic hepatitis B virus infection in humans. California ground squirrels (*Spermophilus beecheyi*) persistently infected with ground squirrel hepatitis virus (GSHV) develop hepatitis and hepatocellular carcinoma, but at a lower frequency than that associated with WHV. Arctic ground squirrels (*Spermophilus parryi*) infected with arctic ground squirrel hepatitis virus (AGSHV) have a high incidence of hepatocellular carcinoma, as well. Pekin ducks (*Anas domesticus*) infected with duck hepatitis B virus (DHBV) also develop hepatitis; however, the role of DHBV in producing hepatocellular carcinoma in ducks remains to be elucidated.[4]

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