The Armed Forces Institute of Pathology
Department of Veterinary Pathology
WEDNESDAY SLIDE CONFERENCE
2003-2004

CONFERENCE 5
8 October 2003

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CASE I – Case 2 (AFIP 2889963)

Signalment: Juvenile female cynomolgus monkey, *Macaca fascicularis.*

History: Colony monkey presented with abdominal distention. Supportive care was given with no clinical improvement. As a result, the animal was electively euthanized.

Gross Pathology: At necropsy, there were severe diffuse intra-abdominal adhesions involving the gastrointestinal tract, liver, diaphragm, and uterus.

Laboratory Results: None reported.

Contributor's Morphologic Diagnoses:
1. Colonic serosa, mesentery: Fibromatosis, severe, diffuse, with neovascularization, edema, and lymphoplasmacytic and histiocytic infiltrates.
2. Mesenteric lymph nodes: Atrophy, lymphoid, mild, diffuse.

Contributor's Comment: Microscopically, the colonic serosa and the mesentery were severely thickened by a disorganized fibroblastic proliferation infiltrating the fat and superficial region of the tunica muscularis longitudinal layer and surrounding the mesenteric lymph nodes. The microscopic changes are consistent with retroperitoneal fibromatosis characterized by two dominant morphologic patterns: proliferative and sclerotic. These can occur separately or, as in this case, the lesion can contain both variants. The proliferative pattern is characterized by randomly arranged plump fibroblasts with an interwoven network of collagen fibers and numerous blood vessels of variable size. In some areas, slit-like neovascular spaces are present with hypertrophic endothelium. There is a high nucleus-to-cytoplasm ratio. Mitotic figures are viewed occasionally (i.e., 0 to 2 at HPF). Edematous and myxomatous areas are observed as well as perivascular lymphocytes, plasma cells, and histiocyte infiltrates. The sclerotic pattern consisted of sparsely scattered elongated fibroblasts within a densely packed

bundle of collagen fibers with fewer blood vessels and inflammatory cells compared to the proliferative pattern[1].

Retroperitoneal fibromatosis was first recognized as a disease syndrome in 1976[2]. It is characterized by an aggressive proliferation of highly vascular fibrous tissue subjacent to the peritoneum[3]. Animals in the later stages of retroperitoneal fibromatosis disease often develop SAIDS, a simian acquired immunodeficiency syndrome, and present the following clinical signs: lymphoid depletion, weight loss, depressed immune functions, recurrent diarrhea, and chronic infections unresponsive to antibiotic therapy[1]. Affected monkeys often experience sudden death due to complications such as intestinal obstruction[1].

Simian retroperitoneal fibromatosis has many morphological and epidemiological similarities to human Kaposi's sarcoma (KS), which is highly associated with an immunodeficiency syndrome caused by viral infection (HIV, Simian retrovirus-2, SV40 and recently human herpes virus-8). While manifestations of KS are most severe in individuals with an immunodeficiency syndrome (epidemic KS), KS also can occur in immunosuppressed organ transplant recipients (iatrogenic KS). Furthermore, KS is often present in elderly Mediterranean men (classic KS) and is endemic in sub-Saharan Africa (endemic KS) where it is presently the most common malignancy[4].

AFIP Diagnosis: Colon, mesentery: Atypical mesenchymal proliferation (retroperitoneal fibromatosis), diffuse, cynomolgus monkey (*Macaca fascicularis*), nonhuman primate.

Conference Comment: Although the retroviral status of this particular monkey is not provided, the contributor points out the well-known association between retroperitoneal fibromatosis and type D simian retrovirus, serotype-2 (SRV-2). The mechanism of cellular transformation by SRV-2 is not known but several hypotheses have been proposed, including transformation of multipotential mesenchymal stem cells toward endothelial cells, fibroblasts, and pericytes; promotion of cell growth by basic fibroblast growth factor (bFGF); and the presence of elevated levels of the growth factor IL-6 in SRV-2 infected monkeys.[1,5,6]

Simian retrovirus can cause simian acquired immunodeficiency syndrome (SAIDS), which is often seen in animals in the later stages of retroperitoneal fibromatosis. The association between retroperitoneal fibromatosis and SAIDS is very similar to the association between Kaposi's sarcoma (KS) and human immunodeficiency virus-1 (HIV-1). Another similarity that makes retroperitoneal fibromatosis a good model for studying the relationship of HIV-1 and Kaposi's sarcoma is the presence of herpesviruses in both entities. Human herpesvirus-8 (HHV-8) has been identified in KS tumors, and is thought to be a cofactor in the development of KS. Retroperitoneal fibromatosis-associated herpesvirus of macaques (RFHV) is a gammaherpesvirus closely related to HHV-8 that has been identified in macaques with retroperitoneal fibromatosis and is

activated by immunosuppression or SRV infection.[7] The association of these tumors with herpesviruses adds another dimension to this valuable animal model of KS.

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CASE II - 02-427x (AFIP 2888842)

Signalment: 7 month old, female C57BL/6B2m-/-(B2-Microglobulin knockout) mouse, *Mus musculus*.

History: Mice from this group are part of a study that investigated the function of certain proteins that control cancerous proliferation of cells infected by oncogenes of a rodent virus called *Polyomavirus*. These mice were inoculated intraperitoneally with Polyomavirus at the neonatal stage (< than 18 hours old), then monitored for 28-33 weeks for the development of tumors. Most of them developed salivary gland masses, others became depressed, ill or paralyzed in the hindlegs. Salivary tumors are submitted for histopathological evaluation.

Gross Pathology: Salivary glands markedly enlarged, firm, pale tan.

Laboratory Results: None reported.

Contributor's Morphologic Diagnosis: Salivary gland, parotid, anaplastic / mixed type carcinoma.

Contributor's Comment: Polyoma virus of mice is a DNA *Papovavirus*, which has been extensively studied as an oncogenic virus that induces many (*poly*) types of tumors (*oma*). Polyoma-induced tumors are primarily a laboratory phenomenon and seldom occur under conditions of natural infection, except in nude mice. Nude mice also develop multifocal necrosis and inflammation, followed by tumor formation in multiple tissues reminiscent of experimentally inoculated neonatal mice.

Inoculation of neonatal mice with contaminated biologicals or cell cultures is a potential source of spread. Tumors appear 2-12 months after inoculation and, in most strains of mice, the parotid salivary gland is the prevalent site for tumor development. However, tumors can occur at other sites, especially skin, gastrointestinal tract, kidneys, and spinal cord. Paralysis is due to vertebral tumors as well as demyelination.

AFIP Diagnosis: Salivary gland, parotid: Malignant spindle cell neoplasm, C57BL/6B2m-/-(B2-Microglobulin knockout) mouse, rodent.

Conference Comment: This case was reviewed in consultation with the AFIP Department of Soft Tissue Pathology. We cannot further classify this tumor with immunohistochemistry because our laboratory uses anti-mouse primary antibody. Attempts to use Mouse on Mouse (M.O.M.) immunodetection were unsuccessful.

Polyoma virus-induced neoplasms in the salivary glands of mice most commonly consist of a mixed population of mesenchymal-like cells and epithelioid cells with occasional acinar and ductular structures. Less frequently, there is a pure population of either epithelioid cells or mesenchymal-like cells.[2]

Polyomaviruses belong to the papovaviridae family (PAPOVA from the 3 originating viruses of the family - PApillomavirus, POlyomavirus, and VAcuolating agent). Other polyomaviruses in animals include Simian virus 40 (SV40) in macaques, budgerigar fledgling disease virus, K-virus of mice, hamster polyomavirus, and rabbit kidney vacuolating virus.[5] Important polyomaviruses in humans include JC virus, which causes the fatal demyelinating disease, progressive multifocal leukoencephalopathy (PML) in AIDS patients, and BK virus, which is associated with kidney infection in renal transplant patients.[8] Polyomavirus is also significant in humans because rhesus kidney cell cultures used in production of polio vaccines were contaminated with SV40. Many thousands of people were infected between 1954 and 1961 with no apparent harmful effects, but recent studies using PCR have demonstrated the presence of SV40 in some

human neoplasms. The causal relationship linking SV40 to human tumors is controversial and is an active area of research.[8,9]

Simian virus 40 causes inapparent infection in healthy macaques, but causes lesions in the brain (similar to PML in humans), kidney, and lung of immunocompromised macaques. It is oncogenic in suckling or young hamsters, causing undifferentiated sarcomas at the site of virus inoculation.[5] Budgerigar fledgling disease is an acute disease (unusual for a polyomavirus) that causes high mortality in budgerigars and other psittacines. This disease is characterized by hydropic degenerative changes in the epidermis, follicular epithelium, tubular and glomerular epithelium, splenic lymphoid depletion, hepatic necrosis, and amphophilic intranuclear inclusion bodies.[6] K-virus of mice is mostly of historical significance since it rarely occurs in laboratory mouse colonies today. It causes pulmonary vascular edema and hemorrhage in neonatal mice.[1] Hamster polyomavirus is the cause of transmissible lymphoma and keratinizing skin tumors of hair follicle origin. Like mouse polyomavirus, it causes multisystemic infection and is shed in the urine.[1] Rabbit kidney vacuolating virus is a common, nonpathogenic virus of cottontail rabbits that causes only latent infection.[7]

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CASE III – MK0302215 (AFIP 2892676)

Signalment: Adult, 4.65 kg intact female rhesus monkey (*Macaca mulatta)*.

History: The animal was inoculated with simian immunodeficiency virus (SIV) on 1/9/01. Several months prior to euthanasia gradual weight loss was observed. Three weeks prior to euthanasia the animal appeared to be completely blind. An MRI conducted on 12/16/02 revealed a large tumor in the left brain and possibly a small tumor infringing on the optic chiasm. The animal developed ataxia and had difficulty eating and was euthanized on 12/17/02.

Gross Pathology: The entire left caudal lung lobe is adhered by fibrous adhesions to the costal and diaphragmatic pleura. Tonsils are enlarged approximately 2x normal size. A cylindrical mass measuring approximately 1 cm in length by 4 mm in diameter is attached to the inner leaflet of the left atrioventricular valve. Diffuse reddening and hemorrhage of the dura is observed in the distal thoracic spinal column. The left cerebral hemisphere is swollen. No significant mass is observed in the brain. Petechiation is noted within the white matter of the left cerebral hemisphere. The spleen is slightly enlarged with prominent follicular structures. Bone marrow is diffusely reddened. Inguinal, axillary, mandibular, hilar, mesenteric and colonic lymph nodes are all enlarged approximately 2-3x normal, however there is a distinct cortico-medullary junction. Upon formalin fixation an approximately 1 cm in diameter light gray mass is observed in the left cerebral hemisphere white matter.

Laboratory Results: None reported.

Contributor's Morphologic Diagnosis: Brain, meningoencephalitis, granulomatous, with numerous multinucleated giant cells, multifocal to coalescing, marked.

Contributor's Comment: The lesions seen in this monkey are highly suggestive of simian immunodeficiency virus (SIV) infection. SIV is a retrovirus of the lentivirus family that is both immunosuppressive and neurovirulent. Lentiviruses often cause immunodeficiency (loss of CD4+ T-cells) in their hosts in addition to slow, progressive wasting disorders, opportunistic infections, neurodegeneration and death[1]. CD4+ T-cells coordinate a number of critical immunologic functions and the loss of these cells causes progressive impairment of the immune system and a deteriorating clinical course.

Cellular entry of SIV is quite complex. The SIV envelope contains two glycoproteins, surface gp120 that is noncovalently attached to transmembrane gp41. CD4+ T-cells, Langerhans/dendritic cells and monocytes/macrophages are primary targets of SIV because of the affinity of the gp120 glycoprotein component of the viral envelope for the CD4 molecule. The binding of gp120 to the CD4 molecule causes a conformational change in the gp120 glycoprotein that creates a new recognition site for a coreceptor.

Coreceptors for the SIV virus include CCR5, a beta-chemokine receptor and CXCR4, an alpha-chemokine receptor. Macrophage-tropic strains of SIV can infect monocytes, macrophages and T-cells by binding to the coreceptor CCR5. T-cell-tropic strains infect T-cells utilizing the CXCR4 coreceptor. After the virus binds to the coreceptor conformational changes occur in gp41 that result in the insertion of a fusion peptide at the tip of gp41 into the cell membrane of the T-cell or macrophage. The binding of the virus results in the entry of the genome into the cell[1].

The most common means of retroviral infection is through sexual transmission at the genital mucosa. In this route of infection, Langerhans' cells are the first targets of the virus. After infection, these cells then infect CD4+ lymphocytes, spread to deeper tissues and within a few days reach regional lymph nodes[2]. Once monocytes are infected, they allow for transport of the virus throughout the bloodstream to the nervous system, a major target of SIV infection. SIV initially gains access to the CNS when infected monocytes/macrophages cross the blood-brain barrier[3]. The infection of the CNS occurs as early as one-week post infection[4].

Neurologic disease is common in SIV-infected macaques with simian AIDS, and 50% of rhesus macaques inoculated with SIV show a giant cell encephalitis. Histologically, this is characterized by multifocal, perivascular aggregates of macrophages and multinucleated giant cells in all levels of the CNS[5]. In this case, the monkey was injected with SIVsmE660, a macrophage-tropic strain of SIV known to cause granulomatous encephalitis with viral antigen-positive multinucleated giant cells. Multifocal infiltrates of multinucleated giant cells are present in the pia arachnoid and meninges, and multifocal, perivascular lymphocytic infiltrates are observed in the leptomeninges. The most severe infiltrates of macrophages and lymphocytes are in the cerebrum. Numerous individual, small grouped and large aggregates of multinucleated giant cells admixed with foamy macrophages and lymphocytes are present in the white matter as one large mass, a lesion atypical for SIV infection.

Various cytokines are involved in the formation of multinucleated giant cells and the spread of the virus. Multinucleated giant cells form when macrophages in the brain engulf viral particles and present them to T-cells. The T cells are then activated and secrete various cytokines such as IL-2 and IFN-gamma. The IL-2 activates other T-cells, perpetuating the response, while the IFN-gamma aids in the transformation of the macrophages into epithelioid cells and multinucleated giant cells[1].

In a study of rhesus macaques inoculated with SIV, viral antigen was found in the CNS regardless of the presence or absence of giant cell encephalitis. Viral antigen was found consistently within the CNS in infiltrates of macrophages and multinucleated giant cells with the cerebral white matter and cerebellum most commonly affected. Viral antigen was not limited to mononuclear cells and multinucleated giant cells and was also found commonly associated with scattered capillaries and small vessels in the brain, spinal cord, meninges and choroid plexus. Viral antigen was found less commonly in the same tissues associated with cells or cell clusters but not in association with vessels. Antigen was found in the walls of vessels in the CNS in areas

with and without macrophage/giant cell lesions. In SIV infected macaques, lentiviral transcripts were seen in vessels in the non-inflamed CNS. It is thought that the infection of vessels is key in the pathogenesis of SIV encephalitis. It is not clear whether both endothelial cells and mononuclear cells in the vessel wall and perivascular space are infected with the virus or if the endothelial infection is actually infected mononuclear cells in transit through the vessel wall. Many SIV-positive cells were found in the vessels in the parenchyma and choroid plexus suggesting these sites as the primary routes of infection of the CNS with parenchymal vessels being the major route. The meninges is less likely to be a major route of infection due to the fact that lesions are rarely seen in the adjacent cortical gray matter as compared with the cortical white matter[5].

AFIP Diagnosis: Cerebrum: Meningoencephalitis, histiocytic and lymphocytic, multifocal to coalescing, severe, with numerous multinucleated Langhans and foreign body-type giant cells, rhesus monkey (*Macaca mulatta)*, non-human primate.

Conference Comment: The contributor provides an excellent overview of simian immunodeficiency virus and its pathogenesis. It is interesting to note that this remarkable lesion was diagnosed antemortem as a possible tumor via MRI.

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CASE IV - CP02-2337 (AFIP 2889949)

Signalment: 4 month old, male, WAS -/- Background strain: 129S7/SvEvBrd /C57BL/6J, *Mus musculus*.

History: Mice were irradiated and transplanted with stem cells. Several mice in the group developed rectal prolapse and were submitted for necropsy.

Gross Pathology: There was a 1.5mm prolapse of the rectum. The distal colon was moderately thickened.

Laboratory Results: PCR on fecal pellets was positive for *Helicobacter hepaticus*.

Contributor's Morphologic Diagnoses:
1. Large intestine: Severe inflammatory proliferative colitis and proctitis.
2. Rectum: Rectal prolapse.

Contributor's Comment: In the colon and rectum there is a focal area of mucosal ulceration and marked mucosal epithelial hyperplasia. Mucosal epithelial cells lining crypts are well differentiated. These cells are crowded and frequently pile up. Mitotic figures are numerous. The hyperplastic crypts extend upward toward the lumen and deep into the submucosa, and are often observed transversing the mucosa muscularis. Crypts are dilated and mucinous lakes are present in the submucosa. Inflammation is extensive in the lamina propria, submucosa, and tunica muscularis. The inflammatory infiltrate is composed of neutrophils, lymphocytes, plasma cells, macrophages, and eosinophils. The luminal surface is ulcerated, and coagulative necrosis of the superficial mucosa is observed. The invasion of the crypts deep into the submucosa and, in some slides, into the tunica muscularis suggests that over a period of time these lesions may progress to a neoplastic state. In this animal this process is considered benign because the mucosal epithelial cells were well differentiated, and there was no evidence of lateral migration of epithelial cells or metastasis to regional lymph nodes.

Helicobacter species of mice have been associated with hepatitis and inflammatory bowel disease.[1,2,3,4] Members of this genus are microaerophilic, have curved to spiral rod morphology, and are propelled by flagella that vary in number and location. Transmission of these organisms is through the fecal-oral route. *Helicobacter hepaticus* and *H. bilis* have received the most attention because of their prevalence in rodent populations and their association with disease.

These organisms cause a chronic active hepatitis characterized by portal, perivascular, or randomly distributed aggregates of lymphocytes, macrophages, and few polymorphonuclear cells. In some cases hepatocellular necrosis may be a predominant finding. Progression to hepatocellular carcinoma has been reported.[1,2,3,4] Histologically the lesion in the large intestine consists of mucosal hyperplasia (sometimes atypical) and inflammation. Inflammatory infiltrates vary from predominately neutrophils to a mixed population consisting of neutrophils, mononuclear cells, and macrophages, with the latter predominating in chronic lesions.[1,2,3,4]

Helicobacter hepaticus was first identified as a pathogen in a long-term carcinogenicity study when hepatitis developed in untreated A/JNCr mice. Later, the

organism was identified in chronic proliferative typhlocolitis and proctitis in immunodeficient mice. *Helicobacter bilis* has been reported to cause similar lesions.[1,2]

Recently, *H. rodentium* and other novel urease-negative *Helicobacter* sp. have been associated with hepatic and inflammatory bowel lesions similar to those described for *H. hepaticus* and *H. bilis*.[3,4] Susceptibility to infection varies among mouse strains, with immunocompromised mice having severe infections.
Understanding *Helicobacter* infections is important because infection with this organism provides an important model for bacterial induced carcinogenesis, infections can significantly skew results for some research studies, and certain species may prove to have important zoonotic potential.[4]

AFIP Diagnosis: Rectoanal junction: Proctitis, ulcerative, acute, focally extensive, severe, with crypt loss, herniation, abscesses, and regeneration, 129S7/SvEvBrd /C57BL/6J strain, mouse, rodent.

Conference Comment: As the contributor mentions, *Helicobacter* infection in laboratory mouse colonies not only causes disease in immunodeficient mice, but may also have a significant impact on research results.

In addition to the intestinal lesions described here, other mice may develop focal non-suppurative necrotizing hepatitis that progresses to chronic active hepatitis with minimal necrosis, often accompanied by erosion and ulceration of gallbladder mucosa. In these cases, *Helicobacter* organisms are best demonstrated in the bile canaliculi with silver stains, such as Warthin-Starry or Steiner.[5] In this case, a Warthin-Starry was performed but no organisms were identified.

In the A/JCr mouse strain, *H. hepaticus* has been associated with hepatocellular carcinoma. A more recent study was not able to replicate these findings, suggesting that bacterial strain and environmental conditions may be important factors in development of hepatic lesions.[6]

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*Sponsored by the American Veterinary Medical Association, the American College of Veterinary Pathologists and the C. L. Davis Foundation.