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Department of Veterinary Pathology
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Conference Moderator: MAJ Greg Saturday, DVM, Diplomate ACVP
Armed Forces Institute of Pathology
Washington D.C.

CASE I – N85-2570 (AFIP 2994518)

Signalment: A geriatric female rhesus macaque, *Macaca mulatta*, nonhuman primate.

History: This rhesus monkey had a history of chronic weight loss and was being fed and medicated via nasogastric tube. The monkey was found dead during a routine morning health check.

Gross Pathology: Emaciated
Diffusely pale liver with accentuated centrilobular pattern (not submitted)
Cervical mass (not submitted)
No gross lesions were observed in the heart

Histopathologic Description: Multifocally expanding the epicardium, myocardium, and endocardium, and surrounding and replacing degenerate and necrotic myocardiocytes, are variable numbers of lymphocytes, plasma cells, macrophages, and fewer neutrophils. Degenerate myocardiocytes are characterized by fragmentation, pale to hypereosinophilic vacuolated sarcoplasm, loss of cross striations, and occasional mineralization. Multifocal myocardiocytes contain variably sized oval, intrasarcoplasmic pseudocysts that contain numerous amastigotes. The amastigotes are 2-4 um in diameter, round to oval, and contain a nucleus and a variably distinct rod shaped kinetoplast oriented parallel to the nucleus.

Contributor's Morphologic Diagnoses: 1. Heart: Myocarditis, necrotizing, subacute, multifocal, moderate, with intrasarcoplasmic amastigotes, etiology consistent with *Trypanosoma cruzi*, rhesus macaque, *Macaca mulatta*, nonhuman primate.

2. Liver: Vacuolar change, lipid-type, diffuse, severe. (not submitted)
3. Cervix: Leiomyoma. (not submitted)

Contributor's Comment: *Trypanosoma cruzi* is a hemoflagellate protozoal organism that is the cause of American trypanosomiasis, or Chagas' disease. Unlike many other protozoal parasites it has little host specificity and has been isolated from over 100 mammalian species and dozens of insect vectors. Two forms of trypanosomiasis exist, American trypanosomiasis and African trypanosomiasis. In the United States, the American form is most prevalent in the southern states and has been reported in Maryland. Important reservoir host include dogs, raccoons, opossums, armadillos, and rodents.

Trypanosoma cruzi is passed between animals, and to humans, by reduviid bugs (family Reduviidae), also called cone-nose bugs, assassin bugs, or kissing bugs. The life cycle involves three morphologic forms. Two of the forms, trypomastigotes (blood form) and amastigotes (leishmanial or intracellular form), are found in susceptible animals. The other form, the epimastigote, is found in the digestive tract of the reduviid bug. The reduviid bug is infected when it ingests trypomastigotes in a blood meal from an infected host. Ingested trypomastigotes transform into epimastigotes and undergo asexual reproduction in the vector's gut. The epimastigotes move to the hind gut and transform back into the trypomastigote form. When the reduviid bug feeds it also defecates. Infection occurs when trypomastigote containing feces comes in contact with the broken skin at the site of the bite. Other means of transmission include ingestion of an infected bug, infected feces coming in contact the mucous membranes (eyes or mouth), ingestion of food contaminated with infective feces, and blood transfusions. Once the trypomastigote gains access to the host's blood stream it can enter smooth, skeletal, and heart muscle cells, and cells of the reticuloendothelial system. Transformation into the amastigote stage requires brief exposure to an acidic phagolysosome. The trypomastigote stimulates an increase in intracellular calcium promoting fusion of the phagosome with the lysosome. This results in an acidic environment and also actives hemolysins which disrupt lysosomal membranes and release the trypomastigote into the cell's cytoplasm. Within the cytoplasm trypomastigotes form pseudocysts, and reproduce as amastigotes. Amastigotes develop flagella; rupture the host cell eliciting an inflammatory response, and gain access to the blood stream. Upon entering the blood stream trypomastigotes penetrate smooth, skeletal, and heart muscles, or infect reduviid bugs when the insect takes a blood meal. *T. cruzi* also has the ability to disable the host's alternative pathway of the complement system. The parasite contains a surface homologue of the human complement regulatory protein decay-accelerating factor (DAF). DAF binds C3b, inhibiting C3 convertase formation and alternative pathway complement activation.

Natural infection with *T. cruzi* has been reported in numerous New World primates from South America and Panama. Old World Monkeys, including macaques and lemurs, become susceptible when located in a geographic area containing reduviid bugs or when experimentally infected. Infection is often subclinical or can result in non-specific clinical signs including generalized edema, anorexia, fever, dyspnea, anemia, leukocytosis, hepatosplenomegaly, lymphadenopathy, and myocarditis. The most frequently occurring lesion in nonhuman primates is myocarditis. The degenerating pseudocysts and destruction of myocardial fibers elicits a mononuclear cell inflammatory response. In conjunction with myocardial cell damage, damage to the conductance pathways in the heart eventually result in dilated cardiomyopathy and cardiac arrhythmias. A similar pathogenesis can occur in the digestive tract resulting in damage to smooth muscle and the myenteric plexus, causing megacolon and megaesophagus.

A histopathologic differential diagnosis for *T. cruzi* in a rhesus monkey would include *Toxoplasma gondii*. Tissue cysts of *T. gondii* can be found in cardiac and skeletal muscle, and contain small (1-3um) oval, PAS-positive bradyzoites that lack kinetoplast. Other non-protozoal causes of myocarditis in some species of nonhuman primates include encephalomyocarditis virus and coxsackie B virus, both members of the family Picornaviridae.

AFIP Diagnosis: Heart: Myocarditis, necrotizing, subacute, multifocal, moderate, with rare intrasarcoplasmic amastigotes, etiology consistent with *Trypanosoma cruzi*, rhesus macaque (*Macaca mulatta*), primate.

Conference Comment: The contributor provides a thorough review of American trypanosomiasis, or Chagas' disease. Conference attendees discussed the infectious causes of myocardial necrosis and developed a differential diagnosis list for "dit-dot", intracellular microorganisms.

Differential Diagnosis list for intracellular "dit-dot" microorganisms:

- *Toxoplasma/Neospora*: No kinetoplast
- *Leishmania*: Larger kinetoplast perpendicular to the nucleus (parallel in *T. cruzi)*; restricted to macrophages (not myocytes); no trypomastigote form
- *Sarcocystis* spp: No kinetoplast
- *Histoplasma capsulatum*: Intracellular yeast; no kinetoplast
- Other *Trypanosoma* spp: No tissue amastigote form

Other causes of myocarditis that attendees considered include malaria as well as encephalomyocarditis virus (EMCV), coxsackie B virus, bacterial infections and vitamin E deficiency.

In addition to *T. cruzi*, several other species of trypanosomes have long been associated with both human and animal disease. Below is a simple chart listing those diseases and the species that cause them:

Species	Disease	Definitive Host	Intermediate Host	Geographic Distribution
T. cruzi	Chagas' disease; American Trypanosomiasis	Man, dog, cat, monkey, opossum, armadillo	Kissing bug	Central and South America and southern U.S.
T. evansi	Surra	Equidae, ruminants, dogs, elephants	Horse flies	Africa, Asia, S. America, Far East
T. equiperdum	Dourine	Equidae	Transmitted by coitus	Cosmopolitan; rare in the United States
T. vivax	Souma	Cattle, sheep, horse, goat, camel	Tsetse fly	Central and South America
T. brucei	Nagana	Man, domestic and wild mammals (not goats)	Tsetse fly	Tropical Africa
T. congolense	Trypanosomiasis	Equidae, ruminants, pig, dog, camel	Tsetse fly	Tropical Africa
T. rhodesiense, T. gambiense	African Sleeping Sickness	Man, antelope	Tsetse fly	East and Tropical Africa
T. equinum	Mal de Caderas	Equidae		Tropical and Subtropical South America
T. hippicum	Murrina de Caderas	Horses and mules		Central America

Chagas' disease in humans can be divided into acute and chronic forms. In the acute form, myocarditis and focal myocardial cell necrosis predominates, often with generalized lymphadenopathy or splenomegaly. The chronic form occurs in 20% of infected patients 5 to 15 years after initial infection and is characterized by intense lymphoplasmacytic and histiocytic interstitial and perivascular inflammation with scattered myocardial cell necrosis and fibrosis. Lesions are believed to be the result of either an immune response directed against the remaining parasites or the production of T-cells and antibodies which cross react with host myocardial and nerve cells. Damage to myocardial and myenteric plexus nerve cells results in dilated cardiomyopathy, megaesophagus and megacolon. (5)

As mentioned by the contributor, infection occurs when feces containing trypomastigotes comes in contact with broken skin at the site of the reduviid bug's bite. Interestingly, in contrast to the vectors found in South America, the vectors identified in the United States exhibit delayed defecation following ingestion of a blood meal, resulting in decreased chance of transmission.

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CASE II – 5-2556-6-2 (AFIP 2991407)

Signalment: Adult female beluga whale (*Delphinapterus leucas*) with no evidence of reproductive activity.

History: One of 11 hunter harvested animals sampled from the Mackenzie Delta, NWT, Canada, July 1-13, 2004

Gross Pathology: There was diffuse moderate enlargement of the thyroid gland and on sectioned surface, immediately below the capsule and extending randomly within the parenchyma, there were numerous 0.2-1.0 cm, well circumscribed, firm white nodules. There were no other significant gross internal or external lesions.

Laboratory Results: PCR negative for *Brucella* spp. and dolphin morbillivirus. Liver mercury = 8.8 ppm, selenium = 32.44 ppm. Bacteriology yielded light growth of

Staphylococcus epidermidis and *Corynebacterium* spp. from the liver and lymph nodes and there was no significant growth from the brain, small intestine, or lung.

Histopathologic Description: Randomly throughout the parenchyma, there are multiple variably sized, well delineated, moderately cellular, to multifocally hypercellular and cystic, partially encapsulated nodules which compress and distort adjoining thyroid follicles. The cells are arranged as sheets, bi- to multilayered cords and entrapped follicles that are occasionally cystic. There is a moderate amount of fibrovascular stroma. Throughout the intervening parenchyma, the follicles are variably sized, occasionally distended by colloid and multifocally bound by micropapillary proliferations. In smaller follicles, there is multifocal follicular hyperplasia with apical cytoplasmic vesiculation.

Contributor's Morphologic Diagnosis: Thyroid gland: Hyperplasia, adenomatous, multifocal, moderate with follicular cyst formation and micropapillary proliferations

Contributor's Comment: Beluga whales (*Delphinapterus leucas*) are an integral part of the folklore and natural history of the Inuvialuit and federal legislation in Canada affords an inalienable right to these people to hunt and harvest marine mammals for consumption. Marine mammals are exempt from inspection by the Canadian Food Inspection Agency and monitoring and reporting of the health status and public health implications of disease processes in wild beluga stocks has been informally under the purview of the Department of Fisheries and Oceans. Due to ongoing concerns about human consumption and the potential impact of oil exploration and development in the Mackenzie delta, a baseline health assessment was initiated. Between 1 July to 13, July, 2004, 13 beluga whales were harvested by Inuvialuit in the vicinity of Hendrikson and Kendall Islands, North West Territories (NT). Nine animals were females and 4 were males. Two animals were severely emaciated. In 4 whales, there was moderate verminous pneumonia and 2 additional animals had diffuse interstitial pneumonia. Two animals were not available for diagnostic evaluation.

One of the most significant and consistent microscopic findings were within the thyroid gland (in 9 of 11 animals). These nodular proliferations have previously been reported in beach cast and hunter harvested beluga whales in the St Lawrence estuary and Hudson Bay, Quebec. The pathogenesis of these proliferations remains unknown. The nodules are expansile and encapsulated suggestive of adenomas; however, adenomatous hyperplasia may be differentiated from this neoplasm by multifocal glandular involvement, varying degrees of encapsulation, more cellular pleomorphism and similarity to follicular epithelia within the adjoining parenchyma. In humans, hyperplastic nodules are polyclonal; whereas, adenomas are monoclonal. Endocrine disruption associated with contaminant exposure has been proposed; however, tissue loads do not correspond

to the degree of thyroid follicular involvement and there is considerable variation in contaminant exposure between the sampled regions. Representative tissues, including thyroid gland, heart, lung, kidney, adrenal gland, spleen, skin and small intestine were collected at the time of harvest and characterization and quantification of thyroid hormone receptors is currently underway.

AFIP Diagnoses: Thyroid gland: Hyperplasia, adenomatous, multifocal, moderate, with follicular cysts and micropapillary proliferations, beluga whale (*Delphinapterus leucas*), cetacean.

Conference Comment: An interesting case of a common lesion in an uncommon species. Conference attendees returned to the age-old debate of adenoma versus hyperplasia. In general, thyroid adenomas are focal, compressive and encapsulated neoplasms; whereas, thyroid adenomatous hyperplasia is multinodular, non-compressive and unencapsulated. Attendees were divided over whether to assign one morphologic diagnosis of adenomatous hyperplasia or two morphologic diagnoses addressing both adenomas and hyperplasia. Some stressed that the likelihood of multiple neoplasms arising in the same tissue simultaneously is slight; however, others argued that if the same tissue is subjected to oncogenic promoters over a given period of time then the likelihood of multiple neoplasms increases.

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CASE III – W6922-3 (AFIP 2987457)

Signalment: Two five-month-old pigeons, one female and one male (columbiformes; *Columba livia*)

History: Several pigeons became ill. Clinical signs: lethargy, severe weight loss and acute mortality. Examination of two animals revealed severe anorexia. They were euthanized to do a post mortem examination.

Gross Pathology: Anorexia, content of intestines: mucinous, faces in the rectum were normal. Congested lungs. Liver, spleen, kidney, brains: normal. Heart: dilated. Atrophic m. pectoralis. Bursa of Fabricius: small, dilated

Laboratory Results: Parasitologic examination faces: normal.
Microbiologic examination content of intestine: negative for Salmonella
Microbiologic examination liver sample: Escherichia coli

Histopathologic Description: Bursa of Fabricius: lymphocyte depletion, multifocal aggregates of intracytoplasmic, basophilic globular and botryoid inclusions in epithelial cells and macrophages.

Contributor's Morphologic Diagnosis: Pigeon circovirus infection

Contributor's Comment: Circovirus infection should be suspected as a possible primary agent in young pigeons with various clinical problems. This is due to a circovirus-induced immunosuppression with subsequent concurrent secondary infections. The clinical signs are associated with the secondary infections, which are often the cause of death.

Definitive diagnosis can be made by histopathology or electron microscopy[1,2]. On electron microscopy, the inclusions are nonenveloped and 14-17nm in diameter, arranged in a paracrystalline array.

AFIP Diagnosis: Bursa of Fabricius, follicles: Lymphoid depletion, diffuse, severe, with multifocal histiocytosis and intrahistiocytic basophilic and botryoid cytoplasmic inclusion bodies, pigeon, avian.

Conference Comment: Pigeons with Pigeon circovirus (PiCV) infections develop lesions in the spleen, bursa of Fabricius, gut-associated lymphoid tissue, and bronchus-associated lymphoid tissue. Changes in the spleen can range from lymphofollicular hyperplasia with scattered lymphocyte necrosis to lymphoid depletion and histiocytosis. Bursal changes can also range from scattered

lymphocyte necrosis to severe cystic bursal atrophy. Basophilic, botryoid, intracytoplasmic inclusion bodies can be seen in macrophages in splenic, bursal, gut-associated, and bronchus-associated lymphoid tissue and in bursal epithelial cells.

Other avian circoviruses include:

- Psittacine Beak and Feather Disease Virus (PBFDV): feather loss, abnormal feathers, and beak abnormalities in psittacines; basophilic intracytoplasmic inclusions in follicular epithelium
- Chick Infectious Anemia Virus (CIAV): acute, immunosuppressive disease of young chickens characterized by anorexia, depression, anemia and bone marrow hypoplasia with thymic and bursal atrophy in young chicks
- Canary circovirus: "black spot"; abdominal enlargement and gall bladder congestion; feather dystrophy and circoviral inclusions
- Gulls and geese: "runting syndrome"; circovirus-associated disease

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CASE IV – EM (AFIP 2995867)

Signalment: 11 month old, female, DBA, mouse.

History: 2 cage mates had a 2 day history of conjunctivitis and were found dead in the cage. This animal was sacrificed and investigated for suspected ectromelia virus infection.

Gross Pathology: Lesions in various cage mates ranged from conjunctivitis (Fig 1) to ulcerative dermatitis (Fig 2).

Laboratory Results: PCR was positive for mouse pox virus.

Histopathologic Description: Histologically, there was multifocal proliferative and ulcerative dermatitis with large, eosinophilic, intracytoplasmic inclusions (Fig 3F). Skin lesions were immunohistochemically positive for vaccinia virus. (Fig 3)

TEM description: Conjunctiva: There are multiple epithelial cells that lie on a basement membrane and are covered by lamellations of keratin. The cytoplasm of most cells contains a large, generally round, moderately electron dense, amorphous inclusion that occasionally displaces the nucleus. All cells contain numerous, small, round, electron dense particles. On inset, these particles are round, measure 200-250 nm in diameter, and contain an elliptical or peanut-shaped, electron dense core (pox virus).

Contributor's Morphologic Diagnosis: Conjunctiva: Degeneration, with numerous intracytoplasmic pox viruses and few electron dense inclusions.

Contributor's Comment: Ectromelia virus is an orthopoxvirus closely related to Variola virus and Monkeypox virus. It is a useful model for the study of poxviral pathogenesis and both antiviral and vaccine testing.[1] There are generally three clinical forms of the disease. Susceptible mice, such as C3H, DBA, and BALB/c develop acute, fatal disease with coagulative necrosis of the liver, spleen, and other organs. Moderately susceptible mice develop chronic skin lesions with erosive and ulcerative dermatitis that can lead to amputation of the distal limbs and tail. Resistant mice, such as B6, are asymptomatic.[2,3] Resistant mice often exhibit a stronger and more rapid immune response when compared to susceptible strains.[1]

Grossly, livers can be swollen and friable with pinpoint, white foci of necrosis. There is conjunctivitis, cutaneous erythema, crusting, alopecia, and dry gangrene of extremities. Microscopically, there is multifocal and random coagulative necrosis of hepatocytes. Adjacent hepatocytes undergo degenerative changes and often contain basophilic, to amphophilic, intracytoplasmic inclusions (type B). Within the skin there is epidermal hyperplasia, ballooning degeneration, and prominent eosinophilic, intracytoplasmic inclusions (type A). Similar lesions can be found in the conjunctiva, mucous membranes, and intestinal epithelium.

Ultrastructurally, infected cells exhibit typical degenerative changes. Within hepatocytes there is loss of glycogen, vesicular swelling of the endoplasmic reticulum, mitochondria, and Golgi, and sparse lipid droplets.[2] The cytoplasm is

often displaced by low electron-dense matrices thought to be the ultrastructural correlate of type B inclusions.[2] Immature viral forms emerge that have a dense, eccentric body and a less dense matrix of viroplasm enclosed by a membrane with surface projections.[4] Mature virions are often brick-shaped and are 300 to 450 nm in diameter. They consist of an electron-dense, often dumbbell-shaped core, which contains viral DNA, and is surrounded by an intermediate coat and a lipoprotein envelope.[4]

Pox viruses encode several proteins that promote infection and survival. They often encode growth factors that mimic epidermal growth factor and stimulate keratinocytes. The stimulated keratinocytes have an increased susceptibility to pox viral infection.[4] In addition, ectromelia virus further promotes infection by encoding a protein that inhibits UV-induced apoptosis.[4]

AFIP Diagnosis: Conjunctiva (per contributor): Epithelial cell degeneration, with numerous intracytoplasmic pox virions, and few electron dense inclusion bodies, DBA mouse, murine.

Conference Comment: The contributor provides an excellent review of the ultrastructural characteristics of pox viral infections. Attendees described the normal ultrastructural anatomy of epithelial cells and then discussed the key features supportive of poxviral infection i.e. lamellations of keratin indicative of hyperkeratotic orthokeratosis; electron dense matrices interpreted as inclusion bodies; increased lucency within the cytoplasm supportive of intracellular edema (ballooning degeneration) and the characteristic 300-400 nm in diameter "brick-shaped" virions with a "dumbbell-shaped" DNA core.

Ectromelia virus was discovered in England in 1930 and has been extensively studied as a model of the pathogenesis of exanthematous diseases. The study of ectromelia virus led to the concept of a primary and secondary viremia as well as the role of cell mediated immunity, particularly T-lymphocytes and macrophages, in the recovery from infection. (5) Mousepox has a restricted host range and causes severe disease with a high mortality rate (50-100%). Voles are believed to be the natural host.

There are two recognized forms of mousepox: the rapidly fatal form with few, if any, cutaneous lesions and the chronic form with ulceration of the skin, particularly on the snout, feet and tail often resulting in loss of limbs or tail.

The typical gross findings in mice include conjunctivitis, alopecia, crusting and erythema of the skin and dry gangrene of the extremities and tail. The liver and

spleen swell and develop multifocal hemorrhages and pinpoint white foci. Lymph nodes and Peyer's patches may be enlarged and hemorrhagic.

Typical light microscopic findings include intracytoplasmic eosinophilic A-type (Marchal) inclusion bodies within the epidermis, pancreas and intestine. Early in the disease there is epidermal hyperplasia, hypertrophy, spongiosis and ballooning degeneration with inclusion bodies. Later, the epidermis becomes necrotic and ulcerated. The liver develops multiple foci of coagulative necrosis, hepatocellular syncytia and vacuolar degeneration with minimal inflammation. There is splenic necrosis involving both lymphoid follicles and red pulp. Additionally, there may be intestinal mucosal erosions and bone marrow degeneration. The combination of hepatic and splenic necrosis along with cutaneous lesions and characteristic eosinophilic intracytoplasmic inclusion bodies is pathognomonic. (3)

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