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Conference Moderator: Dr. Laura Richman, DVM, PhD, Diplomate ACVP
MedImmune Inc.
Gaithersburg, MD

CASE I – 2 or 3 (AFIP 2983562)

Signalment: 11 year old, wild-caught, female cynomolgus macaque

History: This macaque was imported from the Philippines in 1990 to augment the breeding colony at the California Regional Primate Research Center. Four years later she was brought to the attention of the veterinary service because of an equivocal tuberculin reaction and the presence of a skin rash. A follow up skin test using mammalian tuberculin, avian tuberculin and a sterile saline control produced a small induration at 24 and 48 hours to only the avian tuberculin inoculation. The result was considered equivocal for avian and negative for mammalian tuberculosis. She had previously been noted to have intermittent epistaxis, crusting of the nares, ulcerated nasal philtrum and nasal discharge. Thoracic radiographs revealed no significant findings.

Gross Pathology: On physical exam there was extensive necroulceration of the nasal philtrum, depigmentation of hands and feet, and multiple ulcerated 2-3 mm diameter nodules present symmetrically on the skin of the hands, wrists, ankles, feet, and tail base. Left axillary and bilateral inguinal lymphadenopathy were noted.

Laboratory Results: The animal was negative for type D retrovirus by ELISA. Tissue homogenates prepared from a skin biopsy specimen demonstrated acid fast bacteria (AFB) and positive reactivity for PCR amplified *Mycobacterium leprae.* Serum drawn at the time of the animal's arrival at the Primate Center was strongly positive by ELISA for the IgG anti-PGL-I (phenolic glycolipid-I), which is specific for *M. leprae*. Retrospective analysis of stored sera demonstrated a significant rise in IgM anti-PGL-I and IgM LAM (mycobacterium common lipoarabinomannan) as early as 6 months prior to the detection of cutaneous lesions.

Histopathologic Description: Two tissue samples have been submitted; ulcerated lesions from the foot and from the nares. Much of the dermis is effaced by multifocal to coalescing granulomas comprised of a central area of necrosis with few degenerate neutrophils surrounded by a well demarcated band of epithelioid macrophages admixed with multinucleated giant cells which is in turn is surrounded by a band of lymphocytes, plasma cells and reactive fibroblasts. The superficial dermis is diffusely infiltrated by large numbers of macrophages, neutrophils, lymphocytes and plasma cells that are associated with a focal ulceration of the overlying epidermis. The inflammatory infiltrate also extends into the deep dermis and in many sections is identified surrounding or infiltrating nerve bundles. In sections from the nares there is necrosis of cartilage. Acid fast stains revealed small numbers of AFB in the surface exudates, in the cutaneous histiocytic infiltrate, and within dermal nerve bundles. Immunohistochemical staining with Bacillus Calmette-Guérin (BCG) antibody was also positive.

Contributor's Morphologic Diagnosis: Skin, chronic multifocal to coalescing granulomatous and necrotizing dermatitis with cutaneous neuritis and epidermal ulceration (consistent with infection with *Mycobacterium leprae*)

Contributor's Comment: Submitted tissues are from archived samples of the first reported case of spontaneous leprosy in a cynomolgus macaque (1). Naturally occurring leprosy has been previously documented in only two species of nonhuman primates from West Africa – the chimpanzee and the sooty mangabey (2,3,4). Host immune response to *Mycobacterium leprae* is critical for control of the infection and is also responsible for the damage to skin and nerves, which is the basis for the clinical spectrum of disease. Different categories of leprosy exist as classified by Ridley and Jopling (5). Tuberculoid leprosy is characterized by a strong lymphocytic infiltrate and an effective histiocytic response to *M. leprae*, resulting in well-localized granulomas and few surviving organisms. The lesions are typical of the chronic delayed-type (type IV) hypersensitivity response. Lepromatous leprosy is characterized by a selective unresponsiveness to *M. leprae* antigens and an ineffective, diffuse histiocytic reaction with numerous intralesional organisms. Between these two groups are borderline forms of leprosy characterized by progressive reduction in the cellular-immune response and an increasing number of skin and nerve lesions, greater bacteria load and increasing antibody levels. The combination of the variably organized granulomatous inflammation, the paucibacillary nature of the lesions, the antibody responses to LAM and PGL-I, and the immunohistochemical data, place this animal in the paucibacillary mid-borderline category of leprosy.

Invasion of nerves by AFB and granulomatous inflammation in the submitted slides was variable but distinct and constitutes a defining characteristic of *M. leprae* lesions.

AFIP Diagnosis: Skin and subcutis, foot (per contributor): Dermatitis and panniculitis, pyogranulomatous, multifocal and coalescing, marked, with granulomatous neuritis, and focal ulceration, cynomolgus macaque (*Macaca fascicularis*), primate.

Conference Comment: There is some variation among slides with some of the contributors receiving a section of nares with cartilage. *Mycobacterium leprae* is an acid-fast obligate intracellular organism and the etiologic agent of leprosy, also known as Hansen's disease in humans. *M. leprae* causes a chronic granulomatous disease that primarily affects the skin and peripheral nerves. It is a zoonotic and is most common in tropical climates. Naturally acquired infections have been reported in wild nine-banded armadillos, sooty mangabey monkeys, and a cynomolgus macaque.

As mentioned by the contributor, there are two forms of the disease: the lepromatous form and the tuberculoid form, with a spectrum of intermediate stages between the two. The T-helper lymphocyte response to *M. leprae* determines whether an individual develops tuberculoid or lepromatous leprosy. (6)

Lepromatous leprosy (malignant disease) results from a lack of T cell immunity (anergy - unresponsiveness of host immune system) and is characterized by numerous macrophages filled with many mycobacteria (multibacillary). Lepromatous leprosy lesions lack effective CD4+ type 1 helper T cells but contain many CD8+ suppressor T helper 2 cells which secrete IL10 (inhibits helper T cells; mediates anergy), IL4 (induces antibody production by B cells), and IL-5 which may suppress macrophage activation. Antigen-antibody complexes may be produced resulting in vasculitis, glomerulonephritis and erythema nodosum. IL-12, produced by antigen presenting cells is important in the generation of T helper 1 cells, and low levels or unresponsiveness of T cells to this cytokine may reduce the T helper 1 response, leading to lepromatous leprosy. (6)

Tuberculoid leprosy (benign disease) is characterized by granuloma formation with few mycobacteria (paucibacillary). Numerous CD4+ type 1 helper T cells are located at the periphery of lesions where they secrete IL-2 and interferon gamma. Interferon gamma is critical to mobilizing an effective host macrophage response. (6) Few CD8+ lymphocytes are located in the center of the granuloma.

M. leprae grows more slowly than other mycobacteria and grows best at 32° to 34° C, the temperature of human skin and core temperature of armadillos. (6) Because of this affinity for cooler temperatures, human lesions are more common on the distal extremities, scrotum and upper respiratory tract. Typical clinical

findings include macular, nodular and papular lesions with hypoesthetic or anesthetic skin lesions and paralytic deformities in the extremities. The ulnar and perineal nerves are most often affected resulting in loss of sensation to the hands and feet. Skin lesions may become ulcerated and are most common in the subperiorbital area, lips, chins, ears, and scrotum.

Mycobacteria lepraemurium or murine leprosy affects rats and mice and has also been reported in cats, but is not considered zoonotic. *M. lepraemurium* primarily affects the skin and viscera; but very rarely affects peripheral nerves. (7)

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CASE II – N05-436 (AFIP 2994519)

Signalment: 12 yr old female Olive Baboon (*Papio cynocephalus anubis*)

History: This wild-caught African baboon presented with multiple subcutaneous nodules (fig 1). Hematologic and serologic testing of the animal demonstrated a moderate monocytosis, slight eosinophilia and hyperglobulinemia. Surgical biopsy of one of the nodules revealed several parasitic granulomas containing cestode larvae. Attempts to treat the animal with an antiparasitic drug proved unsuccessful. The animal was euthanized for humane reasons.

Gross Pathology: Multiple (too numerous to count) nodular tapeworm cysts ranging in size from 0.1 to 1.5 cm and containing viable cestode larvae were observed in the skin and subcutis. Infestation was particularly heavy in the lower right quadrant of the animal. Larvae were also observed grossly associated with lymphatic tissue, mesentery, skeletal muscle, and in pericardial, diaphragmatic and peripancreatic connective tissue (fig 2).

Contributor's Morphologic Diagnosis: Haired skin and subcutis: Granulomas, eosinophilic, multifocal, with epithelial hyperplasia, necrosis, hemorrhage and intralesional cestodes, etiology consistent with Spirometra sp.

Contributor's Comment: Multiple viable and degenerating cestode larvae are in the dermis and subcutis, forming eosinophilic granulomas. The parasites are morphologically consistent with plerocercoid larvae, or spargana (fig 3), of the pseudophyllidean cestode *Spirometra* spp. Histologic features that help identify the parasites as cestodes include an outer tegument surrounding a solid but loose mesenchymatous stroma containing calcareous corpuscles, excretory ducts, skeletal muscle bundles, and the absence of a digestive tract. Pseudophyllideans like *Spirometra* also lack anterior suckers that are present in Cyclophyllidean cestodes. Examples of cyclophyllidean larval stages include cysticercus, coenurus, hydatid cyst and the tetrathyridium of *Mesocestoides* spp.

The normal life cycle of *Spirometra* involves two intermediate hosts. The adult worms live in the definitive host, typically wild canids and felids. Water contamination with the eggs of *Spirometra* leads to infection of the primary intermediate host, a copepod (water flea), where it develops into the first larval stage (procercoid). The migrating second larval stage (plerocercoid or sparganum) of the cestode develops in the second intermediate host following ingestion of infected copepod. Infection with the plerocercoid stage, referred to as sparganosis, is known to occur in many different tissues and a wide variety of vertebrate hosts throughout the world, including small mammals, amphibians, reptiles, birds, and occasionally humans. It is also true that any number of mammal or avian predators

can serve as paratenic hosts (transport hosts) by consuming infected tissues of second intermediate hosts, resulting in serial transmission of the plerocercoid stage. The plerocercoid eventually develops fully into the adult tapeworm in the intestine of the definitive host.

Sparganosis has previously been reported in non-human primates including baboons, vervets and a highland Syke. The disease is also well documented in feral pigs, where it poses a particular hazard for transmission to people. Although people typically acquire the parasite by eating raw or undercooked meat of plerocercoid-infected animals, other possible routes of infection include direct ingestion of procercoid-infected copepods, and also direct contact in cultures that use animal tissues as poultices. In humans, spargana larvae are most commonly found in the subcutis, but have been reported to migrate into the CNS, breast, eye, urinary bladder, and lung.

AFIP Diagnosis: Haired skin and subcutis: Granulomas, eosinophilic, multifocal, with necrosis, hemorrhage, and numerous larval cestodes**,** olive baboon (*Papio cynocephalus anubis*), primate.

Conference Comment: The contributor provides an excellent example and review of sparganosis in a nonhuman primate. As noted by the contributor, sparganosis may be acquired by humans through the ingestion of undercooked meat, in which the plerocercoid larvae remain alive, and through the application of infected fresh animal tissue poultices, as is practiced in some cultures. Frogs are most commonly used in this practice. The sparganum invades the human tissue where the poultice is applied, most often the eye. Additionally, humans may contract the disease through drinking water contaminated with infected copepods.

A rare form of human sparganosis has been described in which the infective plerocercoids proliferate and invade every tissue except bone. The underlying pathogenesis of this variant of sparganosis is unknown. In general, sparganosis is a relatively benign human and animal disease; it may be more prevalent than reported due to this benign nature.

The main groups of cestodes encountered in histological section are the cyclophyllideans and the pseudophyllideans. Histologically it is almost impossible to determine the exact species of the parasite in question. However, two differences between members can be used to narrow the differential. Both the adult and larval forms of cyclophyllideans have four suckers on their anterior end. Pseudophyllideans lack these suckers.

Cyclophyllideans also have muscles (within the parenchyma) that separate the medullary and cortical regions. Pseudophyllideans lack these muscles. (4)

For a simple algorithm to help identify parasites in tissue sections, readers are encouraged to review WSC 15, case 3, 2005-2006. Additionally, readers are encouraged to review Wednesday Slide Conference 5, case 4, 1998 for a case of sparganosis in a pig.

This case was reviewed by Dr. C.H. Gardiner, parasitology consultant for the Department of Veterinary Pathology, AFIP.

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CASE III – PA-4195 (AFIP 2986824)

Signalment: Adult, male baboon (Papio sp.)

History: This adult male animal had a multiple month history of malaise with mild-moderate anorexia and some weight loss. The animal had peri-orbital hyperemia that was treated empirically with antihistamines. General physical exam findings and blood work at that time were inconclusive. The anorexia and malaise subsequently progressed significantly and the baboon experienced more marked body weight loss. It was also noted to be tachypneic, with increased respiratory efforts. On more recent physical exam a markedly enlarged spleen was palpated. A patchy, macular rash was present in the groin area. Thoracic radiographs

showed severe infiltrates, especially in the left hemithorax (see Figures 1 & 2). Hematologic assessment revealed a lymphocytosis. The animal was euthanized. Prior to sacrifice, a bronchioalveolar lavage was performed under general anesthesia (see Figure 3).

Gross Pathology: The body condition was considered thin but not cachetic. The spleen was markedly enlarged but of regular general contour. A fine, diffuse nodular granularity was noted on the capsular surface, although the organ had normal architecture on cut surfaces (see Figure 6). The lungs were totally adherent to the adjacent parietal pleura with disseminated fine adhesions. The visceral pleura was markedly thickened and opaque. Lung parenchyma in the entire left lung and the right diaphragmatic and middle lobes was firm, tan and of "meaty" consistency and did not float in formalin (see Figures 4 and 5). Some remaining aeration was noted in the right upper lobe. Thoracic para-spinal and hilar lymph nodes were markedly enlarged.

Contributor's Morphologic Diagnosis: 1) Diffuse, severe mixed cellular infiltration including prominent interstitial lymphoid aggregates with a significant blastic component and mixed epithelioid macrophage and granulocytic alveolar infiltrates, with numerous syncitialized giant cells (most prominently noted in slides labeled 1 & 1A) (see Figures 7 and 8)
2) Alveolar edema, patchy to diffuse, marked
3) Pleural thickening and fibrosis, focally extensive, marked

Contributor's Comment: The microscopic findings are consistent with STLV-1 associated lymphoma. This entity in baboons has been well described in the literature and is often associated with severe pulmonary tumor involvement. This animal was serologically positive for STLV-1, as well as for a variety of other retroviruses. The lung findings in this case included a significant associated pulmonary inflammatory process and this is also a well-documented finding in animals with advanced disease. Numerous syncytia (multinucleated giant cells) are seen (again, as previously described in this disease entity). Their pathogenesis is not immediately apparent, however, HTLV-1 (the closely related human counterpart) does induce syncytia formation in susceptible cell lines upon contact with virus-producing cells – in fact syncytial assay is a tool used in the detection of neutralizing antibody and cellular receptors. The extra-pulmonary disease distribution and pattern in this case (spleen, skin & lymph nodes) are also typical. It is not clear whether the late-course hematologic findings reported as peripheral lymphocytosis may have represented a leukemic component of the process. Peripheral smears are not available for review. STLV-1 seroprevalence is at high levels (>40%) in some colonies and this agent is closely related to HTLV-1, a type C retrovirus that has been linked to both adult T-cell leukemia and neurological disorders in humans. Other nonhuman primates, including rhesus macaques are

susceptible to infection with STLV-1, and intraspecies transmission (macaques to baboons) has been linked to large outbreaks at some centers.

AFIP Diagnosis: Lung: Lymphoma, with marked alveolar edema, histiocytosis, and numerous multinucleate giant cells**,** baboon (Papio sp.), primate.

Conference Comment: Simian T-cell lymphotropic viruses (STLV) are currently listed within the genus Deltaretrovirus, family Retroviridae. Other viruses belonging to the genus Deltaretrovirus include the type species Bovine Leukemia Virus, as well as the human T-cell lymphotropic viruses (HTLV). (5) As mentioned by the contributor, HTLV and STLV share many similar characteristics and, in some primate colonies, lymphomas are recognized that have all the hallmarks of adult T-cell leukemia/lymphoma (ATLL). (2)

Transmission of HTLV is dependant on the transfer of infected lymphocytes. In humans, the known routes of infection include the transfer of blood, milk and semen, with breast milk considered to be the most common mode of transmission. Clinically, most baboons with non-Hodgkin lymphoma have been diagnosed because of severe dyspnea followed by radiographic findings of diffuse interstitial pneumonitis and multifocal, circumscribed lesions consistent with neoplasia. Generalized lymphadenopathy and obliteration of nodal and pulmonary architecture by pleomorphic lymphocytes with hyperlobulated nuclei is another prominent finding. Additional clinical findings include: lymphocytosis or leukemia with significant numbers of atypical lymphocytes and dermatologic lesions with lymphocyte infiltration. (2)

Like HTLV, the life cycle of STLV includes the random integration of proviral DNA into the host genome. In most cases of HTLV, leukemic cells display an activated CD4+ T-cell phenotype. The viral transcriptional regulatory gene *tax* is directly or indirectly responsible for the expression of interleukin-2 receptor alpha-chain (IL-2R alpha), interleukin-2 (IL-2), and other cell surface markers that may lead, in some cases, to overt leukemias and lymphomas. Increased expression of IL-2R alpha coinciding with the CD4+ T-cell population is considered the hallmark of HTLV/STLV infection. In both humans and nonhuman primates, the *tax* gene presumably plays a pivotal role in the induction and immortalization of peripheral blood lymphocytes leading to lymphoid cancers. By up-regulating IL-2R alpha, IL-2, and other cytokines, an autocrine loop for T-cell activation and proliferation is established. (2)

Conference attendees considered Simian Immunodeficiency Virus (SIV) in the differential diagnosis. Like STLV, SIV is a retrovirus; however, SIV belongs to the genus Lentivirinae. SIV targets lymphoid tissues, specifically cells expressing the

CD4 molecule on their surface (helper/inducer T lymphocytes and antigen-presenting cells of monocyte-macrophage origin). Experimentally, SIV is readily transmissible via infected blood or serum, and through the genital mucosa. Pulmonary lesions associated with SIV infection include: interstitial pneumonia with lymphocytic infiltration of the interalveolar septa and peribronchial lymphoid hyperplasia (early infection); a characteristic giant cell pneumonia with multinucleated giant cells (syncytial cells) in alveoli and interalveolar septa; and, in some cases, diffuse alveolar fibrosis and bronchiolar epithelial metaplasia, especially in cases complicated by the atypical fungus, *Pneumocystis carinii*.

For a more complete list of retroviruses important in veterinary medicine, readers are encouraged to review Wednesday Slide Conference case 1, conference 15, 2005-2006.

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CASE IV – 05-1294 (AFIP 3007305)

Signalment: 2 yr old, male, Sprague Dawley rat, *Rattus norvegicus*

History: This rat was found moribund and died less than one hour later. No experimental manipulations had been performed.

Gross Pathology: There is little fat throughout the body. A small amount of ingesta is present in the stomach and intestines. The pleural and pericardial cavities are filled with blood. Both auricular walls and the left ventricular wall are expanded by a thin, tan infiltrative mass. (Fig 1)

Histopathologic Description: Heart: Expanding the endocardium and infiltrating the myocardium is an unencapsulated neoplasm that consists of spindle cells arranged in short interlacing streams and occasional whorls. Neoplastic cells have indistinct cell borders and are surrounded by a moderate amount of eosinophilic, fibrillar matrix. Nuclei are oval with finely stippled chromatin or are elongate and hyperchromatic. Mitoses are not observed. Rarely, there are spindle cells with markedly elongate, wavy nuclei (Anitschkow cells). Occasionally, neoplastic cells infiltrate and surround myocardial cells that are swollen, vacuolated, with loss of cross-striations (degeneration). Multifocally, along the endocardial surface, neoplastic cells are more polygonal with round nuclei that contain a single, prominent nucleolus.

Contributor's Morphologic Diagnosis: Heart: Endocardial Schwannoma

Contributor's Comment: Endocardial proliferative lesions are rare in rats. One study of over 19,000 rats found 44 cases of endocardial hyperplasia (0.2% prevalence) and 16 cases of neoplasia (0.085% prevalence).[1] The nomenclature for proliferative endocardial lesions in rats has been confusing due to the controversy over the cell of origin. Common diagnoses include endocardial schwannoma, neurofibroma, subendocardial fibrosis, Anitschkow cell sarcoma, and endocardial mesenchymal tumor.[1-5]

Grossly, there is a variably sized, firm, gray to white mass that lines the luminal wall, most often of the left ventricle.[2,3] Histologically, endocardial schwannomas often consist of two distinct cell types. The superficial layer contains mostly round to polygonal cells, with ovoid nuclei, prominent nucleoli, and finely vacuolated cytoplasm. The deeper and thicker layer, adjacent to the myocardium, is composed of spindle cells with elongated, hyperchromatic nuclei interspersed between collagenous fibers.[3] In larger neoplasms, spindle cells sometimes exhibit nuclear palisading and form Verocay bodies (Antoni type A).[3,4] Anitschkow cells are typically present. These cells have elongated, ribbon-like heterochromatin and are thought to be macrophages or regenerative myofibers.[6]

Ultrastructurally, there are again two types of cells. The spindle cells contain mitochondria, rough endoplasmic reticulum, and occasional filaments. They are surrounded by a convoluted basement membrane with few desmosomes. These features are typical of neoplastic Schwann cells. The second cell type is

pleomorphic with vesicular nuclei and short, densely packed cell processes and most likely is of mesenchymal origin.[2] Immunohistochemically, neoplastic cells are often positive for S100 and neuron-specific enolase.[4]

Endocardial schwannomas must be differentiated from endocardial hyperplasia. The latter consists of sharply demarcated subendocardial proliferation usually less than 20 cell layers thick. Neoplasia, however, exhibits active invasion with finger-like projections into the myocardium and increased mitotic activity. Hyperplasia and neoplasia can occur simultaneously. Metastasis is rare.[1,2,4]

Endocardial schwannomas appear to be unique to the rat. Heart tumors morphologically similar to endocardial schwannomas in the rat have been reported in hamsters, dogs, and man but they lack the subendocardial appearance of the rat tumor.[2]

AFIP Diagnosis: Heart, endocardium: Schwannoma, Sprague Dawley rat, rodent.

Conference Comment: The contributor provides an excellent review of endocardial schwannomas in rats. Schwannomas that arise within the hearts of rats can be either endocardial or intramural. Although both apparently arise from Schwann cells and form patterns that are typical of nerve sheath neoplasms, they have certain differences. Endocardial schwannomas always involve the left ventricle but can extend into the subendocardium and any of the adjacent cardiac chambers. In the present case, neoplastic cells are predominantly located within the left ventricle; however, some sections also have neoplastic cells within the right ventricular endocardium. The smallest endocardial schwannomas are little more than a subendocardial layer of spindle cells. As they enlarge, they infiltrate the adjacent myocardium, sometimes nearly replacing the intraventricular septum. They may also extend into the pericardial connective tissue or metastasize to other organs. In comparison, intramural schwannomas tend to form more discrete nodular masses and usually arise within either the left ventricular wall or intraventricular septum. They grow by expansion with minimal infiltration and do not metastasize. (7)

There are rare Anitschkow cells within the neoplasm. The nuclei of Anitschkow cells are ellipsoidal, have distinct nuclear membranes, and are pale except for an intensely stained central bar of chromatin along the long axis. As mentioned by the contributor, Anitschkow cells have been thought to represent either a cell of muscle origin or a cardiac histiocyte. In a study of fetal and neonatal hearts from humans, cells displaying the Anitschkow chromatin pattern were the predominant

cell type in the myocardium and it was concluded that the Anitschkow pattern probably indicates cellular immaturity rather than a specific cell type. (8)

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