Joint Pathology Center
Veterinary Pathology Services

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CASE I: Case 1 G9312 (JPC 4085100).

Signalment: 6-year-old, male, mouse lemur (*Microcebus murinus*), non-human primate.

History: Within a captive, indoor housed colony of grey mouse lemurs (*Microcebus murinus*), a male intact, six-years-old animal presented with acute onset of clinical symptoms including hematuria, decreased general condition, weight loss, and inappetence. General examination revealed a poor body condition and blood-smeared coat in the genital region. Injuries were not detected. Therefore, an acute hemorrhagic cystitis was suspected. Therapy consisted of parenteral application of enrofloxacin, meloxicam, fluid therapy, as well as vitamins and supplementary food as supportive care. Two days after initial presentation, the lemur was found dead.

Gross Pathology: At necropsy, hemorrhages were found within different organs. Hemorrhages were most prominent within lung parenchyma and urinary bladder and less severe within renal pelvis and the subcutis. Furthermore, there was splenomegaly.

Thoracic viscera, mouse lemur. Sections of heart and lung are submitted for examination. At low magnification, thick cuffs of a cellular exudate surround pulmonary arteries. (HE, 4X)

Laboratory Results (clinical pathology, microbiology, PCR, ELISA, etc.):

Bacteriology: culture: negative

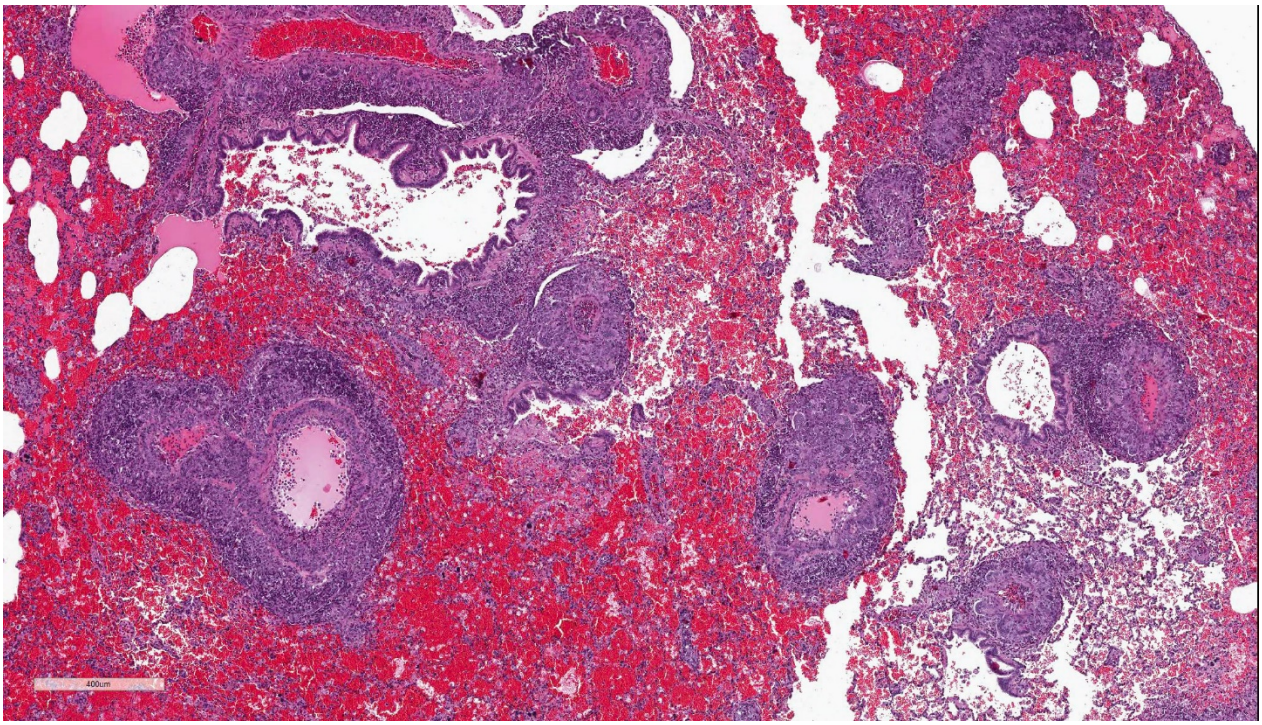
Virology: PCR for agents inducing respiratory disease (Influenza, Paramyxovirus, Human Metapneumovirus, Respiratory syncytial virus, Adenovirus): negative

Special stains used for histology: Ziehl-Neelsen stain for acid fast bacteria: negative; PAS reaction: negative; silver impregnation: negative

Microscopic Description:
The main histologic finding within the lung parenchyma was a severe granulomatous inflammation of small- and medium-sized arteries. The intima of affected vessels showed mild fibrinoid necrosis and proliferation. The tunica media and adventitia were heavily infiltrated with a mixed cellular infiltrate. Giant cells of foreign body and Langhans' type represent the dominant cell type. Eosinophilic cells were also present in high numbers. The lesions were accompanied by alveolar hemorrhage and histiocytosis. Comparable vascular alterations of milder degree were found within the kidneys. In the kidneys, giant cells were missing. Furthermore a mild lymphocytic interstitial myocarditis was found. Reactive extramedullary hematopoiesis was prominent within the spleen and with lesser extent within the liver.

Contributor's Morphologic Diagnosis:
Lung: vasculitis, chronic, granulomatous and eosinophilic, multifocal, severe, with prominent giant cell formation, alveolar histiocytosis and alveolar hemorrhage, idiopathic, non-human primate.

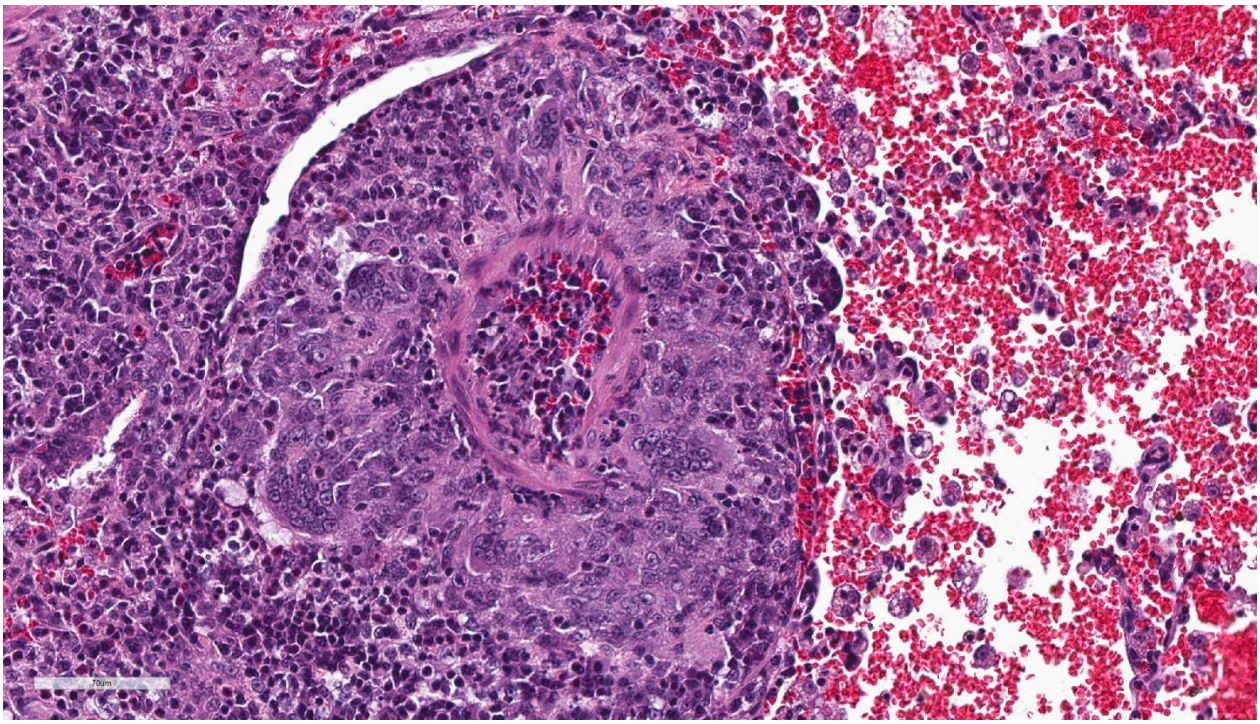
Contributor's Comment: A unique case of an idiopathic granulomatous generalized vasculitis in a mouse lemur is described. The cause of disease remains unclear. The most



Lung, mouse lemur. A dense cellular infiltrate expands the adventitia of medium-sized arterioles. There is also expansion of bronchiolar-associated lymphoid tissue. Surrounding alveoli are filled with acute hemorrhage. (HE, 45X)

important infectious agents inducing granulomatous inflammation such as tuberculosis, leprosy, aspergillosis and leishmaniasis were ruled out histologically by special stains. No hints were found for a foreign body reaction or foreign body disease by histologic investigation. A drug induced vasculitis could be excluded because the animal did not receive drugs like propylthiouracil, methimazole, sulfasalazine, D-penicillamine, or minocycline capable to induce microscopic polyangitis. Therefore, an autoimmune or allergic disorder was suspected.

Several forms of idiopathic disseminated giant cell arteritis are recognized in humans and should be discussed as differential diagnosis for this case (Table 1). They mainly differ in their distribution, and a rough classification can be done according to the type of vessels involved. On this basis, arteritis temporalis (classic giant cell arteritis Horton) and Takayasu arteritis could be excluded in the present case because they mainly affect the aorta and other large-sized vessels. With the same argumentation polyarteritis nodosa (PAN), an idiopathic multisystemic necrotizing vasculitis, could be excluded too, because it mainly affects medium-sized vessels and rarely lung vasculature. The disease is well recognized in humans, and a PAN-like syndrome has been observed in a number of other species. In non-human primates, the disease is only described in cynomolgus monkeys (*Macaca fascicularis*).[1,6] The two case reports describe a necrotizing arteritis affecting vessels in the kidney, small intestine, colon, heart, spleen, mesentery, urinary bladder, and pancreas. The pulmonary vasculature was not involved. The lesions were segmental in distribution



Lung, mouse lemur. At higher magnification, the adventitia of affected arteries is expanded and effaced by large numbers of epithelioid macrophages and fewer multinucleated giant cell macrophages, neutrophils, and eosinophils. Adjacent alveolar septa are hyperpcellular with increased numbers of activated intravascular macrophages and neutrophils. Hemorrhage is present within alveoli. (HE, 45X)

and of varying severity and stage of development. A transmural mixed inflammatory cell infiltrate was present, often accompanied by fibrinoid necrosis of the tunica media.[6] Main differences to the present case exist in the lack of giant cells and the amount of fibrinoid necrosis. For the given reasons, PAN was excluded as a diagnosis in the present case.

The eosinophilic nature of the lesions are indicative for another form of idiopathic vasculitis called eosinophilic granulomatosis with polyangitis or Churg-Strauss vasculitis. This is an autoimmune condition associated with asthma.[3] The clinical history of the diseased animal gives no evidence for a preexisting asthmatic syndrome. The inflammatory character of Churg-Strauss vasculitis is predominantly eosinophilic, whereas giant cells are more prominent in the present case. For these reasons, Churg-Strauss vasculitis was also excluded as a diagnosis in the present case.

The described lesion shows more similarities with the entity granulomatosis with polyangitis (GPA), previously known as Wegener granulomatosis. The disease is an idiopathic vasculitis of medium and small arteries of the respiratory tract with coexisting glomerulonephritis. As in the presented case, hematuria is a frequent finding. The main histologic criteria are presence of giant cells and fibrinoid necrosis of the vessel wall. GPA is generally characterized by anti-neutrophil cytoplasmic antibodies (ANCA).[8]

Nevertheless, the most probable diagnosis in this case is disseminated visceral giant cell arteritis, a giant cell arteritis of extracranial arteries and arterioles. Histologic similarities are the presence of giant cells, a mixed inflammatory infiltrate with eosinophils and less extend of fibrinoid necrosis of the vessel wall.[5]

The pathogenesis of all vasculitides discussed above is poorly understood and most likely involves immunopathogenic mechanisms. Most speculation centers on immune complex deposition, with subsequent activation of the complement cascade, neutrophil and monocyte chemotaxis, and the release of lysosomal enzymes, oxygen-free radicals, and proinflammatory mediators. Anti-neutrophil cytoplasmic antibodies (ANCA) have been identified in patients suffering from some forms of vasculitis. The identification of ANCA antibodies may help to discriminate among the different forms. In the present case, there was no possibility for further investigations. Therefore, the final diagnosis and pathogenesis remains speculative.

Table 1: Disseminated visceral giant cell arteritis, differential diagnoses.[5]

Pathologic entity	**Principle affected vessel**	**Giant cells**	**Fibrinoid necrosis**	**Eosinophilic infiltrates**	**ANCA**
Arteritis temporalis (Classic giant cell arteritis Horton)	cranial arteries occasionally large systemic arteries	+	±	±	
Takayasu arteritis	aorta and aortic arch branches	±	-	-	
Polyarteritis nodosa	medium sized and small arteries	±	+++	+++	negative

Eosinophilic granulomatosis with polyangitis (Churg-Strauss vasculitis)	extracranial small arteries and veins, perivascular tissue	+	+++	+++	positive
Granulomatosis with polyangiitis (Wegener granulomatosis)	small vessel of upper respiratory tract, lung, kidney	+++	+++	+++	positive c-ANCA
Disseminated visceral giant cell arteritis	extracranial small arteries and arterioles	+++	±	-	negative

Legend: -: absent; ±: occasionally present; +: usually present; +++: always present; (adapted from Lie, 1977)

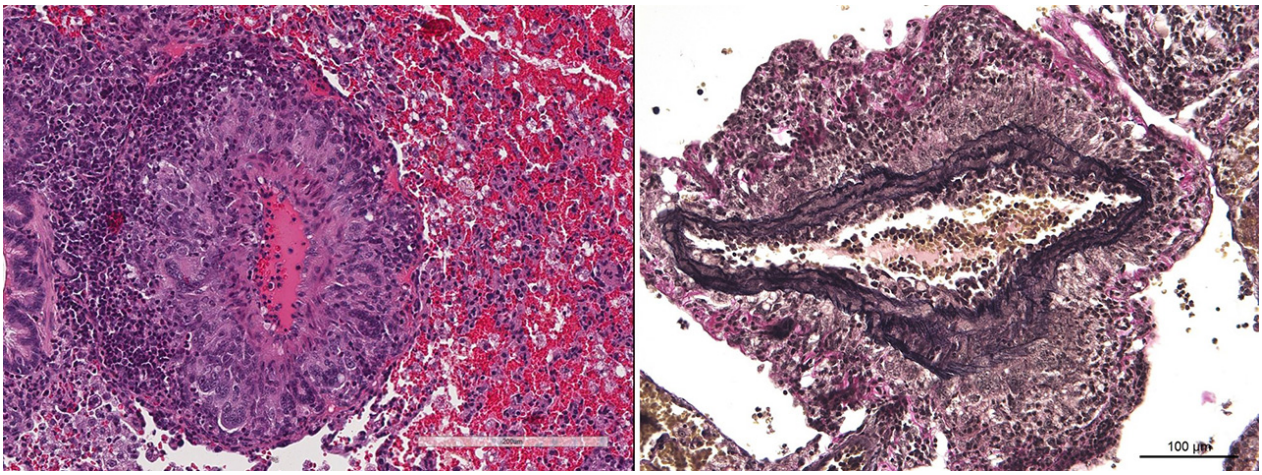
JPC Diagnosis:

1. Lung, small and medium caliber pulmonary arteries: Arteritis, granulomatous, segmental, severe with diffuse, severe alveolar hemorrhage and edema, mouse lemur (*Microcebus murinus*), non-human primate.
2. Heart, aorta and coronary artery: Arteritis and periarteritis, granulomatous, segmental, moderate with multifocal aortic valvular endocarditis.
3. Heart: Myocardial degeneration and necrosis, multifocal, mild.

Conference Comment: In humans, there are two common vasculitides of medium to large vessels that can cause both peripheral and coronary artery disease: Takayasu's arteritis and giant-cell arteritis. Giant-cell arteritis typically affects older females (greater than 50 years old) and has two variants: cranial giant-cell arteritis and large-vessel giant-cell arteritis. Clinical signs for cranial giant-cell arteritis include headaches, scalp pain, jaw claudication, and loss of vision. Patients with large-vessel giant-cell arteritis generally suffer from aortic dissection or aneurysm, claudication of the limbs, myocardial ischemia, and acute aortic insufficiency.[4]

Ultrasound can raise suspicion of giant-cell arteritis by identifying the "halo sign" which represents diffuse edema of the vessel wall with adjacent normal vascular wall (known as "skip lesions"). Diagnosis is by temporal-artery biopsy, but this method can result in false-negatives for two reasons: (1) sampling of the "skip lesion" region or (2) the temporal artery is not involved. The latter is fairly common in large-vessel giant-cell arteritis, in which 40% of patients do not have temporal artery involvement.[4]

The most commonly recommended treatment for giant-cell arteritis in humans is glucocorticoids with many patients requiring long-term treatment to prevent worsening of the arteritis and eventually occlusion of large vessels.[4] New research has shown the efficacy of tocilizumab (an interleukin-6 receptor alpha inhibitor) in combination with glucocorticoids in sustaining disease remission in patients and avoiding the side effects of long-term glucocorticoid use.



Lung, mouse lemur. Affected artery on left, with demonstration of the elastin network of the unaffected tunica intima and media on the right. The cellular infiltrate is present within the adventitia, indicating a periarteritis rather than a true arteritis. (HE and Movat pentachrome , 200X)

Elevated serum levels of interleukin-6 result in increased concentration of C-reactive protein and other acute phase proteins which correlate with disease severity. Tocilizumab, an interleukin-6 receptor alpha inhibitor, allows for reduced concentrations of glucocorticoids and decreased levels of acute phase proteins.[7]

There is significant variability between the submitted unstained slides and the digital slide provided to conference recipients. The moderator thought the only vessels affected were small and medium-sized pulmonary arteries because on the digital slide, the aorta and coronary arteries were not involved, but they were inflamed in our stained slide. Conference participants noted the recent article written about this case, which states that the aorta was unremarkable.[2] The moderator theorized that the article was written based on initial cuts from the block, and emphasized the segmental and stochastic nature of many vasculitides.

Two special stains were run, Verhoff van Giesson and Masson's trichrome. In the elastin stain, the tunica media of the medium pulmonary arteries generally has intact elastic lamina with smooth muscle cells in between. In the Masson's trichrome, surprisingly no fibrosis is identified within the tunica intima or media of affected arteries. In many arteries the lesions are more of a periarteritis because the tunica intima and media are largely spared. A discussion of the abundant acute hemorrhage in the alveoli included possible pulmonary hypertension leading to rupture of small alveolar capillaries. This condition is characterized by small arteries that exhibit medial hyperplasia and fibrosis, as well as pathognomonic plexiform lesions, and right ventricular hypertrophy, none of which were identifiable in this case.

In humans, the current vasculitis nosology (the Chapel Hill consensus) was revised in 2012[4] and is subdivided by: vessel type, characteristics of the infiltrate, and if the individual has ANCA antigen (anti-neutrophil cytoplasmic antibodies). The moderator believes the closest classification for the entity presented here is Wegener granulomatosis and Churg-Strauss vasculitis (see chart above), but that trying to pigeon hole this into a human classification may not

be useful. Certain features vary slide to slide, and the amount of fibrinoid vasculitis is a minor component in the slides examined.

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CASE II: F1755364 (JPC 4101079).

Signalment: 18-year-old, male, castrated, domestic shorthair (*Felis catus*), feline.

History: An 18-year old male castrated domestic short-haired cat presented acutely non-responsive to the emergency veterinarian. The cat had an approximately 1 year history of intermittent neurologic signs including ataxia, right-sided head tilt, paresis and paralysis, as well as progressive weight loss. Previous diagnoses included chronic kidney disease and systemic hypertension (180-220mmHg systolic). Fundic evaluation at a prior examination revealed microhemorrhages and partial retinal detachment. The cat was euthanized due to poor prognosis.

Gross Pathology: Extending from the left mid-thalamus caudally through the brainstem to the level of the obex is a poorly demarcated 4 x 1.5 x 1.0 cm region of hemorrhage with softening of the neural parenchyma (malacia) (Figure 1). Hemorrhage extends along the leptomeninges of the cerebellum, caudal cortex, and ventral brainstem. The ventral cervical and lumbar spinal cord has multifocal linear dark red foci on midline, centered on the ventral spinal artery.

Bilaterally, the kidneys are small (half normal size), pale, and firm, with diffusely pitted capsular surface that correlates with linear white streaks of fibrosis radiating from the medulla to the cortical surface.

Laboratory Results (clinical pathology, microbiology, PCR, ELISA, etc.):

Clinical Pathology: BUN 54 mG/dL (normal 18-35 mG/dL); Creatinine 3.6

Cerebellum and brainstem, cat: There is a large focus of acute hemorrhage and malacia within the brainstem extending from the thalamus to the obex. (HE, 5X) (Photo courtesy of: Colorado State University, , http://csu-cvmbs.colostate.edu/academics/mip/Pages/default.aspx)

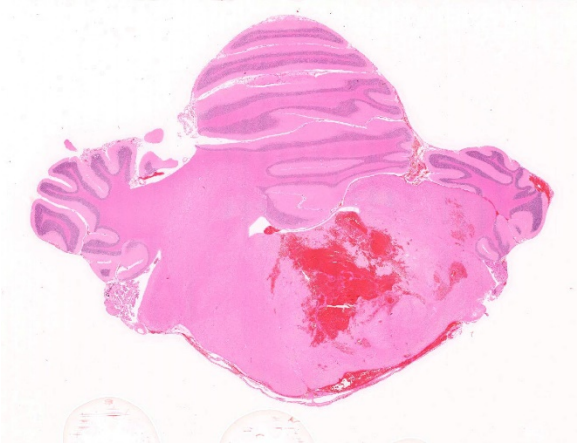
mG/dL (normal 0.8-2.4 mG/dL); urine specific gravity: 1.015.

Microscopic Description:

Cerebellum/brainstem: Multifocal meningeal and parenchymal arteries and arterioles are segmentally to diffusely thickened by bright eosinophilic amorphous, hyalinized, and occasionally granular material admixed with rare mural karyorrhectic debris (hyaline degeneration to fibrinoid necrosis). Endothelial cells are often plump with large nuclei and open chromatin (reactive) or vacuolated (degeneration). Multifocal vessels within the ventral leptomeninges and central brainstem are disrupted and replaced by severe regionally extensive hemorrhage partially organized by fibrin strands. Hemorrhage focally effaces approximately 40% of the brainstem cross-sectional area and tracks along the leptomeninges. Neuropil abutting the regions of hemorrhage is moderately vacuolated with edema and infiltrated by minimally increased numbers of glial cells. Multifocal neurons contain finely granular golden brown cytoplasmic lipofuscin pigment. There is rare mild meningeal and choroidal mineralization.

Spinal cord (not shown): Elsewhere along the spinal cord there were several similar sites of hemorrhage, each associated with similar vascular changes as those previously described. Some of these sites were more subacute to chronic with deposits of hematoidin and a more developed parenchymal reaction.

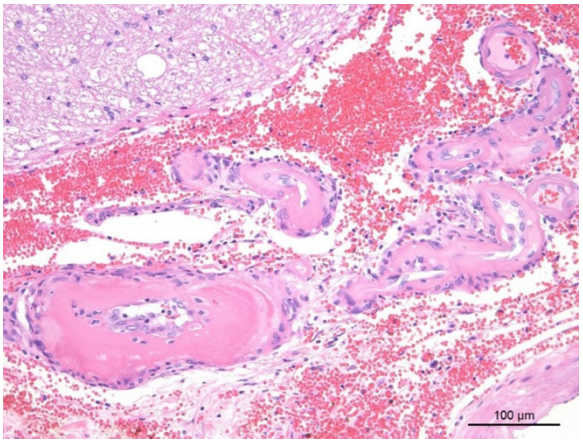
Kidney (not shown): The capsule is bossellated with multifocal depressions that correspond to radiating regions of marked interstitial fibrosis which dissect, separate,



Cerebellum and brainstem, cat. Multiple areas of hemorrhage are present within the brainstem, and the adjacent meninges and 4th ventricle. (HE, 7X)

and replace approximately 40% of cortical tubules and glomeruli. Concentric perivascular, periglomerular, and peritubular fibrosis is frequent. High numbers of lymphocytes and plasma cells infiltrate the fibrous connective tissue. Glomeruli are often shrunken and sclerotic and Bowman's capsules are moderately to markedly thickened and occasionally lined by plump reactive parietal cells. Tubules have moderately to severely thickened basement membranes and exhibit one or more of the following changes: tubular ectasia lined by attenuated epithelium, swollen vacuolated epithelium (degeneration), plump slightly basophilic epithelial lining (regeneration), or rare individual necrotic epithelial cells with shrunken cell borders, hypereosinophilic cytoplasm, and pyknotic nuclei. Tubules often contain proteinaceous fluid, occasional mineral or rare refractile crystals.

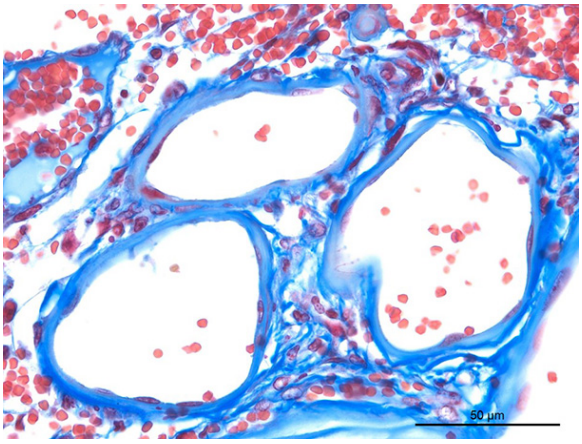
Contributor's Morphologic Diagnosis:
Brainstem, cerebellum and spinal cord, arterioles: Severe chronic hyaline degeneration and fibrinoid necrosis with acute severe perivascular hemorrhage and necrosis (malacia).



Brainstem, cat: High magnification image of the arterioles at the base of the brainstem. The arteriolar walls are diffusely replaced with collagen, which appears hyaline on HE. (HE, 400X)

Kidney (not shown): Severe chronic tubulointerstitial nephritis with marked interstitial fibrosis, glomerulosclerosis, and tubular proteinosis.

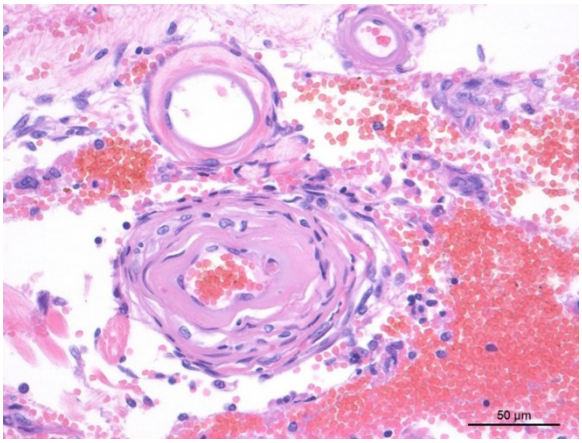
Contributor's Comment: Hyaline degeneration of arteries is a non-specific pathologic change that refers to loss of normal cellular structure and deposition of amorphous material of the intima and media of a muscular artery or arteriole. The hyalinized appearance is a result of deposition of plasma protein, amyloid deposits, and/or necrosis of vascular smooth muscle.[5] Hyaline degeneration can be



Brainstem, cat: A Masson's trichrome demonstrates the wall of affected arterioles are replaced by collagen, rather than protein. The arteriolar walls are diffusely replaced with collagen, which appears hyaline on HE. (HE, 400X)

associated with hypertension, uremia, diabetes mellitus, aging, hepatosis dietetica, organomercurial poisoning, mulberry heart disease, and cerebrospinal angiopathy/edema disease (among others).[4,5]

In this case, vascular changes are secondary to persistent hypertension (hypertensive vasculopathy) and chronic kidney disease. Other conditions that may result in secondary hypertension include: hyperthyroidism, diabetes mellitus, hyperaldosteronism, pheochromocytoma, chronic anemia (cats),



Brainstem, cat: In addition to collagen replacement of the arteriolar smooth muscles, there is whorling of fibroblasts with interspersed mature collagen around small arterioles. (HE, 400X)

hypothyroidism (dogs), erythropoietin therapy, and acute and chronic laminitis (cattle, horses).[5] Hypertension can also be essential (primary). Essential hypertension is characterized by an increase in total peripheral vascular resistance due to a primary decrease in lumen diameter and increase in media thickness.

Renal disease is a common cause of hypertension in dogs and cats and contributed to the systemic hypertension identified in this case. Renal disease can be both a cause and effect of hypertension, complicating the pathogenesis in individual cases. Chronic renal disease results in impaired sodium and water excretion and thus increased blood volume. Furthermore, a hypertension-induced decrease in renal perfusion activates the renin-angiotensin-aldosterone system, which also results in increased blood pressure. Impaired renal perfusion and progressive vascular injury further exacerbates chronic kidney disease.

A common clinical presentation of animals with hypertensive vasculopathy is acute blindness secondary to retinal arterial degeneration with associated retinal vascular tortuosity, intraocular hemorrhage, and retinal detachment (hypertensive retinopathy).[3] In cats and people a similar manifestation involving arteries of the central nervous system (hypertensive encephalopathy) has also been rarely described.[1] Under normal conditions the vascular tone of cerebral arteries and arterioles are tightly regulated to maintain constant and appropriate perfusion of the brain. When systemic blood pressure reaches the upper limit of the capacity of cerebral autoregulation, the cerebral arterioles segmentally constrict and dilate. The appropriate autoregulatory response is maintained in constricted regions. In dilated regions, however, vascular overdistension disrupts endothelial tight junctions, allows leakage of plasma proteins into the extracellular space (vasogenic edema), activates endothelial cells into increase expression of adhesion molecules (ICAM-1, PCAM-1) and cytokines (IL-1, IL-6, IL-8, TNF-α), induces neutrophil and monocyte adhesion and migration, and over time results in repetitive injury to the endothelium and vascular wall with subsequent vascular degeneration, necrosis and hemorrhage.[1,7] This case exhibits an end-stage response to chronic vascular damage as a result of persistent systemic hypertension. The intermittent nature of neurologic signs is consistent with repetitive small hemorrhages within the central nervous system and subsequent resolution. In fact, several other sites of more chronic hemorrhage were identified histologically in this cat's spinal cord. These had deposition of hematoidin and a more developed tissue reaction. A final massive hemorrhage within the brainstem ultimately yielded the patient non-responsive.

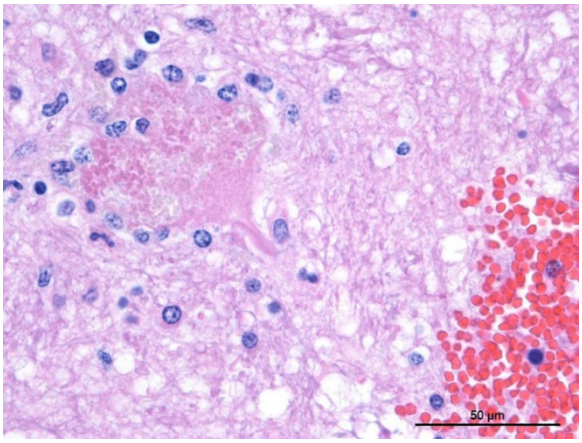
JPC Diagnosis: Brainstem, arteries: Hyaline vascular necrosis, multifocal, moderate with perivascular fibrosis, multifocal, severe, acute parenchymal and meningeal

hemorrhage, domestic shorthair (*Felis catus*), feline.

Conference Comment: There are three key terms regarding arterial degeneration to bear in mind: arteriosclerosis, atherosclerosis, and arteriolosclerosis.[2]

Arteriosclerosis (from the Greek, *arterio-* for artery and *-sclerosis* for hardening) is a chronic change consisting of: lumen narrowing, hardening, and loss of elasticity. Arteriosclerosis most commonly occurs in the abdominal aorta and points of arterial branching in older horses, ruminants, and carnivores secondary to a proliferative and degenerative change rather than inflammatory. A key feature is the lack of lipid deposition, which is a feature of atherosclerosis. The pathogenesis of plaque formation has not been fully explained but there are two main theories: (1) platelet microthrombi form in areas of turbulence or endothelial damage leading to release of platelet-derived growth factor (PDGF) and transforming growth factor-β, the former resulting in migration and proliferation of smooth muscle cells; and (2) the damage to the endothelium results in the endothelial cells themselves producing mitogens like PDGF. In reality, the pathogenesis is most likely a combination of the two. Microscopically, those mitogens cause migration of smooth muscle cells (or myointimal cells) from the media to the intima which act similarly to fibroblasts surrounding arteries by producing the matrix that forms the plaque composed of: collagen, elastic tissue, and proteoglycans.[6]

Atherosclerosis, which is characterized by the formation of an atheroma, a focal, raised, intimal fibrofatty plaque composed of cholesterol esters, is most common in humans and is only applicable to domestic animals in relation to animal models of



Brainstem, cat: Adjacent to an area of hemorrhage, a swollen, degenerating neuron is surrounded by astrocyte nuclei. (HE, 400X)

human disease. Some animals are susceptible to the formation of atheromas (rabbits, chickens, and pigs) and are thus, good animal models for research purposes. Dogs, cats, cattle, goats, and rats, on the other hand, are atheroresistant (with few exceptions, see below). In general, pigs and non-human primates are the most widely used large-animal models and variations of genetically modified mice are becoming available as well. Clinically, atherosclerosis in humans often results in myocardial infarction, stroke, and peripheral vascular resistance. More common in domestic animals are fatty streaks, another type of intimal lesion, which are often found in the aorta and larger arteries of ruminants and swine. These appear grossly as soft, smooth, flat lesions of varying sizes that are stained bright orange with Sudan IV. There is no known correlation of fatty streaks with the formation of atherosclerotic plaques. The cause of atherosclerosis is multifactorial and explained by the "response to injury" hypothesis which states that endothelial injury or dysfunction can result from hyperlipidemia (mainly cholesterol from low-density lipoprotein and very-low-density lipoprotein). The following steps (platelet adhesion and smooth muscle migration and proliferation) are the same as for

arteriosclerosis. As mentioned above, the key microscopic feature differentiating the two is the presence of lipid, which can be extracellular or intracellular (within activated macrophages or smooth muscle cells) called "foam cells". In fatty streaks, lipid in activated macrophages is most prevalent and in atherosclerosis, lipid in smooth muscle cells predominates. In pigs, atheromas most frequently form in the aorta and extramural coronary arteries, cerebral and iliac arteries. The main predisposing factor is a diet containing excess cholesterol and the plaques, unlike humans, rarely lead to fully occlusive thrombus formation. Dogs, although generally atheroresistant, can develop atherosclerosis secondary to hypercholesterolemia from hypothyroidism or diabetes mellitus. Additionally, Miniature Schnauzers have a genetic predisposition towards idiopathic hyperlipoproteinemia which often results in atherosclerosis. Microscopically, in dogs the lipid accumulates in the tunica media, whereas, in humans, it is present in the intima. As an aside, historically the term "xanthomatosis" has been used to describe this condition in animals. Current literature dictates that xanthomas are accumulation soft lipid-laden foam cells in the subcutaneous and cutaneous tissues only, and is a well-known condition in cats deficient in lipoprotein lipase.[6]

Finally, arteriolosclerosis describes a variable group of lesions in arterioles which may be predominantly hyaline or hyperplastic, both of which are initiated by endothelial damage. Hyalinosis or hypertrophic hyalinization is characterized by brightly eosinophilic, amorphous material which expands vessel walls, and results from leakage of plasma proteins. In domestic animals, hyalinosis is most frequently seen in older dogs, and pigs within splenic arterioles. Additionally, in dogs, hyaline deposition may affect the intramural coronary arteries, meningeal arteries, and cerebral arteries. In the heart, it can result in multifocal intramural myocardial infarction (MIMI) which leads to congestive heart failure when paired with valvular endocardiosis (commonly found in older dogs). In pigs, pathologic changes associated with hyaline arteriolar deposits occurs with organomercurial poisoning (meninges), edema disease (gastric and colonic submucosa and cerebellar folia), and hepatosis dietetica and mulberry heart disease (heart). Hyperplastic arteriolosclerosis, is characterized by intimal changes (smooth muscle proliferation and concentric fibrosis, AKA "onion skinning") with fibrinoid necrosis of the tunica media.[6]

In humans, the most common cause of arteriolosclerosis is systemic hypertension which can occur via primary or secondary means. In domestic animals, the most common cause of systemic hypertension is primary renal disease which is associated with primary or secondary hypertension. Primary systemic hypertension leads to decreased renal perfusion, subsequent activation of the renin-angiotensin-aldosterone system, and additional hypertension. Conversely, chronic renal disease can result in secondary hypertension by poor excretion of sodium and water and increased blood volume. One important and dangerous feature of hypertension is that it is self-perpetuating and can result in the death of the animal. The causes of hypertension and main clinical signs are described above by the contributor.[6]

In this case, side-by-side viewing of the affected arterioles on HE and with a Masson's trichrome deomonstrated the marked fibrosis of the vessel wall, which appeared as simple hyaline change on HE. The Masson's trichrome identified abundant collagen (type I or III) that has effaced the

tunica intima and media, smooth muscle cells. Additionally the Masson's trichome helped to demonstrate the perivascular whorling of fibrocytes around the adventitia of smaller arterioles, in an attempt to stabilize them against the systemic hypertension.

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http://csu-cvmbs.colostate.edu/academics/mip/Pages/default.aspx

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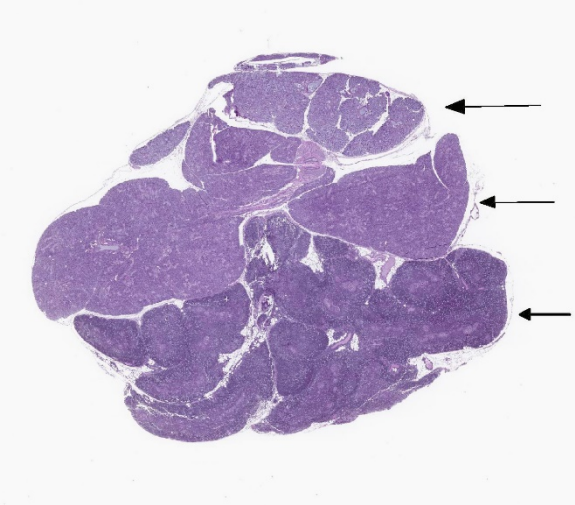
CASE III: G071 (JPC 4100982).

Signalment: 4-week-old, female, outbred Hartley guinea pig (*Cavia porcellus*), guinea pig.

History: Experimentally infected with Ebola virus (guinea pig adapted Mayinga isolate) by intraperitoneal route 8 days prior to necropsy.

Gross Pathology: The animal was mildly dehydrated. The liver was pale and friable. Lungs were mottled and multifocally hemorrhagic. The gastrointestinal tract was filled with digested blood.

Laboratory Results (clinical pathology, microbiology, PCR, ELISA, etc.): None provided.



Salivary gland and thymus: *In the guinea pig, the cervical location of the thymus puts it in apposition with salivary glands (Sublingual salivary gland (top arrow), parotid salivary gland (middle arrow), thymus (bottom arrow). (HE, 6X)*

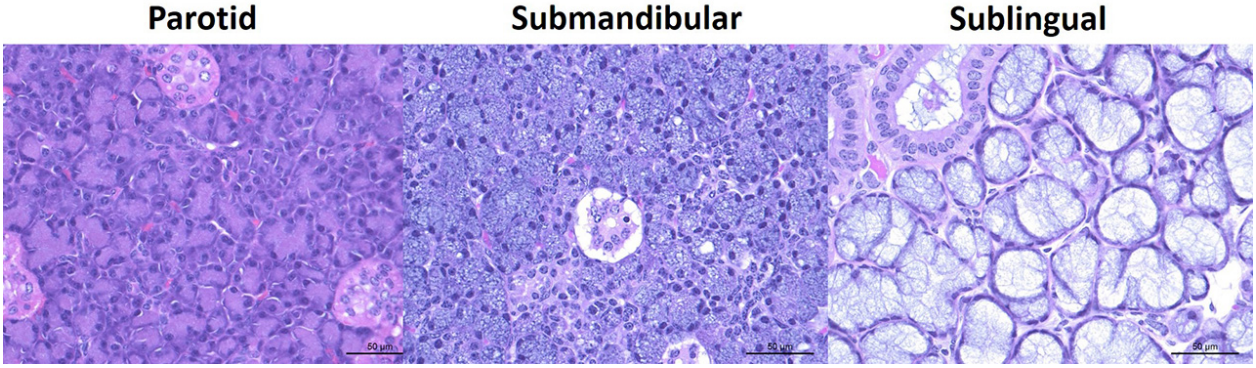
Microscopic Description: Slide contains sections of thymus and sublingual and parotid salivary glands. In the thymus, there is moderate diffuse lymphocytolysis with tingible body macrophages containing apoptotic cellular debris in the cortex and medulla, with blurring of the distinction between the two. Low numbers of macrophages with abundant vacuolated cytoplasm and small to large eosinophilic intracytoplasmic inclusion bodies are present in the medulla and occasionally cortex. Within the center of the Hassall's corpuscles, there is pyknotic nuclear dust admixed with viable and degenerate heterophils and cornified epithelial cells, with scattered rare coarse mineralized concretions (normal feature of this species).

Within the both salivary glands there are low numbers of individual necrotic ductal cells. There are scattered individual and small clusters of apoptotic and necrotic acinar cells with rare ICIB. There are low numbers of vacuolated and inclusion bearing macrophages and fibroblasts in the interacinar and periductal interstitium. Within several small and medium ducts in the parotid gland, there are karyomegalic ductal epithelial cells containing very large eosinophilic to amphophilic (owl's eye) intranuclear inclusions with a clear halo and peripheral margination of the chromatin (Cowdry type A). In both salivary glands there are several medium ducts that are mildly dilated and filled with wispy (sublingual) to homogenous (parotid) pale basophilic acellular material (inspissated saliva).

Contributor's Morphologic Diagnosis:

1. Thymus, lymphocytolysis, diffuse, moderate, with intrahistiocytic intracytoplasmic inclusion bodies
2. Salivary glands, parotid and sublingual, sialoadenitis, necrotizing and histiocytic, multifocal, acute, mild with intracytoplasmic inclusion bodies
3. Salivary gland, parotid, ductal epithelial cell karyomegaly, multifocal, mild with intranuclear inclusion bodies

Contributor's Comment: Ebola virus, a filovirus, is an important high consequence pathogen causing significant human disease outbreaks, most recently in West Africa from 2014 to 2016, and again in 2017. Guinea pigs remain an important model for infectious disease research, and have a number of unique anatomical features. The guinea pig thymus is located in the cervical region, and the pustule like appearance of the Hassall's corpuscles is normal for this species.[1] Lesions in the thymus are consistent with experimental manipulations.[4,5] Macrophages are a main target cell type of Ebola virus infection, with frequent (and often severe)

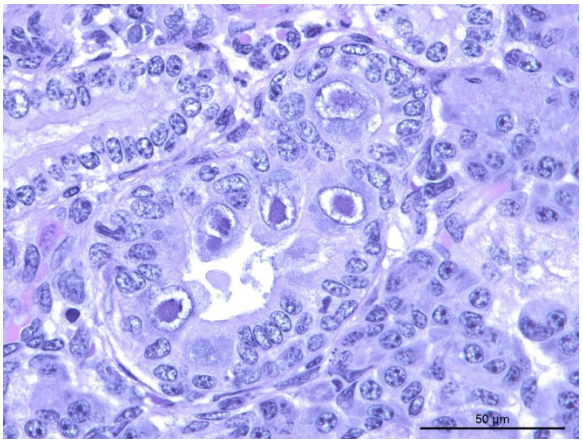


Salivary glands, guinea pig. Histologic differences in the salivary glands of the guinea pig. (HE, 315X)

bystander necrosis of lymphocytes. Ebola does not infect lymphocytes.[9,10] Lympho-cytolysis of the thymic cortex can be seen in a number of infectious disease processes, as well as corticosteroid administration or stress.

Lesions in the salivary glands represent two distinct processes, and are a mixture of experimental manipulation and adventitious spontaneous (background) infection. There is apoptosis and necrosis of ductal and acinar epithelial cells, with viral cytoplasmic inclusions present in acinar epithelial cells as well as interstitial fibroblasts and macro-phages. These lesions are consistent with experimental Ebola virus infection, and saliva may transmit the virus during acute infections. Saliva is also one of several fluids that may remain positive for the Ebola genome in convalescent human disease survivors, although virus generally cannot be isolated from the saliva.[2] Human disease transmission via semen from recovered individuals has been documented.[3]

Intranuclear inclusions in the parotid ductal epithelium are consistent with *caviid betaherpesvirus-2* (guinea pig cytomegalovirus).[1] In other species (rat, mouse), polyomavirus would be a differential etiology; guinea pigs have no described polyomavirus. *Caviid betaherpesvirus-2* is not excluded by the supplier of these animals, and CMV is typically an incidental finding in this species. Systemic disease can occur in pregnant or weaned pigs. There were no CMV type inclusions in any other organ sampled in this guinea pig, nor in any of the other pigs in this study.

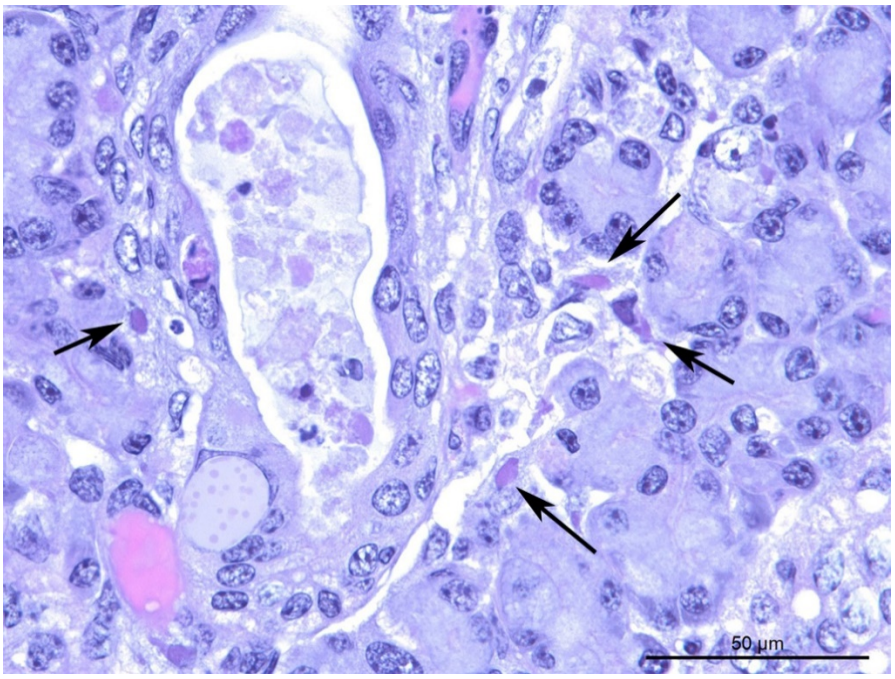


Salivary gland, guinea pig. Ductal epithelial nuclei are swollen by a large viral inclusion consistent with cytomegalovirus. (HE, 400X)

JPC Diagnosis:

1. Thymus, lymphocytes: Apoptosis, diffuse, moderate, with numerous tingible body macrophages, outbred Hartley guinea pig (*Cavia porcellus*), guinea pig.
2. Thymus & salivary gland, macrophages: Intracytoplasmic viral inclusions, occasional.
3. Salivary gland, glandular epithelium: Necrosis, multifocal, minimal to mild.
4. Salivary gland, ductal epithelium: Rare, intranuclear, karyomegalic viral inclusions.

Conference Comment: The family *Filoviridae* (negative-sense RNA viruses) has three genera: *Marburgvirus* (Marburg and Ravn viruses), *Ebolavirus* (Sudan virus, Ebola virus, Reston virus, Bundibugyo virus, and Tai Forest virus), and *Cuevavirus* (Lloviu virus). Filoviruses enter cells via macropinocytosis with subsequent binding to Niemann-Pick C1 (NPC1) receptor protein (a



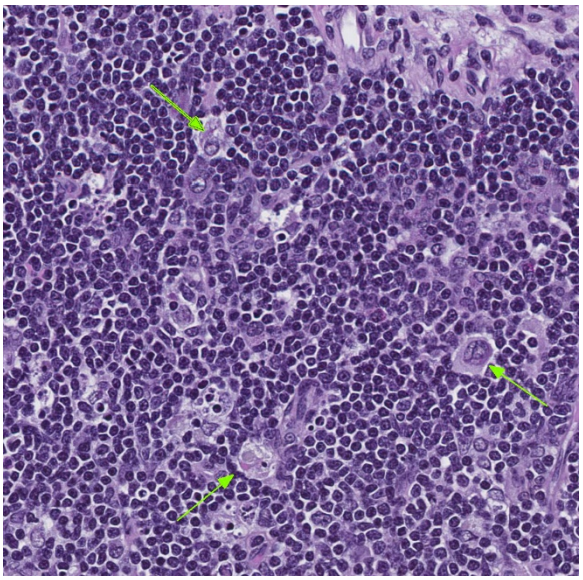
Salivary gland, guinea pig. Fibroblasts and macrophages within the salivary gland contain irregular eosinophilic viral inclusions consistent with filoviral inclusions (arrows). The duct contains necrotic cellular debris, likely from glandular necrosis

host cholesterol transport protein). Other cellular attachment molecules include: C-type lectins, phosphatidylserine, actin filaments, and cellular microtubules. Virus replication takes place in the cytoplasm and form prominent intracytoplasmic inclusion bodies. Viral maturation occurs via budding of preassembled nucleocapsids from the plasma membrane. As RNA viruses, Filoviruses mutate rapidly within infected individuals or reservoirs (different species of fruit bats).[7] The mutation rate has been calculated to be similar to seasonal influenza at 2.0 x 10^{-3} substitutions per site per year.[6]

Non-human primates (NHPs) are highly susceptible to filovirus infections with outbreaks reported in wild gorillas (*Gorilla gorilla*) and chimpanzees (genus *Pan*). The incubation period is about 3-6 days, followed by onset of clinical disease characterized by petechiae, ecchymoses, hemorrhagic pharyngitis, hematemesis, melena, and prostration. The pathogenesis of filovirus infections is similar in NHPs and humans but the clinical course of disease in NHPs is shorter and almost always ends in death. Mice and guinea pigs are not susceptible to field strains of Marburg virus or Ebola virus but rodent-adapted strains have been developed for vaccine and therapeutics testing.[8]

In experimentally infected NHPs, filoviruses replicate in macrophages, dendritic cells, and endothelium resulting in dissemination throughout the body and necrosis of various organs which is most flagrant in the liver. Infected monocytes, macrophages, and dendritic cells also release inflammatory mediators like tumor necrosis factor and interleukin-8, as well as, nitric oxide which effect vascular permeability and coagulation, and tissue factor from infected macrophages and monocytes. Additionally, loss of functional hepatocytes yields reduced synthesis of clotting factors and further aggravation of dysfunctional hemostasis dramatically ending with disseminated intravascular coagulation.[8]

Conference participants failed to recognize the eosinophilic intracytoplasmic viral inclusion bodies in macrophages and fibroblasts within the salivary gland. According to the moderator (who is also the contributor of this case), viral inclusions were seen in the glandular epithelial cells as well with immunohistochemistry; the saliva is also a way that this virus may be spread. ,potentially contributing to virus spread via



Thymus. Tingible body macrophages contain irregular cytoplasmic viral inclusions consistent with filoviral inclusion (arrows). There is an increased number of tingible body macrophages as a result of increased lymphocyte turnover. (HE, 400X)

saliva. Ebolavirus results in lymphocytolysis in the thymic cortex indirectly as "bystander necrosis". The main microscopic differential for this lesion is stress-induced lymphocytolysis.

Contributing Institution:
Pathology Department
NIH/NIAID
Integrated Research Facility
https://www.niaid.nih.gov/about/integrated-research-facility

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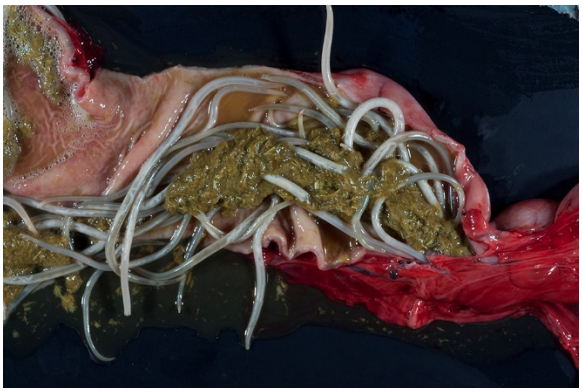
CASE IV: 16N-3473 (JPC 4101312).

Signalment: 6-month-old, female, Quarter horse (*Equus caballus*), equine.

History: This filly came from a farm at which two other horses reportedly had neurologic disease over the past five years. The patient was grade 4/5 ataxic. Cervical radiographs were unremarkable. She was down in the trailer and was unable to stand without assistance upon arrival to the



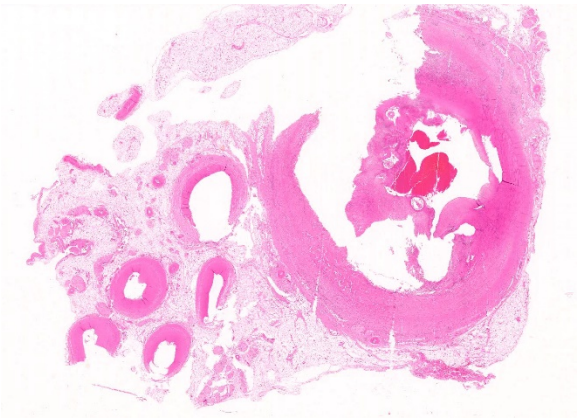
Small intestine, horse. Numerous adult ascarids (Parascaris equorum) were present within the small intestine of this individual. (Photo courtesy of: UC Davis School of Veterinary Medicine, http://www.vetmed.ucdavis.edu/index.cfm)

clinic. Neuroaxonal dystrophy was suspected. The animal was eventually euthanized due to the poor prognosis. Deworming and vaccination history were unknown.

Gross Pathology: Four 0.4- to 0.5-cm in diameter ulcers were present on squamous epithelium of the cardia. Hundreds of large robust nematodes consistent with *Parascaris equorum* filled the duodenum and jejunum. Approximately fifty slender elongate, white nematodes consistent with strongyle larvae were present in the large intestine, most notably in the right dorsal colon. The abdominal aorta at the level of the root of the cranial mesenteric artery was segmentally thickened. Other lesions were insignificant and/or were not relevant to the presenting complaints or the slide shown here.

Laboratory Results (clinical pathology, microbiology, PCR, ELISA, etc.): None provided.

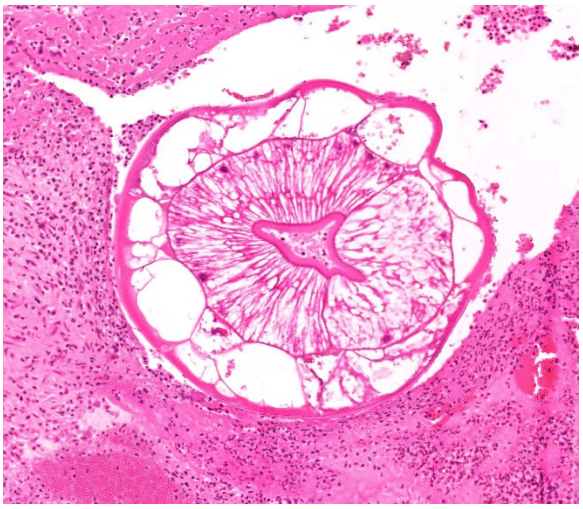
Microscopic Description:
Aorta: The artery is asymmetrically thickened, and the intima is expanded and partially effaced by multifocal to coalescing necrosis, inflammation and multiple cross-sections of nematodes. The nematodes are covered by a superficial layer of fibrin with abundant erythrocytes neutrophils and small amounts of cellular debris. Endothelial cells are commonly plump and crowded along the affected surface. Endothelium is often absent in regions lined by the thrombus with adjacent nematodes. The nematodes are approximately 400 um in diameter with a smooth, glassy eosinophilic, 8.0-um-thick cuticle, platymyarian muscle, a pseudo-coelom, and a large central intestine lined by a few multinucleated cells with a bright-eosinophilic brush border. The reproductive tracts are not visible or are underdeveloped (consistent with larval forms). The adjacent internal elastic lamina appears disrupted and the nearby tunica media and adventitia are multifocally vacuolated and distorted with moderate to abundant numbers of infiltrating lymphocytes, plasma cells and neutrophils. This region also contains multifocal small areas of necrotic cellular debris and some scattered erythrocytes. Similar, small aggregates leucocytes are scattered throughout the adjoining adipose tissue. The adventitia of the smaller nearby arteries are occasionally cuffed by small numbers of lymphocytes and plasma cells.



Muscular artery, horse. A cross-section of the cranial mesenteric artery contains a large fibrin thrombus and cross sections of larval nematodes in the lumen. (HE, 5X)

Contributor's Morphologic Diagnosis:
Aorta (at the junction of root of cranial mesenteric artery): Severe, multifocal to coalescing, neutrophilic, lymphoplasmacytic, endarteritis with luminal thrombosis and larval nematodes (presumed *Strongylus vulgaris* larvae)

Contributor's Comment: The lesions in the abdominal aorta at the junction with the cranial mesenteric artery described above are secondary to *Strongylus vulgaris* larvae invasion. Of the nematodes that affect horses, the small strongyle group, or cyathostomins, are found most commonly. However, *S. vulgaris* is the most important strongyle species affecting horses, as it causes the most damage to the host. *S. vulgaris* develops uniquely as it's the only strongylid that completes a stage of larval maturation in the arterial system of the horse. L3 larvae are ingested from contaminated fields and penetrate through the mucosa to the submucosa in the ventral colon or cecum. The larvae mature and molt to the L4 stage which invade the submucosal arterioles. L4 larvae migrate in or along the intima to the cranial mesenteric artery where they mature for the next 3 to 4 months until molting into the L5 stage. L4 larvae are unable to penetrate the internal elastic lamina and therefore cannot invade the media of vessels. Blood flow to the intestinal subserosal arteries transports the L5 larvae back to the subserosa of the cecum and colon where they are encapsulated forming nodules. When nodules rupture, adult worms return to the gut lumen where they become sexually mature in another 6 to 8 weeks.[6]



Muscular artery, horse. A cross section of a larval nematode (consistent with Strongylus vulgaris) is embedded in a fibrinocellular thrombus. The nematode has a thick cuticle, a pseudocoelom, platymyarian-coelomyarian musculature, and a large intestine with multinucleate columnar epithelial cells. (HE, 175X)

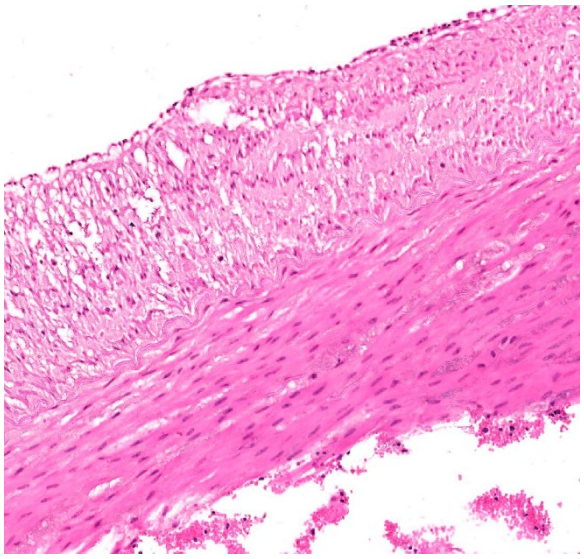
The cranial mesenteric artery and a communicating branch, the ileo-cecocolic artery, are the vessels most commonly affected by *S. vulgaris* migration. Lesions associated with *S. vulgaris* migration have also been identified in the aorta, the celiac artery and its branches, the renal arteries, and the spermatic vessels. Lesions range from common but incidental tortuous intimal tracks to uncommon occlusive thrombosis resulting in non-strangulating intestinal infarction leading to severe colic signs. Other possible outcomes of larval migration include thickening of mesenteric vessels leading to increased pressure on the abdominal autonomic plexi, which interferes with intestinal innervation. Toxins produced from degenerating larvae can also lead to signs of colic. Aberrant migration of *S. vulgaris* larvae can cause CNS signs, hind limb lameness, or even renal infarction.[6]

Characteristic histologic findings of *S. vulgaris*-induced endarteritis are present in the current case and include proliferation of the intima, adventitia and endothelium; associated fibrin deposition; regions of hemorrhage and necrosis within the vessel wall, and chronic ongoing inflammation of the intima associated with the nematodes. This case also exhibits area of internal elastic lamina disruption with subsequent thickening

of the media and associated inflammation. The nematode larval characteristics include a thick cuticle, platymyarian musculature, a pseudocoelom, prominent lateral cords, and an intestinal tract lined by only a few multinucleated cells with a prominent, bright-eosinophilic brush border.[4]

Broad-spectrum anthelmintics, primarily the macrocyclic lactones, have been used to control the effects of *S. vulgaris* on for approximately the last 50 years.[7] Nematode control has followed interval treatment regimens involving the frequent administration of anthelmintic products based on established times for the re-appearance of strongyle eggs in feces after treatment. This interval-based treatment has been successful in significantly reducing the prevalence of strongyle infections and the incidence of large strongyle-associated disease.[5] Anthelmintic drug resistance, however, has been an unfortunate side-effect of this type of therapy, and there are now several reports of resistance in stronglyes after ivermectin or moxidectin administration in numerous countries.[1,5,6,7]

Due to recent regulatory changes in Denmark, anthelmintics can only be acquired with a veterinarian prescription, and only after parasitological diagnosis.[4] Veterinarians in Denmark now have a more active role in regulating responsible anthelmintic drug use to reduce drug resistance. Regular interval-based treatment without attaining fecal egg counts is still commonly practiced in most countries, many of which are reporting anthelmintic drug resistance. Recently, there has been increased support for implementation of similar regulations in some of these countries.[6]



Muscular artery, horse. The tunica intima is thickened to 250um by fibrous connective tissue. (HE, 200X)

The presenting clinical signs in this horse were suggestive of neuroaxonal dystrophy (NAD), and lesions in the medulla oblongata and thoracolumbar regions found on postmortem histologic examination were consistent with NAD. Inflammation of the intestinal lamina propria as well as lymphadenopathy were secondary to infestation with *Parascaris equorum*, *S. vulgaris*, and small *Strongyles* in the small and large intestine.

JPC Diagnosis: Muscular artery: Arteritis, proliferative and necrotizing, transmural, chronic, severe with mural thrombosis and numerous larval strongyles, Quarter horse (*Equis caballus*), equine.

Conference Comment: Verminous arteritis is most often caused by larvae of the *Strongylus* and *Ascaris* genera.[6]

Table 1: Causes of verminous arteritis[3,6]

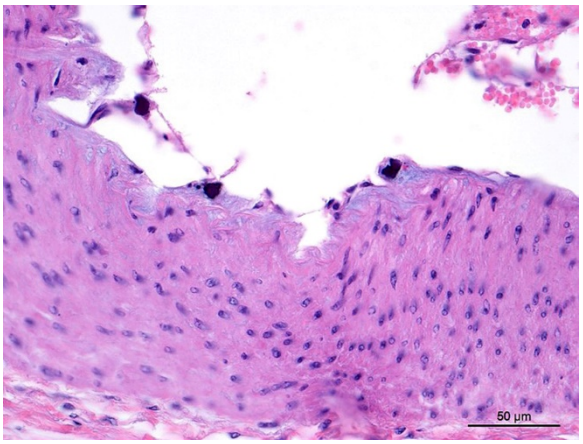
Nematode	Location	Species affected
Angiostrongylus vasorum	Pulmonary arteries	Dogs
Spirocerca lupi	Thoracic aorta; esophagus	Dogs
Dirofilaria immitis	Pulmonary arteries; right heart	Dogs
Strongylus vulgaris	Cranial mesenteric and ileo-cecocolic arteries	Horses
Oncocerca armillata	Aorta	Cattle, water buffaloes, goats, camels
Elaeophora poeli	Aorta	Cattle and related species
Elaeophora schneideri	Common carotid arteries	Mule deer, black-tailed deer
Elaeophora bohmi	Arteries and veins of the metacarpus, metatarsus, more distal extremities	Austrian horses
Crassicauda magna	Mesenteric and gastroepiploic arteries; thoracic and abdominal aorta	Cuvier's beaked whales (*Ziphius cavirostris*)[3]

Equine strongylosis is caused by members of the family *Strongylidae* which are common nematode parasites of the cecum and colon and often present in mixed infections. There are two subfamilies: *Strongylinae* (large strongyles – genera *Strongylus, Triodontophorus, Oesophagodontus,* and *Craterostomum*) and *Cyathostominae* (small strongyles). The large strongyles are plug feeders or blood suckers, of which *Strongylus* sp. undergoes extensive migration with wide-reaching effects. The small strongyles feed on intestinal contents and are mostly non-pathogenic in adults.[9]

Of the large strongyles, *Strongylus vulgaris* is the most significant. Larval forms cause endoarteritis in mesenteric vessels leading to arterial infarction of the large bowel and colic. Adult forms cause anemia and ill-thrift. The terms "endoarteritis" and "endarteritis" are often used interchangeably, however, endarteritis implies that end arteries are primarily affected.[6] Verminous endoarteritis is succinctly summarized by the contributor above. The other large strongyles, *S. edentatus and S. equinus,* rarely cause lesions. However, subserosal hemorrhagic plaques, termed hemomelasma ilei, are often attributed to trauma by migrating *S. edentatus* larvae but could be caused by any migrating strongyle.[9]

The cyathostomins, or small strongyles, are non-pathogenic as adults, but as larvae cause a clinical syndrome called larval cyathostominosis. This syndrome is caused by simultaneous emergence of larva from the deep mucosa or submucosa of the cecum and large colon. Emergence corresponds to the climate favorability for the parasites; hypobiosis or developmental inhibition occurs during cold or very hot months. It is only in late winter, spring, and early summer that encysted larvae emerge collectively to continue their development in the intestinal lumen.[9]

Conference participants viewed a Masson's trichrome and the remarkable amount of fibrosis and granulation tissue that effaces the muscular artery, as well as the intimal hyperplasia seen in the section. According to the moderator, the reviewed specimen is likely the cranial mesenteric artery because it is a muscular artery. The aorta, on the other



Muscular artery, horse. Asteroid bodies are common mineralized concretions in the intima of intestinal arteries of horses. (HE, 400X)

hand, is an elastic artery. Paucity of medial elastic lamina was demonstrated in this specimen using a Movat's pentachrome stain which highlights elastin. Additionally, the presence of intimal bodies along the endothelium was noted, a common finding in large arteries of horses.[2]

Contributing Institution:
UC Davis School of Veterinary Medicine
http://www.vetmed.ucdavis.edu/index.cfm

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