Joint Pathology Center
Veterinary Pathology Services
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CASE I: AFIP (JPC 4001563).

Signalment: Female 4 year old cynomolgus monkey (*Macaca fascicularis*).

History: This monkey was a control animal in a 4 week oral gavage toxicity study with an experimental compound. It exhibited no clinical signs while on the study and was euthanized at the scheduled terminal sacrifice. The lesion was found incidentally during routine histopathologic evaluation of tissues.

Gross Pathology: Necropsy findings included a discolored duodenum, liver cyst, small pancreas, and an abnormally shaped spleen.

Laboratory Results: Three days prior to euthanasia, electrocardiography revealed multiple premature ventricular complexes, including periods of ventricular bigeminy and paroxysmal ventricular tachycardia.

Contributor's Histopathologic Description: Heart: There are moderate infiltrates of lymphocytes, plasma cells, macrophages, and rare neutrophils predominantly within the myocardium, and to a lesser extent affecting the endocardium and minimally affecting the epicardium. Inflammatory cell infiltrates and mild edema expand the interstitium and separate cardiac myofibers. Scattered myofibers exhibit degeneration characterized by variation in fiber size, hypereosinophilia, loss of cross striations, fragmentation, and nuclear hypertrophy. Rare myofibers contain protozoal pseudocysts. Pseudocysts are irregularly shaped, approximately 30 microns in length, and contain myriad amastigotes. Amastigotes are spherical, basophilic, approximately 2 microns in diameter, and have a darkly basophilic kinetoplast.

Contributor's Morphologic Diagnosis: Heart: Moderate, chronic, multifocal to coalescing lymphoplasmacytic and histiocytic myocarditis and endocarditis with myofiber degeneration and protozoal pseudocysts containing amastigotes (*Trypanosoma cruzi*)

Contributor's Comment: *Trypanosoma cruzi* is the causative organism of Chagas' disease. *Trypanosoma*, along with *Leishmania*, belongs to the subphylum *Sarcomastigophora. T. cruzi* is a hemoflagellate protozoan that is endemic in South America, Central America, Mexico, and in the southern United States. Natural reservoirs include opossums, armadillos, rodents, dogs, cats, pigs, raccoons, and monkeys.[1,4]

Insects serve as the vector for most *Trypanosoma* species. *Trypanosoma cruzi* resides in the hindgut of reduviid bugs.[1,3] At night these bloodsucking insects emerge to feed upon sleeping hosts. They usually target the face, and because of this are also known as "kissing bugs". Once fed the insects will often defecate, depositing infective organisms onto the skin. Trypanosomes gain entry through a wound in the skin or by crossing mucous membranes.[3] While circulating in the body, they are in a form known as trypomastigotes. Most species of *Trypanosoma* exist solely in this form, which is also the reproductive stage. *T. cruzi* is unique among trypanosomes in that it also forms a tissue pseudocyst containing amastigotes[3], and this is the form that undergoes multiplication in this species.[1] Amastigotes can then differentiate into trypomastigotes, which rupture out from their cysts and can either invade another cell or circulate within the blood to infect another intermediate host. Amastigotes are most commonly found in cardiac and skeletal muscle, but can also occur in reticuloendothelial, neural, and glial cells.[1,4]

T. cruzi infection in primates often results in nonspecific clinical signs including edema, anemia, hepatosplenomegaly, and lymphadenitis. The most severe sequela of infection is myocarditis. Myocarditis can result in dilated cardiomyopathy, arrhythmias, and eventually death.[7] Myocarditis is likely the result of a variety of factors, including a reaction to degenerating parasites as well as an autoimmune component caused by a release of proteins from degenerating myofibers.[6,8]

This case is unusual in that it occurred in a monkey originally from Asia, where *T. cruzi* is not found. This particular monkey originated from China and was shipped to a holding facility in Texas, where it was held indoors in quarantine for approximately 2 ½ months. Following quarantine, the monkey was placed in a single-sex corn crib style outdoor housing unit for 11 months. This is most likely where the animal became infected. The clinical history of this monkey while at the holding facility was unremarkable. A few cases of *T. cruzi* in animals housed at this facility have occurred, and human cases are not uncommon in the surrounding area.

JPC Diagnosis: Heart: Pancarditis, lymphoplasmacytic, and histiocytic, multifocal, mild to moderate, with myocardiocyte degeneration and necrosis and rare intracytoplasmic protozoal amastigotes.

Conference Comment: In most cases of cardiac *T. cruzi* infection,, granulomatous myocarditis with myocyte degeneration and necrosis is most severe in the right atrium and ventricle, while chronic disease, such as in this case, presents as lymphoplasmacytic myocarditis concentrated in the apex of the heart with fewer organisms. In addition the organs listed by the contributor, *T. cruzi* amastigotes have been found within germinal cells in the testicle of dogs surrounded by an intense lymphoplasmacytic interstitial orchitis[4].

Two proteins on the surface of *T. cruzi* are involved in its entry into macrophages and other host cells. Trans-sialidase removes host cell sialic residues and transfers them to a parasite surface protein (Ssp-3), which binds to host cells. Penetrin binds extracellular matrix proteins, heparin, heparin sulfate, and collagen and mediates parasite invasion into host cells. Intramacrophage survival is due to rapid movement from lysosomes to the cytosol, which is mediated by neuraminidase which removes sialic acids from host proteins and destabilizes the lysosomes, and hemolysins, in which lysosomal acid pH stimulates release and the formation of pores in lysosomal membranes[2].

Protozoal pseudocysts were difficult to find, and were often located in myofibers unaffected by the inflammatory response. Due to the low numbers of observable parasites and atypical host, several viral etiologies were also considered in the differential diagnosis including picornaviridae, such as encephalomyocarditis virus or Coxsackie B virus, and morbillivirus (measles), adenovirus, and betaherpesvirus (cytomegalovirus).[5].

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CASE II: G7979 (JPC 3136262).

Signalment: 10 year-old intact female rhesus monkey (*Macaca mulatta*), nonhuman primate.

History: The animal belonged to a breeding group of rhesus monkeys housed in an indoor-outdoor facility with free access to a large outdoor enclosure. This monkey was found dead without prior signs of illness.

Gross Pathology: Gross pathologic findings were limited to the abdominal cavity. Severe hepatomegaly was demonstrable, with fibrous transformation of the liver tissue affecting nearly all lobes and the gallbladder. Multiple cysts of different sizes were distributed throughout the fibrous hepatic tissue. The cysts had a diameter up to 5 cm that were filled with gelatinous to liquid material and contained hydatid sand. A generalized subacute peritonitis was a concomitant finding. The mesenteric lymph nodes appeared enlarged. Similar multiloculated cysts were present in the pancreas.

Contributor's Histopathologic Description: Histopathologic examination revealed metacestodal tissue in all liver samples. The liver parenchyma was destroyed by infiltrative growing cysts of different sizes which were surrounded by a fibrous hyaline membrane. Most cysts appeared empty. Single cysts contained protoscolices, arrays of hooklets and brood capsules. Calcareous corpuscles were present in the vicinity of the germinal layer. The cysts were surrounded by chronic inflammatory cell infiltration with foreign body-type giant cells.

Immunohistochemistry: *Echinococcus multilocularis:* positive

Contributor's Morphologic Diagnosis: Liver: hepatitis, granulomatous, chronic, multifocal, severe, with metacestodes consistent with *Echinococcus multilocularis,* rhesus monkey (*Macaca mulatta*), non-human primate.

Contributor's Comment: *Echinococcus* belongs to the phylum of *Platyhelminthes*, the class of *Cestodea* and subclass of *Eucestodia*. The genus of *Echinococcus* is subordinated to the order of *Cyclophyllidea* and the family of *Taeniidae*. Echinococcosis is a zoonotic disease, caused by adult or larval stages of cestodes which belong to the genus *Echinococcus*. Up to now, four species of *Echinococcus* are known – *E. granulosus*, *E. multilocularis*, *E. oligarthrus* and *E. vogeli*. The life of the parasites shows a cyclic structure.

The alveolar echinococcosis (AE) is an infectious disease which is caused by the second larval stage (metacestode) of the fox tapeworm. The adult parasite lives in the gastrointestinal tract of foxes of the genera *Vulpes* and *Alopex*, which are the definitive hosts. The eggs, including the first larval stage (oncosphere), get outside with the feces and are ingested by intermediate hosts, which typically are rodents of the family *Arvicolidae*. In the intermediate host, the oncosphere penetrates the intestinal wall and enters the blood system. Via the blood stream, the oncosphere reaches different organs, especially the liver. Once the oncosphere has reached the liver it starts to develop into the metacestode stage. In contrast to *E. granulosus* with the development of a unilocular cyst, the typical cyst of *E. multilocularis* shows a multilocular structure. The cyst with brood capsules and protoscolices may disturb the functions of the liver, depending on its size and location. The development of protoscolices can take several months. There may be several thousand protoscolices within a cyst. If protoscolices are ingested by a definitive host, they develop to the sexually mature adult tapeworm, approximately four to six weeks after infection. Thus, the cycle is closed[5].

All mammals (including man and nonhuman primates) in which metacestodes develop may be an intermediate host, but it is important to distinguish between a real intermediate host, which plays a role in the perpetuation of the cycle, and an accidental intermediate host like this monkey, which is a dead end for the parasite.

Many monkey species are susceptible to infection with *E. multilocularis*[1,2,6,7]. In recently described small outbreaks, only a few species were affected (five *M. fascicularis* and two *Gorilla gorilla*[7] or 12 *M. fuscata*[8]). A larger outbreak at the German Primate Center affected three different Old World monkey species simultaneously in a period of 12 years[9]. In this largest reported outbreak, cynomolgus monkeys are the species at risk. As previously reported, the percentage of infected cynomolgus monkeys among colonies of captive primates was conspicuously high (> 50%)[3].

Since the 1990s, *E. multilocularis* infection is spreading geographically and increasing infection rates of red foxes have been noted in Eastern and Western European countries[4]. In Northern Germany, Denmark and Poland, prevalence rates in foxes are usually < 5%, but focal areas of higher prevalence exist. Animals in zoological gardens and in institutional colonies in the northern hemisphere are at risk and alveolar echinococcosis must be considered as an emerging disease. Certain species of non-human primates are very susceptible to alveolar echinococcosis and may thus indicate previously unknown areas of high transmission.

JPC Diagnosis: 1. Liver: Hydatid cyst, multiloculated, with hepatocellular loss and fibrosis, and mild granulomatous hepatitis.
2. Liver: Amyloidosis, diffuse, moderate.

Conference Comment: Amyloid, confirmed by Congo red staining, diffusely expands the space of Disse throughout the liver adjacent to the hydatid cysts. Secondary amyloidosis is frequently the major complication of several chronic inflammatory diseases. The incidence of AA amyloidosis is relatively high in cases with granulomatous diseases of known etiology such as tuberculosis, leprosy and osteomyelitis. Metazoan parasite-induced amyloidosis has also been reported in rodent filariasis, human schistosomiasis, and rodent and non-human primate alveolar hydatidosis. Hydatid cysts trigger a massive influx of leukocytes at the focus of infection.[1] Elaboration of cytokines in chronic inflammation stimulates increased positive acute phase proteins, such as serum amyloid A (SAA). Regulation of synthesis of acute phase proteins is largely modulated by cytokines such as IL-6, IL-1, TNF-alpha, IFN-gamma, and TGF-beta, and has been shown to influence the serum concentration of acute phase proteins. SAA is the most sensitive acute phase protein, and serum levels of SAA have been used both in diagnosis and monitoring of inflammatory and infectious diseases. Amyloidosis is thought to be due to either the defective degradation of SAA or the production of abnormal SAA that is resistant to degradation[10].

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CASE III: AP10-5169 (JPC 4004526).

Signalment: 3-year-old male pigtail macaque (*Macaca nemestrina*) non-human primate

History: The monkey received a total dose of 1200cGy total body irradiation on 9/18 and 9/19/2010. Antibiotic prophylaxis was instituted immediately. Cell infusion was performed on 9/20, during which the monkey had an anaphylactic episode, and was given Benadryl and recovered. Multiple whole blood transfusions were given between then and the time of death. Two weeks post-radiation, the monkey started doing poorly and showed signs of edema, petechiae, and watery diarrhea. Five days later, the monkey became hypothermic and died the next day while under light sedation with ketamine.

Gross Pathology: Multifocal cutaneous petechiae; subcutaneous edema; diarrhea staining in the perianal region; mild hydrothorax; hydropericardium 10 ml; mild ascites; diffuse collapsed/atelectatic lungs due to hydrothorax; marked diffuse edema of the stomach and intestinal wall.

Laboratory Results: Hypoproteinemia, pancytopenia.

Histopathologic Description: Stomach: Diffusely the mucosa is mildly thickened by a combination of necrosis, hemorrhage and innumerable small protozoans which surround, separate, and occasionally replace necrotic gastric glands. Glandular mucosa is multifocally and transmucosally necrotic – glandular epithelium is shrunken, with karyolytic or pyknotic nuclei. Often glands are lined with attenuated epithelium, with dilated lumens which contain sloughed epithelial cells, cellular debris, and protein. Glands are often separated with a combination of hemorrhage, edema, and cellular debris. Innumerable 4-6 um pyriform protozoans with flocculent basophilic cytoplasm and a single round basophilic nucleus are present within the lamina propria, numerous gastric glands, and transmigrate the muscularis mucosa into the submucosa, where they often fill dilated lymphatics and are present in variable concentrations throughout the surrounding submucosa (where they are occasionally phagocytosed by macrophages). The submucosa is markedly expanded by edema, and multifocally, there is marked perivascular hemorrhage. The walls of affected arterioles are often expanded by brightly eosinophilic protein and cellular debris (necrotizing vasculitis). Protozoans are also present within the interstitium and lymphatics of the muscularis and serosa, but rarely associated with significant inflammation.

Contributor's Morphologic Diagnosis: Stomach; mucosa, lamina propria: Diffuse, severe edema and hemorrhage with myriads of extracellular/interstitial and intravascular/intralymphatic protozoa. (trichomonad gastritis.)

Jejunum; mucosa, lamina propria: Diffuse, severe edema and hemorrhage with myriads of extracellular/interstitial and intravascular/intralymphatic protozoa.

Bone marrow; sternum, femur, and tibia: Myeloid hypoplasia, severe, radiation-induced.

Contributor's Comment: Histopathology revealed a severe infection of the stomach and intestines by protozoal organisms; these organisms originated in the lumen and infiltrated through the mucosa into the submucosa and muscular layers, and were also present within blood and possibly lymphatic vessels. This caused marked disruption of the gastric and intestinal walls and was likely the cause of the severe protein loss indicated in the clinical chemistry finding of hypoproteinemia. Hypoproteinemia causes decreased osmotic pressure and loss of fluid from vessels, resulting in interstitial edema and accumulation of fluid in the body cavities. The size and morphology of the protozoal organism is consistent with a trichomonad. Trichomonads are anaerobic flagellated protozoa that are commensal organisms in many species of mammals and birds and, with some exceptions, are considered nonpathogenic. In monkeys, trichomonads may be present in the lumen or within crypts of the gastrointestinal tract but rarely elicit an inflammatory response or other pathologic changes, but have been reported as a cause of gastritis in SIV-infected macaques[1]. It is likely in the present case that the radiation induced hydrochloria and damage to the gastric and intestinal epithelium, resulting in breaks of the mucosal barrier and allowing entry and colonization of the protozoa and that the radiation-induced bone marrow immunosuppression rendered the monkey incapable of eliminating the infection. The protozoan was confirmed to be a trichomonad by electron microscopy.

JPC Diagnosis: Stomach: Gastritis, necrotizing, multifocal to coalescing, moderate to severe, with marked submucosal edema, necrotizing vasculitis, and innumerable protozoan trophozoites.

Conference Comment: Conference participants discussed the histologic changes that are likely attributed to the ablative dose of radiation received by the macaque including the profound lack of inflammation present in relation to the protozoal infection. Non-human primates with simian immunodeficiency virus (SIV) can also be similarly affected, but there is usually accompanying neutrophilic inflammation[1]. The mucosal necrosis is also likely due to the direct effects of radiation providing a route of entry for the normally commensal organism. Radiation injury in the stomach results in parietal cell death, hypochlorhydria, and the increased pH would lead to breakdown of the mucosal barrier and is another route of entry for the protozoa, as well as increased survivability of the parasite within the stomach. The marked submucosal edema is likely due to several factors, including lymphatic obstruction by the protozoa and decreased oncotic pressure due to hypoproteinemia from maldigestion and malabsorption as well as loss from diarrhea.

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CASE IV: 2010-46 (JPC 3166452).

Signalment: Twenty-three month old male Wistar Transgenic, *Rattus norvegicus*

History: This rat was noted to have a swollen testicle on 3/9/2010. Physical examination revealed a quiet but responsive animal with mild ocular porphyrin staining and a swollen discolored scrotum. Only one testicle was found in the scrotum on palpation. The rat was a sentinel animal and was not previously used in research studies. The animal was submitted to necropsy for complete postmortem evaluation on the day after examination.

Gross Pathology: Gross examination revealed pale mottled lungs, an enlarged spleen covered by white material and a mottled liver with a roughened surface. Multiple areas of yellow-brown pigmentation were in the omentum and the mesentery. The right testicle was in the scrotum. The left testicle was in the abdomen. Both testicles were cystic with multiple cysts containing a thick, yellow-tinged fluid.

Contributor's Histopathologic Description: The normal architecture of the testicle is effaced by large sheets of neoplastic cells separated by thin septa and multifocal variably sized cystic spaces which contain eosinophilic material with cysts lined by flattened to cuboidal epithelial cells. The neoplastic cells are polyhedral to cuboidal and have acidophilic, often vacuolated, cytoplasm with small round to oval nuclei. At the periphery occasional seminiferous tubules are observed. These tubules are lined by one layer of cuboidal cells and rare giant cells with minimal evidence of normal spermatogenesis. The surface of the tunica vaginalis has multifocal papillary projections which consist of proliferative cuboidal epithelioid cells overlying a fibrovascular core. Similar neoplastic cell proliferation is associated with the tunica vaginalis of the epididymis.

Contributor's Morphologic Diagnosis: 1. Interstitial cell tumor, left testicle
2. Mesothelioma, left testicle
3. Diffuse severe testicular atrophy and degeneration with cyst formation

Contributor's Comment: The incidence and types of primary testicular neoplasms vary between the different stocks and strains of rats. For neoplasms of gonadal stromal origin, interstitial cell (Leydig cell) tumors occur most frequently in older male rats with incident rates approaching 90% in the Fischer 344 (F344) strain[1] and 11% in the Wistar stock[5]. Interstitial cell tumors are uncommon in the Sprague-Dawley stock[1]. Leydig cells are found adjacent to the seminiferous tubules in the testicle and produce testosterone in the presence of luteinizing hormone (LH). When Leydig cells are stimulated by the pituitary hormone LH, the cells may grow uncontrollably and form a

Leydig cell tumor[6]. These tumors are usually benign[1], however they may be hormonally active and have been associated with concurrent hypercalcemia[4,6]. This neoplasm usually has a nodular growth pattern. In larger neoplasms, testicular architecture may be completely effaced[1]. Mesotheliomas are tumors arising from the serosal membranes of the coelomic cavities. The tunica vaginalis propria testis is one of these cavities, which is formed by an outpouching of the abdominal peritoneum. Mesothelioma occurs most frequently in the pleural or peritoneal cavity, but in rare cases these tumors can also arise from the mesothelial cell lining of the tunica vaginalis testis of the testes and epididymis[1]. Mesotheliomas are occasionally encountered in laboratory rats with a higher incidence (2.3%) in the F344 strain[3]. Spontaneous mesotheliomas have not been reported in the Wistar rat. To the authors' knowledge, this is the first reported case of concomitant interstitial cell tumor and mesothelioma in the testicle of a Wistar rat.

JPC Diagnosis: 1. Testis: Interstitial cell tumor.
2. Testis, vaginal tunics: Mesothelioma.

Conference Comment: Interstitial cell tumors, common in rats and rabbits, often exhibit hemorrhage, necrosis, and mineralization; none of which are features of this case. Typically, interstitial cell tumors demonstrate immunoreactivity for inhibin, and mesotheliomas demonstrate immunoreactivity for vimentin and cytokeratin. Ultrastructurally, interstitial cell tumors contain lipid droplets, lipofuscin, abundant smooth endoplasmic reticulum, desmosomes, and characteristic tubulovesicular mitochondrial cristae; whereas, other testicular and epididymal cells have lamellar mitochondrial cristae. Ultrastructural features of mesothelioma include a microvillous cell membrane, junctional complexes, pinocytotic vesicles, and a distinct basal lamina. Microfilaments are often abundant and may be difficult to differentiate from endothelial cells[2].

Conference participants discussed the atrophy of the seminiferous tubules and lack of sperm in the epididymis; likely due to elevated temperature associated with the intrabdominal location.

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