The Armed Forces Institute of Pathology
Department of Veterinary Pathology
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Conference Moderator:
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CASE I: YN08-443 (AFIP 3134620).

Signalment: 15-year-old, female sooty mangabey (*Cercocebus atys*).

History: This adult female sooty mangabey was born at the Field Station of the Yerkes National Primate Research Center. She was found in her social group recumbent, hypothermic and pale with a tense abdomen. Laboratory analysis revealed a moderately elevated blood urea nitrogen, moderate anemia and hyperglycemia. Abdominal ultrasound revealed a large amount of fluid in the abdomen. Fluid collected by abdominocentesis appeared dark brown/red. Due to the poor prognosis, the animal was euthanized.

Gross Pathology: This animal weighed 8.18 kilograms at necropsy. The lung parenchyma had multiple pinpoint red nodules (2-5 mm diameter). Approximately 200 ml unclotted blood, intermixed with extensive adhesions between the mesentery and serosa of the intestines and uterus, was observed in the abdominal cavity. The uterus was enlarged to approximately five times its normal size. When opened, the endometrium was hemorrhagic and thrown into folds. Clotted blood was present in the uterine lumen.

Laboratory Results: No significant pathogen was isolated from the blood, liver or contents of the colon.

Histopathologic Description: The lung parenchyma has 1-2 foci consisting of glands and periglandular stroma. These foci resemble the glands and stroma in the uterine endometrium. In other sections, disseminated endometriosis is seen in the mesentery and serosa of gastrointestinal tract, urinary bladder and uterus.

Contributor's Morphologic Diagnosis: Lung, endometriosis.

Contributor's Comment: Endometriosis is defined as the appearance of endometrial tissue outside the uterine cavity.(5) Theories about its etiology include shedding of viable endometrial cells through retrograde menstruation and implanting onto the peritoneal surface, or decreased immunological clearance of shed endometrial cells within the peritoneal cavity.(6) Endometriosis is an important cause of reproductive failure in both rhesus and cynomolgus macaques due to blocked fallopian tubes or scarred ovaries.(5) Pelvic adhesions and serosal 'chocolate cysts' are a part of gross appearance of endometriosis.(4) To histologically diagnose endometriosis two of the following three are required: endometrial glands, endometrial stroma, and hemosiderin-laden macrophages.(1) Older lesions may have only hemosiderin deposits and no glands.

Spontaneous endometriosis has been studied in rhesus macaques, cynomolgus macaques and baboons, although the disease has also been reported in other captive and wild species.(3) Risk factors examined for the development of spontaneous endometriosis in nonhuman primates include maternal age, parity, captivity and experimental procedures such as laparoscopies, hysterectomies, and treatment with estradiol implants.(3) Nonprimates (e.g. rats, syngenic mice, nude mice, hamsters and rabbits) do not develop spontaneous disease, but the disease has been experimentally induced in them.(6)

In the present case, metastasis of endometrial cells by lymphatic and/or hematogenous routes could have disseminated the endometriosis to the thorax. To the authors' knowledge, endometriosis has not been reported in sooty mangabeys, and only one case of endometriosis in lung has been reported in a rhesus macaque.(5)

AFIP Diagnosis: Lung: Endometriosis, with uterine stroma, few endometrial glands, and hemosiderin-laden macrophages.

Conference Comment: We thank the contributor for providing this captivating example of a classic condition in an unusual anatomical location. In women, endometriosis occurs more commonly in the following sites, in descending order of frequency: 1) ovaries; 2) uterine ligaments; 3) rectovaginal septum; 4) cul du sac; 5) pelvic peritoneum; 6) large and small bowel and appendix; 7) mucosa of the cervix, vagina, and fallopian tubes; and 8) laparotomy scars. (2)

Because foci of endometriosis respond to hormonal stimulation with periodic bleeding, the diagnosis is not always straightforward, as mentioned by the contributor. In some cases, lesions consist only of endometrial stroma and areas of hemorrhage or hemosiderin; longstanding lesions may be obscured by secondary fibrosis.(2) A rather atypical example with decidualized stromal cells from a rhesus macaque on a therapeutic course of Depo-Provera® (medroxyprogesterone acetate) was reviewed in WSC 2007-2008, Conference 10, case III. In cases lacking the distinctive features of endometriosis described by the contributor, the differential diagnosis may include retroperitoneal fibromatosis and neoplasia of mesenchymal origin. In such cases, immunohistochemistry may be useful; endometriotic stromal cells exhibit markedly upregulated estrogen production due largely to high levels of the aromatase enzyme, which is absent in normal endometrial stroma. Interestingly, high levels of such proinflammatory cytokines as prostaglandin E_2, interleukin (IL)-1β, IL-6, and tumor necrosis factor are also noted in endometriosis. Prostaglandin E_2 stimulates local estrogen synthesis, and endometriotic tissue is resistant to the antiestrogenic effect of progesterone; therefore, the overall inflammatory and endocrine milieu in endometriotic tissue is characterized by the overproduction of estrogen and prostaglandin and resistance to progesterone.(2)

Conference participants discussed the two predominant theories for the development of endometriosis, i.e. the metastatic theory and the metaplastic theory. The former postulates that endometrial tissue is physically transplanted to extrauterine locations through: retrograde menstruation, with subsequent spread to the peritoneum; surgical procedures, with subsequent spread to the cervix, vagina, and laparotomy scars; or metastasis via blood and lymphatic vessels. The metaplastic theory suggests that endometrial tissue arises directly from cell rests in the mesothelium, from which the Müllerian ducts arise during embryogenesis.(2) The mechanism by which endometriosis developed in the lung of the sooty mangabey in this case is unclear. Participants considered hematogenous dissemination, but based on the generally peripheral distribution of the lesions in the sections examined, many speculated that direct extension from the abdominal cavity through the esophageal hiatus, aortic hiatus, or caval opening could have occurred.

In addition to the microscopic features described by the contributor, conference participants noted individualized round cells scattered throughout the endometrial stroma characterized by round, hyperchromatic nuclei and small amounts of cytoplasm containing brightly eosinophilic globules. The round cells are interpreted as endometrial stromal granulocytes, which are likely large granular lymphocytes that reach peak numbers during the secretory phase, the onset of which is marked by ovulation.(7)

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CASE II: 07-A-266 (AFIP 3138297).

Signalment: 16-year-old, female rhesus macaque (*Macaca mulatta*).

History: Two days prior to necropsy, the animal was lethargic and dehydrated with loss of appetite. Physical examination revealed an abdominal mass. Humane euthanasia was elected due to a poor response to supportive therapy.

Gross Pathology: The animal was dehydrated and in emaciated body condition. Multiple thrombi were present within the mesenteric vasculature, distal thoracic aorta, distal abdominal aorta and right iliac artery. An irregular multilobulated tan mass with distinct margins that measured up to 4 cm in greatest dimension was present involving the lateral aspect of the spleen. The liver was diffusely congested and the margins were rounded. Two firm round tan nodules, approximately 0.1 cm in diameter, were present near the margin of the left hepatic lobe. A large thrombus and associated hemorrhage were present in a large vessel within the pancreas. A vessel within the peripancreatic fat was thrombosed. Segments of the jejunum were black with sharply demarcated full-thickness necrosis. Necrosis of the cecal mucosa was present segmentally. The mesenteric vessels supplying necrotic intestinal segments were thrombosed. The contour of the renal cortex was mildly distorted with few depressed foci in the cortex.

Histopathologic Description: Pancreas: The walls of the small and medium sized arteries are circumferentially thickened up to five times normal with fibroblasts, fragmented collagen bundles, a mixed inflammatory infiltrate, extensive, often transmural foci of necrosis, and cellular and karyorrhectic debris (necrotizing vasculitis). The tunica intima and media are disrupted and the endothelium is denuded and necrotic with loss of the internal and external elastic laminae. The walls are multifocally replaced by bands of amorphous to flocculent, brightly eosinophilic material (fibrinoid necrosis). Transmurally, moderate numbers of lymphocytes, plasma cells, macrophages, and variable numbers of neutrophils are present. Lumina are stenotic and are partially or completely occluded with organized or organizing fibrin thrombi. Vasa vasorum of medium sized arteries are similarly affected. There are multifocal areas of hemorrhage and moderate numbers of hemosiderin-laden macrophages present in and around the walls of affected vessels. Multifocally, the lobules adjacent to the affected vessels are edematous with loss of acini and ducts. Diffusely, within the affected areas, acini are dilated and there is zymogen granule depletion. Moderate numbers of fibroblasts within a basophilic matrix are also present. There is variation in the severity, chronicity and degree of inflammation of the lesion among the slides submitted. Within vessel lumina in some slides there is a population of round cells with distinct cell borders, small to moderate amounts of cytoplasm, and round to indented, centrally to eccentrically placed nucleus. Anisokaryosis is marked. There are generally one but up to three prominent nucleoli. Up to seven mitotic figures are present per high power field. Apoptotic cells are numerous.

Contributor's Morphologic Diagnosis: 1. Pancreas: Arteritis, chronic-active, proliferative, necrotizing, circumferential, transmural, severe with fibrinoid necrosis, luminal stenosis and thrombosis and multifocal pancreatic necrosis with atrophy and ectasia of acini.
2. Liver (not submitted): Arteritis, chronic-active, segmental to circumferential, transmural, severe with fibrinoid necrosis, luminal thrombosis, narrowing or obliteration of the vascular lumen, sclerosis and thickening of the arterial wall, perivascular accumulation of hemosiderin-laden macrophages, multifocal hepatic necrosis and loss of hepatic parenchyma rimmed by a lymphohistiocytic plasmacytic inflammatory infiltrate.
3. Kidney (not submitted): Arteritis, interlobular and arcuate arteries, chronic-active, circumferential, segmental, transmural, severe with fibrinoid necrosis, sclerosis and thickening of the arterial wall, hemorrhage, chronic-active, lymphoplasmacytic, tubulointerstitial nephritis, tubular dilatation, distortion, degeneration and regeneration, proteinaceous casts, neutrophilic casts, periglomerular, interstitial fibrosis and loss of nephrons.

Contributor's Comment: The primary finding in this case was severe, multisystemic arteritis with consequent ischemic change and loss of tissue elements in the kidneys, liver, spleen, pancreas, jejunum and cecum. Thrombi were observed grossly in the mesenteric arteries and the right iliac arteries. The gross and microscopic vascular lesions have features of polyarteritis nodosa (PAN).

Polyarteritis nodosa is a commonly occurring entity in humans. It is sporadically reported in many domestic species of animals and is characterized by necrotizing inflammation of small and medium sized arteries and most commonly involves arteries of the tongue, pancreas, heart, kidneys, mesentery, urinary bladder, testes, head and gastrointestinal tract. Impaired perfusion may result leading to hemorrhage, ulceration, infarction, and atrophy of affected tissues. The etiology is not clear; however, deposits of immune complexes have been localized in the affected arteries.(5) Microscopically, acute lesions are characterized by segmental or circumferential necrosis and fibrous thickening of the walls of arteries with varying degrees of inflammation and fibrinoid necrosis. Thrombosis of vessels may lead to infarction and hemorrhage. In chronic lesions, typically the walls may be completely fibrosed. Affected vessels may show lesions of all stages of development and both acute and chronic lesions may be present in the same vessel. (4)

Polyarteritis nodosa is commonly reported in MRL and NZB mice that are prone to autoimmune diseases.(5) In rats with experimentally induced hypertension, the occurrence of PAN is related to amount of sodium chloride in the diet.(7) Also, experimentally, it has been induced with streptozotocin, nicotinamide and several other agents.(1) In dogs, PAN is associated with rheumatoid arthritis, systemic lupus erythematosus, and "beagle pain syndrome."(8) In blue foxes, it has been reported in association with *Encephalitozoon cuniculi* infection. Polyarteritis nodosa has been described in the brains of sows with reproductive disorders(3) and is reported to be associated with Border disease in sheep.(4) A single case of PAN has been reported in a cynomolgus monkey.(6)

The intravascular round cell population in this case was an unexpected finding. These cells were present only in areas supplied by lesioned vessels and were not present in the bone marrow. Nuclear pleomorphism, prominent and multiple nucleoli and high mitotic activity of the intravascular round cell population support malignancy; however, given the distribution it may be a response to the severe inflammation and ischemia present. The tan masses noted grossly within the spleen and liver corresponded to foci of necrosis and replacement fibrosis as a consequence of necrotizing arteritis and thrombosis. No neoplastic mass lesions were present.

AFIP Diagnosis: 1. Pancreas: Arteritis, transmural, proliferative and necrotizing, chronic-active, multifocally extensive, marked, with luminal stenosis and multifocal pancreatic lobular atrophy and necrosis.

Conference Comment: As noted by the contributor, there is marked slide variation, and not all participants' slides featured the atypical proliferation of intravascular round cells described above. This case was reviewed in consultation with pathologists in AFIP's Department of Hematopathology, who concluded that the cells of interest most likely represent either malignant round cell neoplasia (i.e. lymphoma) or extramedullary hematopoiesis. Using additional materials kindly submitted by the contributor, immunohistochemical stains were performed on several serial tissue sections in an attempt to identify the cell of origin for the atypical intravascular round cells. Most of the atypical round cells exhibit positive cytoplasmic immunoreactivity for CD3, consistent with T-cell lymphoid origin; admixed with the CD3-positive atypical round cells are scattered B-cells that stain positively for CD79a and CD20. The atypical round cells are immunonegative for myeloperoxidase, hemoglobin, CD34, and CD117 (c-kit). The histologic and immunohistochemistry findings suggest an atypical lymphoid proliferation of T-cell origin, but we are uncertain whether the finding reflects hematopoiesis or neoplasia; the absence of neoplasia in other organs, as reported by the contributor, argues against a neoplastic process.

The contributor provides a succinct overview of PAN. Conference participants noted histopathologic similarities between the blood vessels in this case and those examined in the hearts of dogs with drug-induced vascular injury due to the administration of a phosphodiesterase inhibitor (see WSC 2009-2010, Conference 2, case III). Indeed, PAN is best regarded as a heterogenous group of arteritides, as evidenced by the assorted list of conditions that have been reported in association with the entity and summarized by the contributor. In humans, PAN is a vasculitis confined to small and medium-caliber arteries, with a predilection for branching points; arterioles, capillaries, and venules are spared, as is the pulmonary circulation. Many of the conditions that have been categorized as PAN in the veterinary literature adhere only loosely to the classic definition of PAN, and would more appropriately be referred to as systemic necrotizing vasculitides.(4)

As alluded to by the contributor, many cases of polyarteritis nodosa are thought to be caused by immune complex-mediated (type III) hypersensitivity, the pathogenesis of which is divided into three phases: 1) immune complex formation, 2) immune complex deposition, and 3) immune complex-mediated inflammation and tissue injury. Phase I, i.e. immune complex formation, occurs when antibody combines with antigen in the circulation (forming circulating immune complexes) or antigen that has been previously deposited in extravascular sites (forming in situ immune complexes). As described in the recent case of membranoproliferative glomerulonephritis (WSC

2009-2010, Conference 17, case III), the inciting antigens may be of either exogenous or endogenous origin. Hepatitis B virus antigens, for example, are incriminated as the inciting cause of a subset of human cases of PAN. Phase II, i.e. immune complex deposition, remains incompletely understood; however, it appears that medium-sized immune complexes formed in slight antigen excess are the most pathogenic. The distribution of immune complex deposition in part determines the distribution of resulting lesions. For example, systemic immune complex-mediated diseases result from immune complex deposition in many organs, while localized disease (e.g. glomerulonephritis, arthritis, or the Arthus reaction) results from deposition confined to specific tissues. Phase III is inflammation and tissue injury. Complement-fixing antibodies, i.e. IgG and IgM, activate complement via the classical pathway, yielding C3b and C4b as by-products; neutrophils and macrophages with receptors for these opsonins contribute to inflammation and tissue injury. The importance of this pathway in tissue injury is underscored by the observation of decreased serum levels of C3, presumably due to consumption of complement, in humans in the active phase of a systemic type III hypersensitivity reaction. Additionally, some subclasses of IgG bind to leukocyte Fc receptors, exacerbating the inflammatory response to immune complex deposition.(2)

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CASE III: 09-A-270 (AFIP 3138303).

Signalment: 11.5-year-old, female rhesus macaque (*Macaca mulatta*) infected with SIVmac251.

History: This animal had been sedated for research related bronchoalveolar lavage several times during a study. The animal had persistent thrombocytopenia and leukopenia for four months before necropsy.

Gross Pathology: The animal was in good body condition. The right cranial lung lobe was soft, enlarged, edematous, and hemorrhagic. The caudal two thirds of the lobe were more severely affected and the caudal margin was overlain with a gray-white fibrinous exudate. The caudal half of the right middle lung lobe was partially demarcated by a serpiginous pale margin with hemorrhage and was depressed, dense, firm and tan. The pulmonary vessels in these lobes contained elongate mottled pale red and gray occlusive thrombi. There was mild, multifocal hemorrhage in the remaining right lung lobes and minimal hemorrhage in the left caudal lung lobe. The left lung lobes exhibited a fine black stippling.

Laboratory Results:

	Test and Value	Reference Range
RBC	5.26 x 10^6/mm^3	5.0 - 6.5 x 10^6/mm^3
WBC	2.0 x 10^3/mm^3	6.0 - 15.0 x 10^3/mm^3
Lymphocytes	56.1%	25.0 - 60.0%
Monocytes	20.5%	0.0 - 8.0%
Eosinophils	0.5%	0.0 - 5.0%
Platelets	66 x 10^3/mm^3	330 - 650 x 10^3/mm^3

Histopathologic Description: Within the section of lung is a focally extensive area of coagulative necrosis, hemorrhage, fibrin accumulation, edema and karyorrhectic and cellular debris (infarct) affecting almost 40% of the tissue. The infarct is rimmed by high numbers of fibroblasts and newly formed blood vessels (granulation tissue). Edema, fibrin and hemorrhage fill the alveolar spaces adjacent to the infarct. The rest of the lung is hyperemic and edematous. Moderate numbers of hemosiderin-laden macrophages, foamy macrophages, fewer neutrophils and occasional lymphocytes fill many alveoli. Multifocally, alveoli are lined by cuboidal epithelium (type II pneumocyte hyperplasia) and the septa are expanded with a small amount of collagen. Multifocally, the tunica intima of medium sized arteries is severely and circumferentially thickened with occlusion of the lumen. The tunica media is also thickened. The pleura is thickened with fibrous connective tissue, hemorrhage, edema, fibrin and an inflammatory infiltrate composed of moderate numbers of neutrophils and few lymphocytes.

Contributor's Morphologic Diagnosis: Lung: Arteriopathy, proliferative, intimal and medial, multifocal, marked with hemorrhagic infarction.

Contributor's Comment: This animal had persistent thrombocytopenia, and grossly a thrombus was identified in a major vessel of one of the affected lung lobes. The three principal causes of thrombosis are endothelial injury, disruption in regular blood flow, and hypercoagulability.(2) As in this case, thrombi may cause infarction of the region downstream from the occluded vessel. Microscopic lesions in the lung included intimal and medial proliferation of the muscular arteries. The intimal proliferation resulted in luminal obstruction, reduced blood flow and consequent ischemic injury. It also served as a platform for clot formation within vessels. Proliferative arteriopathy characterized by endothelial cell activation and proliferation is associated with human immunodeficiency virus (HIV)(8) and simian immunodeficiency virus (SIV)(10,11) infections. Thrombosis of the pulmonary artery and vena cava has been reported in rhesus macaques infected with SIV.(3)

Thrombocytopenia usually results from either impaired production or enhanced destruction of platelets. In most cases it is due to immune mediated destruction of platelets or megakaryocytes or increased utilization of platelets as in disseminated intravascular coagulation. Thrombocytopenia is a common complication in HIV patients and SIV-infected macaques.(7) Although several factors attributable to thrombocytopenia have been identified, the precise mechanism of thrombocytopenia is unclear. Autoantibodies against platelet GPIIIa protein induces a hypercoagulable state by interacting with phospholipids and other clotting factors, thus causing platelet aggregation in HIV patients.(7) In SIV-infected rhesus macaques, synthesis of platelet autoantibodies results in increased phagocytosis of platelets.(1) Also, megakaryocytes express CD4 molecules and are productively infected by HIV/SIV resulting in decreased production of platelets. In addition, SIV-infected macaques develop cold agglutinins resulting in thrombocytopenia.(4)

In this animal, the endothelial cell activation, intimal proliferation, altered hemodynamics and blood hypercoagulability predisposed to clot formation. Vascular obstruction resulted in pulmonary infarction. The cause of thrombocytopenia in this case is most likely multifactorial and may be attributed to destruction of megakaryocytes by replicating virus, production of autoantibodies against platelet autoantigens and/or increased aggregation and removal of platelets.

Infectious diseases associated with thrombocytopenia in animals are provided in the table below:(2,9)

Species	Etiology
Cat	Feline immunodeficiency virus Feline leukemia virus Feline panleukopenia virus
Dog	Canine distemper virus *Ehrlichia canis*
Horse	Equine infectious anemia virus Equine arteritis virus African horse sickness virus
Cattle	Bovine viral diarrhea virus *Theileria parva* *Trypanosoma congolense* *Trypanosoma vivax*

Pig	African swine fever virus Hog cholera virus

AFIP Diagnosis: 1. Lung: Arteriopathy, proliferative, intimal and medial, multifocal, marked, with luminal occulusion, multifocal hemorrhagic coagulative necrosis with peripheral fibrosis (infarcts), and pleural fibrosis. 2. Lung: Alveolar histiocytosis and hemosiderosis, diffuse, mild to moderate, with type II pneumocyte hypertrophy and hyperplasia.

Conference Comment: This conference year we have reviewed several cases representing a variety of complications of SIV infection in rhesus macaques. The contributor's thoughtful comments outline a plausible pathogenesis for this lesion while illuminating the otherwise rather inconspicuous link between thrombocytopenia and thrombosis. The contributor alluded to Virchow's triad of primary abnormalities that lead to thrombus formation, the components of which merit further discussion here.

Endothelial injury resulting in denudation of the endothelium exposes the subendothelial extracellular matrix, allowing platelet adhesion, release of tissue factor, and local depletion of antithrombotic prostaglandin (PG)I_2 and plasminogen activators. More inclusively, this vertex of Virchow's triad might be termed *endothelial dysfunction*, since any disturbance in the balance of pro- and antithrombotic activities may lead to thrombosis. Specifically, dysfunctional endothelium is characterized by relatively increased production of procoagulant factors (e.g. tissue factor, platelet adhesion molecules, plasminogen activator inhibitors) and decreased production of anticoagulant factors (e.g. thrombomodulin, PGI_2, tissue plasminogen activator); insults that lead to this type of endothelial dysfunction are varied and include, among others, turbulent blood flow, hypertension, endotoxins, and hypercholesterolemia.(5)

Altered blood flow, or turbulence, not only causes endothelial dysfunction as described above, but also causes the formation of pockets of stasis. Normal blood flow is laminar, which maintains platelets in the center of the vessel lumen; areas of stasis lack laminar flow, bringing platelets into contact with the endothelium and thus promoting thrombosis. Moreover, blood in areas of stasis becomes stagnant; activated clotting factors are not readily diluted and washed away from these areas, and clotting factor inhibitors do not flow into them.(5)

Hypercoagulability, also referred to as thrombophilia, is the third vertex of Virchow's triad. While a number of hereditary causes of hypercoagulability are described in human medicine, acquired hypercoagulability is more commonly encountered in veterinary medicine, and is often multifactorial. For instance, coagulation factor I may be elevated due to inflammation, stress, tissue necrosis, while factors I and VIII may be elevated due to trauma or hyperthyroidism. Conversely, depletion of antibrombin III, a common complication of the nephrotic syndrome, leads to hypercoagulability via loss of thrombin inhibition.(5,6)

The conference moderator noted that anatomic location is of critical importance in determining the consequences of thrombosis. While thrombosis in the heart or brain is likely to cause catastrophic infarction, organs like the liver and lung which have collateral circulation, are less prone to clinically significant infarction.

Selected causes of thrombosis, categorized by their respective vertices of Virchow's triad, are summarized below:(6)

Causes of Thrombosis	
Mechanism	**Examples**
Endothelial Injury / Dysfunction	Nematodiasis (*Strongylus vulgaris* larvae, dirofilariasis, angiostrongylosis, spirocercosis) Bacterial infection (salmonellosis, mannheimiosis, erysipelas, histophilosis) Viral infection (arterivirus, morbillivirus, herpesvirus, orbivirus, pestivirus) Fungal infection (aspergillosis, zygomycosis) Disseminated intravascular coagulation (DIC) Vitamin E / selenium deficiency Immune-mediated vasculitis Endotoxin

Altered Blood Flow	Gastric dilation and volvulus Intestinal torsion or volvulus Cardiomyopathy Hypovolemia Aneurysm
Hypercoagulability	Increased clotting factor activation (neoplasia, DIC) Antithrombin III deficiency (nephrotic syndrome, DIC, liver disease) Increased platelet activity (diabetes mellitus, neoplasia, dirofilariasis, uremia) Metabolic abnormalities (hyperthyroidism, hyperadrenocorticism)

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CASE IV: 09-22 1 (AFIP 3139388).

Signalment: 23-year-old, male rhesus macaque (*Macaca mulatta*).

History: The animal was part of a long term visual-based cognition study. Cephalic implants and circumferential scleral search coils had been surgically placed. Euthanasia was performed due to a history of chronic weight loss and failure to thrive.

Gross Pathology: Overall, the animal was in fair body condition with petechiae on the skin of the inguinal region bilaterally, as well as multifocally on the abdomen. The liver and spleen were both enlarged with diffuse pallor. There was a 3 mm deep, focal surface depression of the cortex of the left kidney, and on cut section the cortex also contained a focal, 1 cm diameter cyst. Marked degenerative changes were also seen in both stifles, with the left medial condyle in particular being irregular and roughened.

Histopathologic Description: Splenic architecture is diffusely effaced by marked deposits of amorphous, smudgy to finely fibrillar, extracellular eosinophilic substance (amyloid). This material fills and expands the parenchyma, and especially replaces the microanatomic regions of white pulp and also imparts a nodular pattern to its deposition.

There is associated compression of the adjacent red pulp regions, although many of the blood vessels are distended and congested. Foci of hemorrhage are also seen within the nodular amyloid deposits.

Contributor's Morphologic Diagnosis: Diffuse splenic amyloidosis.

Contributor's Comment: Amyloidosis is a disease caused by extracellular deposition of insoluble abnormal fibrils, derived from aggregation of misfolded, normally soluble, protein. The name amyloid originates from results of early crude iodine-staining techniques that led to the mistaken identification of the protein material as starch. Serum amyloid A (SAA) proteins comprise a family of vertebrate proteins that associate predominantly with high density lipoproteins (HDL). All amyloid fibrils share a common cross-β-pleated sheet core structure, with the polypeptide chains running perpendicular to the fibril long axis, regardless of the particular protein from which they are formed. Fibrils are usually about 10 nm in diameter, and are straight, rigid, and nonbranching. Numerous biochemically distinct amyloid proteins have been characterized in humans and animals, but the three most common types are as follows: 1) AA (amyloid-associated) (a unique non-immunoglobulin protein synthesized by the liver); 2) AL (derived from plasma cells and contains immunoglobulin light chains); and 3) Aβ (β-amyloid protein found in cerebral lesions of Alzheimer disease).

Amyloidosis may be primary or secondary. Primary amyloidosis arises due to overproduction of the immunoglobulin light chain and may be neoplastic or genetic in origin. Secondary, or reactive systemic amyloidosis is a complication of chronic infections and inflammatory conditions and is characterized by a sustained acute phase response. Although the pathogenesis of reactive systemic amyloidosis is poorly understood, it is associated with persistently increased production of SAA (thus making SAA a major acute phase reactant). Although its major physiological function remains unclear, SAA is produced under the control of numerous cytokines, including interleukin-1, interleukin-6 and tumor necrosis factor-α released during inflammation. Increased levels of SAA are common in chronic inflammation, but amyloid deposition usually does not occur. In individuals that do develop amyloidosis, there is limited or defective SAA proteolysis with formation and deposition of insoluble AA protein. Proposed underlying mechanisms include failure of degradation due to excess levels of SAA relative to enzyme; an intrinsic proteolytic enzyme defect; or a structural defect in the SAA molecule that makes it resistant to degradation. The end result, however, is that accumulated amyloid deposits cause pressure atrophy of surrounding tissues, thus impairing normal body function and resulting in organ failure and ultimately death.

Reactive systemic amyloidosis is not uncommon in rhesus macaques, and has additionally been reported in other nonhuman primates (including common marmosets, squirrel monkeys, pigtail macaques, Celebes macaques, cynomolgus macaques, a stumptailed macaque, baboons, a mangabey and chimpanzees). The condition has been associated with chronic vascular catheterization, as well as underlying conditions such as rheumatoid arthritis, retroviral infection, parasitism, and enterocolitis. Amyloid deposition is most frequently seen in the space of Disse in the liver, the lamina propria of the gastrointestinal tract, the corticomedullary junction of the adrenal gland, either the red or white pulp of the spleen, and the renal medullary interstitium. The small intestine is the region of the gastrointestinal tract most often and most severely affected. Renal glomerular involvement is rare, except in marmosets.

Clinical signs are related to the affected site as well as the amount of amyloid deposited, but include weight loss, diarrhea, and hepatosplenomegaly. Protein losing enteropathy may accompany enteric amyloidosis. Laboratory findings may include elevated levels of SAA, hypoproteinemia, hypoalbuminemia, hypergammaglobulinemia, and elevated liver enzymes with hepatic involvement. There is, however, no reliable diagnostic assay, preventive measure or treatment for secondary amyloidosis. Although gross postmortem lesions are often absent, the liver and/or spleen may be massively enlarged, pale, waxy and firm. Prominent splenic nodules may be seen cut section, and the intestinal mucosa may be thickened. With the light microscope and hematoxylin and eosin staining, amyloid appears as an amorphous, eosinophilic, extracellular substance. Its differentiation from other similar appearing materials, like fibrin and collagen, depends on the pathognomonic, red-green birefringence observed when preparations correctly stained with Congo red are viewed in intense unidirectional polarized light. This optical effect is produced by alignment of the dye molecules along the protein fibrils.

AFIP Diagnosis: Spleen, white pulp: Amyloidosis, nodular, diffuse, marked, with lymphoid depletion and loss.

Conference Comment: The contributor provides an exemplary review of amyloidosis, and the fairly classic example provided herein features the typical pattern of amyloid deposition in the spleen, with the white pulp being

primarily affected and compressing the adjacent red pulp. The following table, adapted from Snyder summarizes the most commonly encountered amyloidoses in veterinary medicine:(10)

Amyloidosis			
Category	**Associated Diseases**	**Major Fibril Protein**	**Precursor Protein**
Systemic			
Primary amyloidosis (immunocyte dyscrasias)	Multiple myeloma Monoclonal B cell proliferations	AL	Immunoglobulin light chains
Secondary amyloidosis (reactive systemic amyloidosis)	Chronic inflammation	AA	SAA
Familial amyloidosis (may be systemic and/or localized)	Amyloidosis in Shar-Pei dogs (renal medullary interstitium), Abyssinian cats (renal glomeruli), and Siamese cats (liver)	AA	SAA
Localized			
Amyloid of aging	Senile plaques Cerebral amyloid angiopathy Neurodegenerative disease	Aβ	APP
Endocrine tumors	Thyroid C cell tumors	A Cal	Calcitonin, polypeptide hormones and/or prohormones
Islets of Langerhans	Diabetes mellitus	IAPP	IAPP
Isolated amyloid of pulmonary vasculature		Apolipoprotein A-1	Apolipoprotein A-1
Prion diseases	Transmissible spongiform encephalopathies	Misfolded prion protein (PrP^{sc})	Normal prion protein (PrP)
AL = amyloid light chain; AA = amyloid associated; SAA = serum amyloid A; APP = amyloid precursor protein; A Cal = amyloid of hormone origin; IAPP = islet amyloid polypeptide			

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