**Joint Pathology Center**
**Veterinary Pathology Services**

# WEDNESDAY SLIDE CONFERENCE 2022-2023

## Conference #2 — 24 August 2022

**CASE I:** P21-0286 (JPC 4166941)

**Signalment:**
A three-year-old female pot-bellied pig (*Sus scrofa domesticus*)

**History:**
Two-week history of intermittent pelvic limb lameness and abnormal mentation. Brought to the Veterinary Teaching Hospital unable to ambulate in rear. Neuro exam w/CT scan indicated multiple cerebellar masses. Owner elected euthanasia due to deteriorating neurological condition of patient and poor prognosis.

**Gross Pathology**:
Brain: The gyri and sulci are flattened throughout the cerebrum. When removed the cerebrum leaks a large amount of clear cerebrospinal fluid and the cerebrum flattens. The cerebellum is cone-shaped and pushed out the foramen magnum. The vermis is flattened and has loss of detail. After fixation the brain is sectioned. The lateral ventricles are severely dilated and the gray and white matter of the cerebrum compressed. There are several pale tan nodules that distort the cerebellum.

**Laboratory Results:**
Scrolls were cut from formalin-fixed, paraffin embedded blocks of cerebellum. DNA was extracted using the Qiagen QIAmp DNA FFPE Tissue kit according to the manufacturer's directions. Extracted DNA was amplified using forward and reverse primers for the 16S-23S rRNA gene spacer as published.[1] The amplicon was submitted for Sanger sequencing with the product submitted for a BLAST search. The sequence had highest identity (99.63%) with *Mycobacterium avium* subsp. *hominissuis*.

**Microscopic Description:**
Cerebellum: The cerebellar gray and white matter are effaced by large, unencapsulated, compressive nodules composed of large numbers of epithelioid macrophages and multinucleate giant cells with peripheral nuclei. There are smaller numbers of neutrophils, lymphocytes and eosinophils scattered

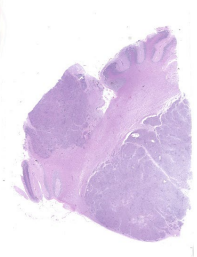

**Figure 1-1. Cerebellum, pig. Approximately 50% of the cerebellar architecture is effaced by a large inflammatory exudate. (HE, 3X)**

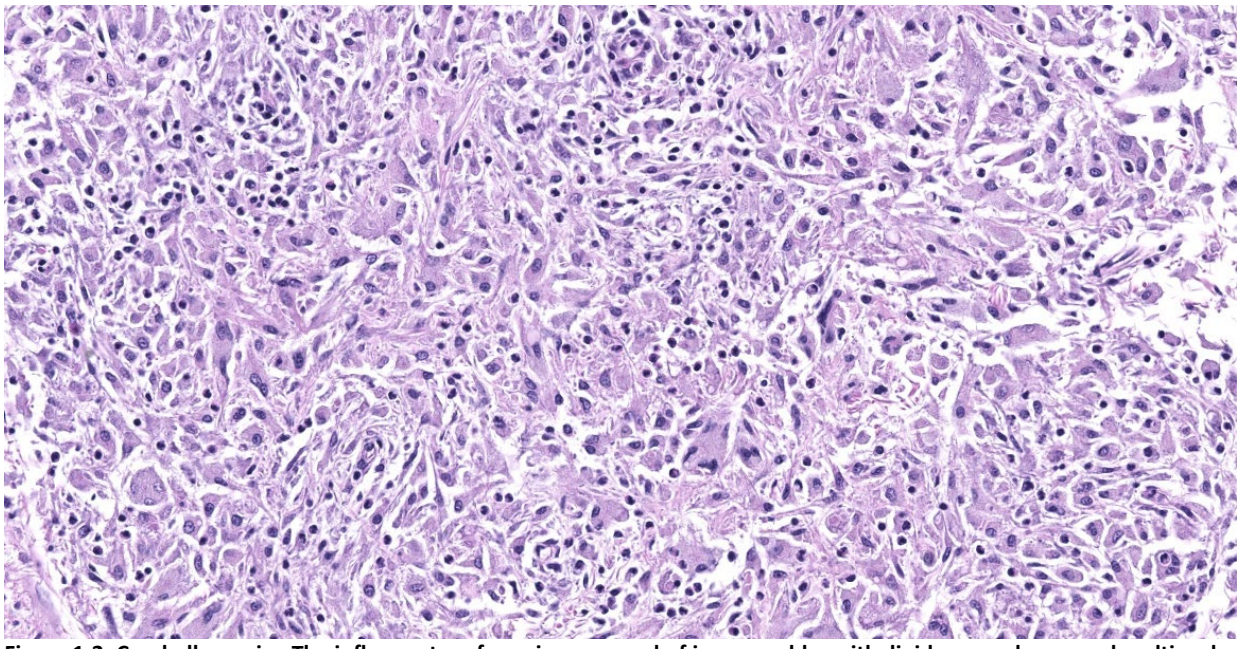

**Figure 1-2. Cerebellum, pig. The inflammatory focus is composed of innumerable epithelioid macrophages and multinucleated giant cell macrophages. (HE, 283X)**

within the nodules. Some of the larger cells have slight heterogeneity of the eosinophilic cytoplasm. Staining with acid fast stain reveals large numbers of bacilli with in the cytoplasm of macrophages and multinucleate giant cells. Large clusters of lymphocytes and plasma cells surround medium-caliber blood vessels.

**Contributor's Morphologic Diagnoses:**
Brain:

1. Granulomas, multifocal, chronic, severe, cerebellum with intralesional acid fast bacteria
2. Hydrocephalus, diffuse, severe with cerebellar coning

**Contributor's Comment:**
At the time of necropsy, cerebellar neoplasia was the primary differential based on MRI and gross findings of space occupying masses that compressed cerebral spinal fluid flow and led to secondary hydrocephalus. On histologic review, granulomatous inflammation was identified and slight granularity of the cytoplasm of epithelioid macrophages and multinucleate giant cells suggested intracellular organisms. Small bacilli consistent with mycobacteria were confirmed with acid-fast staining. Because there was no fresh tissue for culture, the organisms were identified using PCR and Sanger sequencing.[7] *Mycobacterium avium* subsp. *hominissuis* was identified. Deep sequencing was attempted, but host nucleic acid predominated and no reads corresponding to mycobacteria were identified.

Mycobacteria are acid-fast, non-motile, non-spore forming, intracellular, aerobic bacilli. *Mycobacterium avium* subsp. *hominisuis* is a

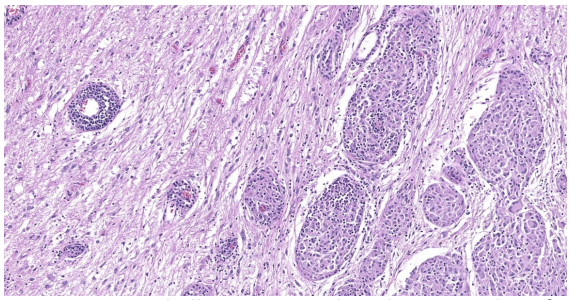

**Figure 1-3. Cerebellum, pig. At the advancing edge of the focus of granulomatous inflammation, macrophages, lymphocytes, and plasma cells, in varying concentrations, expanded the perivascular space. (HE, 347X)**

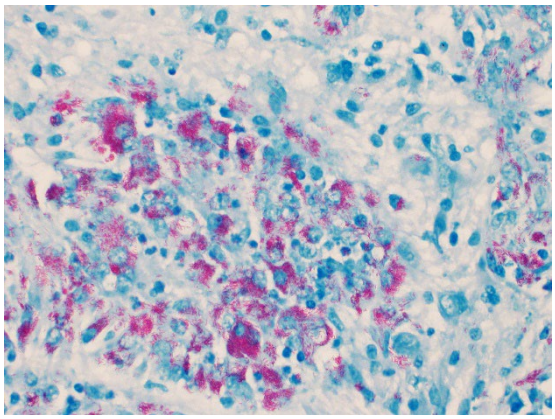

**Figure 1-4. Cerebellum, pig. An acid-fast stain demonstrates innumerable bacilli in macrophages. (Fite-Faraco, 400X)**

member of the *M. avium* complex (MAC) as compared to other mycobacteria in the *M. tuberculosis* complex with members such as *M. bovis, M. tuberculosis,* and *M. microti*. MAC is primarily composed of *M. avium* subspecies and *M. intracellulare* and are commonly found in fresh and salt water as well as soil.[9] Infections are typically associated with immunocompromise in the mammalian host and are typically not contagious. *M. avium* subspecies *hominissuis* is most frequently isolated from humans and pigs as suggested by the nomenclature.

While reports of mycobacterial lymphadenitis are common and worldwide,[9] to our knowledge, the only report of mycobacteriosis in pot-bellied pigs is a single case report of *M. kansasii*, another member of MAC.[8] That case report, as well as reports in other porcine species, typically present as disseminated disease with colonization and inflammation most prominent in lung and lymph nodes.[3] This case is unusual in that the granulomas and organisms were only identified in the cerebellum without lymphadenitis or lesions in thoracic or abdominal tissues. There was no indication of underlying disease or immunocompromise.

**Contributing Institution:**
Virginia Maryland College of Veterinary Medicine.
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Blacksburg, VA 24061
https://vetmed.vt.edu/departments/biomedical-sciences-and-pathobiology.html

**JPC Diagnosis:**
Cerebellum: Meningoencephalitis, granulomatous, multifocal to coalescing, severe, with innumerable intrahistiocytic bacilli.

**JPC Comment:**
Conference participants discussed differentials for granulomatous disease in this case, including mycobacterial and fungal infections. During the pre-conference lecture, the moderator, LTC Erica Barkei, described a case of *Mycobacterium tuberculosis* she diagnosed in a rhesus macaque; the paucibacillary lesions in that case provided a striking contrast to the abundant acid fast bacteria in the multibacillary granulomas seen in this case. The moderator explained that the mycolic acid within cell walls impart the acid-fast character of mycobacteria, though they can also be weakly gram-positive, as demonstrated with B&H staining in this case.

Bacteria of the family *Mycobacteriaceae* may be classified according to the spectrum of disease they cause or their ability to grow in culture. The tuberculous group is composed of closely related zoonotic obligate pathogens *M. tuberculosis*, *M. bovis,* and *M. microti*.[5,6] Tuberculous mycobacteria elicit a

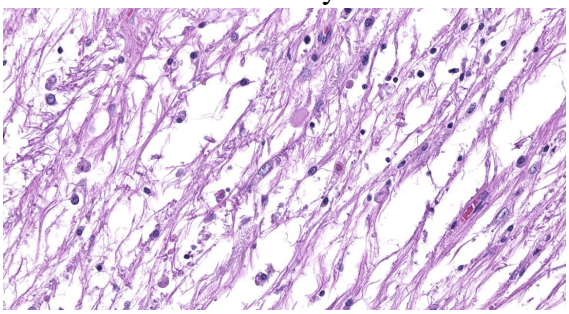

**Figure 1-5. Cerebellum, pig. There are numerous dilated myelin sheaths, spheroids, and Gitter cells in the white matter at the advancing edge of the inflammatory focus. (PAS, 40X)**

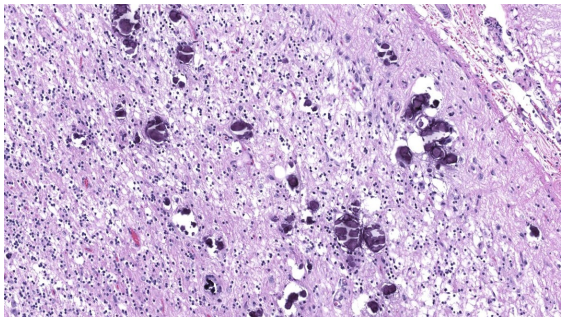

**Figure 1-6. Cerebellum, pig. Vessels within the cerebellar folia, primarily in the molecular layer, but also in the meninges contain luminal or mural crystalline mineral. (HE, 156X)**

Th1 response, where interferon gamma stimulates cell mediated immunity and the increased bactericidal activity of macrophages results in few bacteria within lesions. IFN-gamma also leads to secondary tissue damage, with granuloma formation or potentially caseous necrosis.[2]

Another group of obligate pathogens is the leprosy group, which includes *M. lepraemurium* and *M. visibilis*.[5] In humans, leprosy may incite a tuberculoid (Th1) response, as previously described, or a lepromatous response, in which there is a weak Th1 response and variable Th2 response. In these cases, there is weak cell-mediated immunity, abundant bacteria within lesions, and potential production of non-protective antibodies which lead to antigen-antibody complex deposition.[2]

The nontuberculous group includes, among others, the *M. avium* complex (MAC) with subspecies *avium, sylvaticum, paratuberculosis,* and *hominissuis*.[1] As the contributor mentioned, MAC bacteria are environmental opportunistic pathogens and infection is generally localized to the skin unless there is concurrent immunocompromise.[5] MAC bacteria grow slowly in culture but lesions in animals contain generally contain abundant bacteria.[5] Other nontuberculous mycobacteria which grow rapidly in culture can cause atypical mycobacteriosis, particularly in cats. The lesions similarly depend on the immune status of the animal and vary from chronic panniculitis, granulomatous pneumonia, to systemic disease in immunosuppressed animals.[5] Few bacteria are found within the lesions of atypical mycobacteriosis.[5]

In general, poultry and swine are considered more susceptible to MAC, whereas dogs, cats, and domestic rabbits are more resistant.[1,3] Literature on primary *M. avium hominissuis* (MAH) in domestic animals is sparse; however a couple of recent reports have described MAH infection in a cat and a rabbit without evidence of underlying immunosuppression. The feline case involved a young cat with chronic neurologic signs, pyogranulomatous meningoencephalitis, and generalized granulomatous lymphadenitis with abundant acid-fast bacteria found in multiple organ systems.[4] The rabbit had a focal fibrinonecrotic ulceration within the cecum characterized by granulomatous inflammation, multinucleated giant cells, and intra- and extra-cellular acid-fast bacteria.[1] Granulomatous inflammation was also observed in the spleen, liver, lungs, and cecal lymph node, and only the enlarged cecal lymph node contained bacteria, which were scant. In both the cases, *M. avium* subsp. *hominissuis* was identified.[1,4]

**References:**


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**CASE II**: 17-15645 (JPC 4117035)

**Signalment:**
11-yr-old, F/S, Canine, Labrador cross

**History:**
The dog was diagnosed with suspected immune-mediated keratitis 2 months prior. The dog did very well with treatment for 1.5 months but developed prominent thickening of the scleral wall and infiltrative keratitis laterally. A computed topography (CT) scan also showed severe thickening of the scleral wall without extraorbital irregularities. Due to pain, blindness and now a failure to respond to treatment, enucleation was performed.

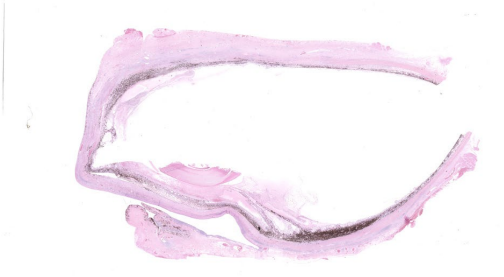

**Figure 2-1. Globe, dog. A tangential section of the globe is presented for examination, with one iris leaflet, one fragment of the lens, no retina, and no optic nerve present in the section. There is an inflammatory exudate within the cornea, uvea, choroid, and sclera, and a hemorrhagic inflammatory within the anterior segment. (HE, 5X)**

**Gross Pathology:**
The right eye was submitted, and no obvious mass was observed in parasagittal bisections.

**Laboratory Results:**
No laboratory findings reported.

**Microscopic Description:**
Right eye: The corneal stroma is infiltrated by large numbers of lymphocytes and plasma cells with fewer neutrophils, small amounts of extracellular melanin pigment and scattered melanophages. The stroma has significant corneal neovascularization, and at the limbus, some corneal epithelial cells have intraepithelial melanin pigment. The remainder of the corneal epithelium is irregularly hyperplastic or eroded, and there are small numbers of interepithelial neutrophils and scattered apoptotic epithelial cells. The sclera is markedly thickened and broadly infiltrated by abundant macrophages, neutrophils, plasma cells, and lymphocytes accompanied by small amounts of necrotic cellular debris and many, large lymphoid aggregates. The scleral

collagen is separated in areas (collagenolysis). The basement membrane separating the choroid and sclera is often obscured by inflammation, which extends into the choroid and vitreous chamber, and aggregates of melanocytes infiltrate the sclera. Multifocal scleral vessel walls are infiltrated by the inflammation (vasculitis), and one vessel is filled with organized fibrin (thrombus). The retina is detached, but obvious tomb-stoning of underlying pigmented epithelium is not apparent (possible artifactual retinal detachment). In addition to abundant large foamy macrophages and neutrophils within the vitreous chamber, there are also aggregates of erythrocytes, fibrin and flocculent eosinophilic material. The iris and ciliary body are expanded by similar inflammation and the anterior iris epithelium is covered by a 2-5 cell layer thick fibrovascular membrane (preiridal fibrovascular membrane), which is adhered to the cornea (anterior synechia) and spreads across the entirety of Descemet's membrane. Additionally, the posterior iris is adhered to the lens (posterior synechia; lens is not within provided sections). The iridocorneal filtration angle and uveal trabecular meshwork are unapparent due to the anterior synechiae, and infiltration by inflammatory cells. The conjunctival propria has multifocal to coalescing aggregates of lymphocytes and plasma cells, generally superficial and periadnexal.

Special stains: No organisms were detected in serial sections stained with Fite's acid fast or Grocott's methenamine silver stains.

**Contributor's Morphologic Diagnoses:**

1. Scleritis, histiocytic, neutrophilic, lymphoplasmacytic and necrotizing, chronic, severe, with vasculitis, choroiditis, endophthalmitis, anterior uveitis, anterior and posterior synechiae, and closure of the iridocorneal filtration angle
2. Keratitis and conjunctivitis, lymphoplasmacytic, chronic, moderate, with corneal erosion and neovascularization

**Contributor's Comment:**

The histologic features are compatible with granulomatous/necrotizing scleritis. Not all submitted slides show all the histologic changes (e.g. retina and lens are absent in most slides), and the audience is urged to focus on the scleral, corneal and uveal changes.

Idiopathic necrotizing/ granulomatous scleritis is a condition manifested as a bilateral, progressive, inflammatory disease of the sclera and cornea that induces significant uveitis, most commonly in dogs, but has been diagnosed in a cat and 2 birds.[4,5] Grossly, the affected area of sclera is usually thickened and solid white, representing the granulomatous infiltrate. The histologic lesions of granulomatous scleritis are characterized by vasculitis, collagen degeneration/collagenolysis, granulomatous inflammation (histiocytes/tissue macrophages) and perivascular lymphoplasmacytic aggregation.[2,4,5] There may be a suppurative component, or in chronic scleritis, a lymphoplasmacytic component may predominate. Less commonly, the sclera may be thin and have dramatic staphylomas associated with a more lymphocyte-rich infiltrate. Retinal detachment is a possible sequela to granulomatous/necrotizing scleritis. A diagnosis of scleritis in one eye implies that the second eye is at risk of developing scleritis. Idiopathic canine necrotizing scleritis shares similar histopathologic features with non-necrotizing scleritis (trauma or foreign-body related) and episcleritis, but these diseases are generally unilateral.[5]

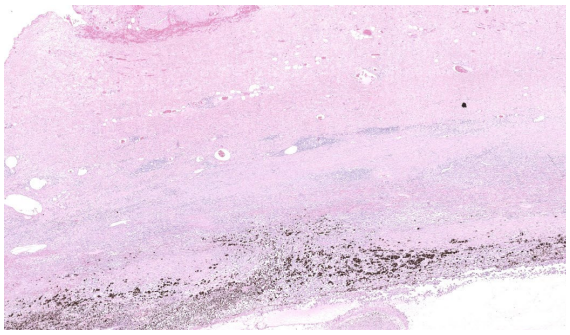

**Figure 2-2. Globe, dog. There is no visible division between the sclera and uvea and uveal melanocytes have migrated into the sclera. (HE, 154X)**

In humans, granulomatous scleritis has been associated with other autoimmune conditions such as rheumatoid arthritis, systemic lupus erythematosus, Wegener's granulomatosis, inflammatory bowel disease and Reiter's syndrome, but this has not been a consistent feature of reported canine cases.[2,5,7,10-13] In humans, necrotizing scleritis is regarded as a type III hypersensitivity reaction (immune complexes), as well as combined with a type IV hypersensitivity.[1,3,6] The condition in dogs is thought to be immune-mediated, and one study demonstrated IgG deposition within blood vessel walls in one dog, suggestive of an immune-complex component (type III hypersensitivity).[2] A primary type IV hypersensitivity was proposed, in addition to an underlying type III hypersensitivity, based on vascular/perivascular granulomatous to lymphoplasmacytic inflammation. This study described a prominent population of T lymphocytes, and proposed that CD4+ T lymphocytes are responsible for the tissue destruction in this disease. However, another study described a mixed population of lymphocytes (B lymphocytes predominated), which may also support the type III sensitivity involvement theory.[4] Response to medical therapy with corticosteroids (topical, systemic) or other immunomodulators such as azathioprine have been reported and also supports an immune-mediated etiology, but relapses and complications resulting in blindness occur frequently. Since little is known about the pathogenesis of idiopathic necrotizing scleritis in dogs, and there are few, somewhat contrasting reports in the literature, comparing the disease to human scleritis may not be appropriate.

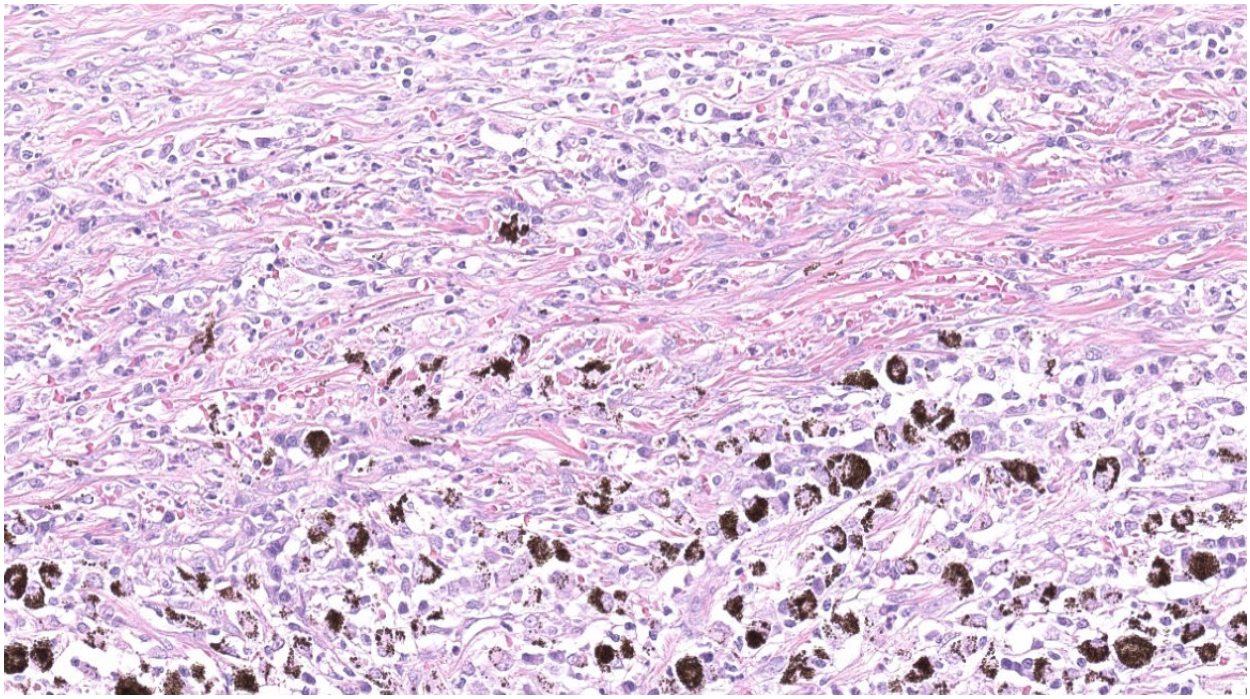

**Figure 2-3. Globe, dog. There is infiltration of innumerable macrophages separating scleral collagen and migration of uveal melanophages into the sclera. (HE, 381X)**

**Contributing Institution:**
Washington Animal Disease Diagnostic Lab
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http://waddl.vetmed.wsu.edu/

**JPC Diagnosis:**
1. Eye: Scleritis, collagenolytic, lymphoplasmacytic, chronic, diffuse, severe, with keratitis, panuveitis, anterior synechia, fibrovascular membranes, and hyphema.
2. Conjunctiva: Conjunctivitis and dacryoadenitis, lymphoplasmacytic, chronic, multifocal, moderate.

**JPC Comment:**
This case provides a classic example of the relatively rare condition necrotizing granulomatous scleritis, and the contributor succinctly describes this condition in veterinary species as well as similar diseases in humans. Two differential diagnoses that may be considered during clinical and histopathologic examination are episcleritis and non-necrotizing granulomatous scleritis. Additional differential diagnoses for granulomatous disease include bacterial, acid-fast, and fungal infections, which were not observed on special stains in this case.

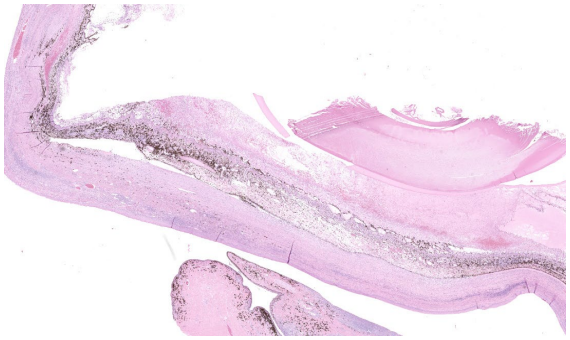

**Figure 2-4. Globe, dog. There is occlusion of the drainage angle and adhesion of the iris leaflet to the choroid. The iris leaflet is expanded by edema and numerous macrophages, and there is a thin pre-iridal fibrovascular membrane. Numerous inflammatory cells, hemorrhage, and fibrin adhere to the posterior surface of the iris. (HE, 14X)**

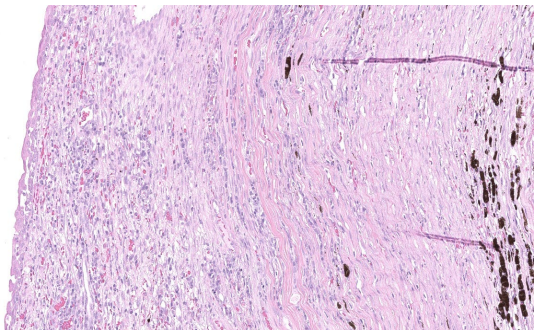

**Figure 2-5. Globe, dog. The cornea is infiltrated by large numbers of macrophages. There is proliferation of vessel within the corneal stroma and mild squamous hyperplasia of the central corneal epithelium. (HE, 190X)**

Episcleritis can occur secondary to severe intraocular or systemic disease, or may be a primary condition, such as in nodular granulomatous episcleritis (NGE), an inflammatory disease affecting the episcleral and adjacent conjunctiva.[6] NGE is more common and has a slower onset than necrotizing granulomatous scleritis. Single or multiple nonpainful elevated fleshy masses develop near the limbus or nictitating membrane and may extend into the adjacent cornea. A recent report described three cases of atypical NGE where the inflammatory infiltrate was limited to the corneal stroma and did not extend into the episclera or conjunctiva; the histologic appearance otherwise was consistent with NGE.[9] Severe cases of NGE may cause exophthalmos.[14] While both nodular granulomatous episcleritis and necrotizing granulomatous scleritis feature histiocytes admixed with lymphocytes and plasma cells, the episcleritis nodules are discrete (compared to the invasive nature of necrotizing scleritis) and lack collagenolysis.[15]

Non-necrotizing granulomatous scleritis also lacks the collagenolysis and perivascular necrosis seen with the necrotizing version of the disease. Additionally, chronic cases may feature fibrosis or formation of cystic spaces, and in general, it is generally milder than its necrotizing counterpart.[8,14] Otherwise, non-necrotizing granulomatous scleritis causes a

similar spectrum of clinical signs, including ocular pain, and can infiltrate to other structures in the eye, causing keratitis, uveitis, and choroiditis, as seen in this case.

**References:**


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**CASE III**: 672918 User 8 (JPC 4166546)

**Signalment:**

Tissue from a 9-year-old neutered female German Shepherd dog (*Canis lupus familiaris)*

**History:**

The patient was presented for bilateral hind limb ataxia. MRI showed an intramedullary spinal cord lesion at L 4-5. Additional masses on the body wall found with ultrasound. Specimens of spleen and mammary gland samples were submitted in addition to spinal

cord, and were diagnosed as nodular lymphoid hyperplasia and benign mixed mammary tumor (not shown).

**Gross Pathology:**
Several cross-sections of lumbar spinal cord contained soft, reddish brown, tissue affecting the gray matter bilaterally.

**Laboratory Results:**
No laboratory findings reported.

**Microscopic Description:**
Much of the spinal cord gray matter and the ventrolateral white matter are soft and malacic. The tissue architecture is obliterated, with endothelial hypertrophy and hyperplasia of remaining blood vessels. Gitter cells fill some of the tissue spaces. The ventral spinal artery is obliterated by a large lumenal thrombus. It and the arteries extending up along the ventral median fissure are blocked by large round cells. Wallerian degeneration affected much of the ventral white matter. Cells are characterized by scant amphophilic cytoplasm and a large cleaved to reniform nuclei. The chromatin is arranged in coarse, irregular clumps; nuclear outlines are very irregular. Intravascular mitoses are present in the population. These cells are not present in smaller blood vessels. A less severely affected section of spinal cord has ventral white matter Wallerian degeneration, with a smaller ventral spinal artery filled with organisms. Two of the spinal nerves are degenerate and inflamed, with several radicular vessels being blocked (not shown). Lymphoplasmacytic inflammation occurs in the meninges and in perivascular cuffs near malacic spinal cord (also in affected roots). Intravascular tumor cells are immunohistochemically CD3 positive, demonstrated along cell membranes.

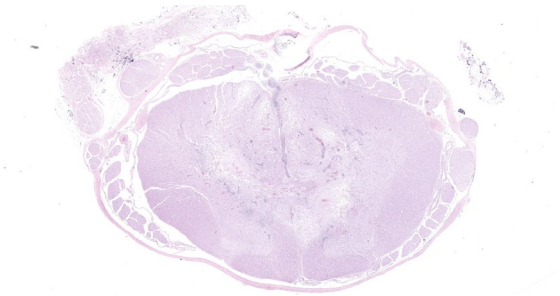

**Figure 3-1. Spinal cord, dog. One section of spinal cord with numerous spinal nerve roots is submitted for examination. There are multiple areas of pallor, representing malacia, in the grey matter; in the white matter they are located primarily in the dorsal and ventral funiculi (HE, 7X)**

**Contributor's Morphologic Diagnoses:**

1. Myelomalacia with ventral spinal and radicular artery tumor embolism
2. Intravascular lymphoma

**Contributor's Comment:**
At first glance the distribution of the spinal cord lesions brings to mind fibrocartilaginous embolism (FCE), due to the commonality of affected blood vessels (primarily the ventral spinal artery and branches, with infarction of the spinal gray matter.[3,6] However, both arteries and veins have been reported affected in FCE, while arteries and arterioles are affected in this case.

The presence of neoplastic cells in the ventral spinal artery and its branches is consistent with a diagnosis of large cell lymphoma, a tumor restricted to growth in the lumens of small- to intermediate-sized vessels.[7] This tumor would be described as the so-called classic form, with involvement primarily in the organ of presentation (usually brain or skin). A hemophagocytic syndrome-associated form can also occur in which patients present with multi-organ failure.[12] In humans, neoplastic cells express B cell markers (such as CD20 or CD79a). T-cell tumors are much less common,[14] but do occur. In people, neoplastic growth can occasionally extend across vascular walls, as in a few areas in this dog,

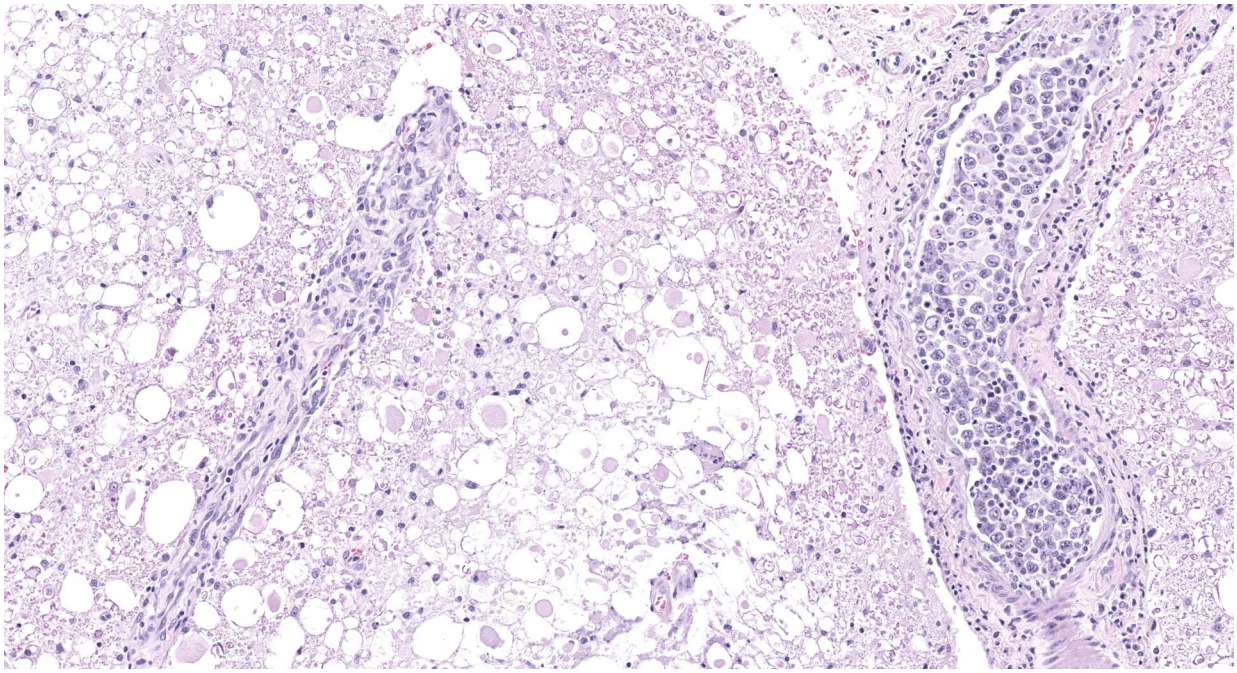

**Figure 3-2. Spinal cord, dog. Meningeal and parenchymal vessels contain pleomorphic neoplastic lymphocytes. Vessel walls contain histiocytes, lymphocytes and plasma cells, and the adventitia is multifocally bounded by plump fibroblasts. Within the adjacent white matter, there are numerous dilated myelin sheaths, spheroids, myelin debris, and Gitter cells. (HE, 174X)**

and can be mistaken for primary parenchymal lymphoma. T cell intravascular lymphomas are rare in humans and have been reported in dogs.[2,5,11] A tally of immunohistochemistry of intravascular lymphomas in 2 case series [2,5] revealed 11 T cell, 4 B cell and 10 Non-T non-B cell tumors. Most human tumor are of B cell origin.[7]

The intravascular location of tumor cells leads to thrombosis and infarction, which are responsible for clinical signs. Intravascular B cell lymphomas in people lack expression of surface adhesion molecules (e.g. cd29 and ICAM 1). Tumor cells proliferate within the blood vessels without being able to exit them, potentially occluding them and causing ischemia without tissue invasion. Cells also lack the expression of matrix metalloproteinase (MMP) 2 and MMP9 involved in the extravascular invasion of other lymphomas. Therefore, intravascular growth is associated with the inability of intravascular lymphoma cells to infiltrate extravascular tissues.[12]

**Contributing Institution:**
University of Missouri
https://vmdl.missouri.edu/

**JPC Diagnosis:**
1. Spinal cord, meningeal and parenchymal vessels: Intravascular lymphoma.
2. Spinal cord: Myelomalacia, multifocal to coalescing, moderate to marked, with thrombosis.

**JPC Comment:**
Historically, intravascular lymphoma in humans was known by the name malignant angioendotheliomatosis due to the unique histologic appearance mimicking proliferation of endothelial cells; however, clinical, immunohistochemical, ultrastructural, and therapeutic studies revealed the disease to be an angiotropic form of lymphoma.[4] In 1988, a case of angioendotheliomatosis in an adult German shorthaired pointer was also confirmed to be angiotropic lymphoma through ultrastructural and immunofluorescence investigation.[4] Since then, this disease has been reported

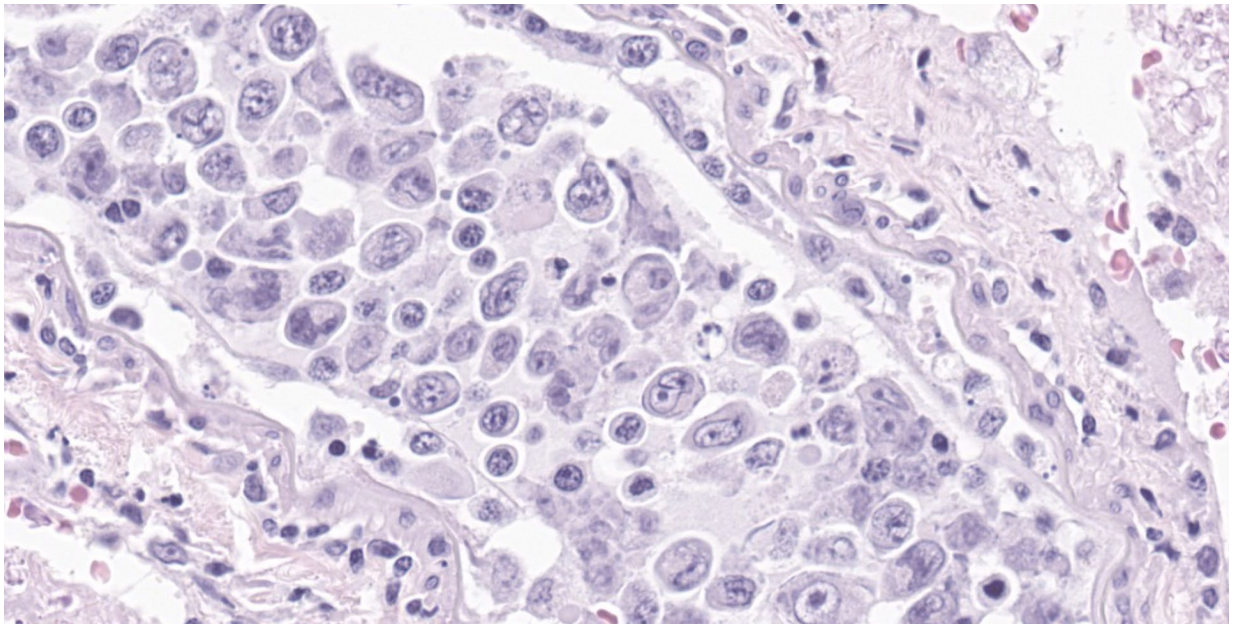

**Figure 3-3. Spinal cord, dog. High magnification of neoplastic intravascular lymphocytes. There is moderate pleomorphism, and occasional apoptosis. (HE, 194X)**

rarely in dogs, and even more rarely in cats and horses.[10]

Intravascular lymphoma most frequently affects the central nervous system and is characterized by rapidly progressive neurologic signs secondary to infarction with death occurring within weeks of initial clinical signs. Diagnosis is always made post-mortem. Rarely, neoplastic cells have been observed ante-mortem on peripheral blood smears or in cavitary effusions; however, even in these cases, refining the diagnosis beyond round cell neoplasm was not possible until post-mortem histopathology.[10,13] Differential diagnoses on histopathology include other round cell neoplasms which form a cuff around blood vessels, vaccine reactions, or systemic reactive angioendotheliomatosis.[15]

As the contributor described, neoplastic lymphocytes appear unable to exit blood vessels in this condition, and studies in human and veterinary patients illustrate altered expression of clusters of differentiation (CD) markers. In humans, neoplastic cells of intravascular lymphoma lack CD11a, 18, and 29 expression.[10]A study of canine intravascular lymphoma found that there was decreased CD29 expression and increased CD44 expression compared to canine primary/metastatic CNS lymphoma.[5] Some of these markers are critical during the leukocyte adhesion cascade and delivery of inflammatory cells to sites of inflammation.

Briefly, the leukocyte adhesion cascade has five steps which are partially propelled by cytokines: margination, rolling, integrin activation, stable adhesion, and transendothelial

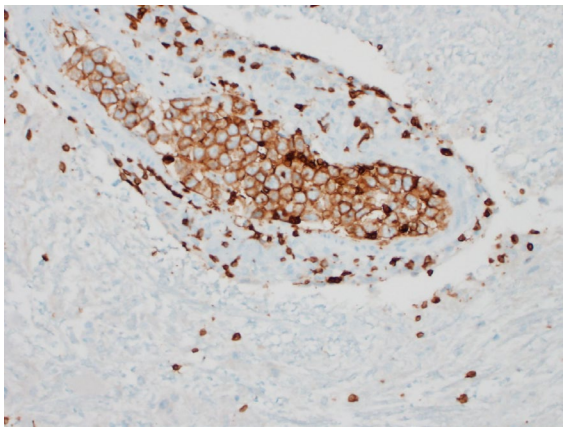

**Figure 3-4. Spinal cord, dog. Neoplastic lymphocytes within meningeal vessels demonstrate strong membranous immunoreactivity for CD3. (anti-CD3, 400X)**

migration.[1,9] Selectins are adhesion molecules which cause marginated leukocytes to slow and begin rolling, and integrins are adhesion molecules which then enforce firm adhesions between endothelial cells and leukocytes. CD11a/18 is the β2 integrin LFA-1 which binds intercellular adhesion molecules (ICAM) 1 and 2 (CD 54 and 102, respectively) on the endothelium during stable adhesion.[9] CD29 is found in β1 integrins (such as VLA-4) which facilitate leukocyte adhesion and transendothelial migration.[1,9] The previously noted alterations in expression of these markers in intravascular lymphoma provide some insight into the intravascular growth and lack of extravasation seen in this neoplasm.

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**CASE IV**: 2019 NHP (JPC 4140673)

**Signalment:**
19-year-old intact female rhesus macaque (*Macaca mulatta*)

**History:**
Several week history of inappetence, weight loss, and chronic non-regenerative hypochromic and microcytic anemia.

**Gross Pathology:**
The abdominal cavity contained ~1 liter of serosanguinous fluid. The mesentery and abdominal visceral serosa contain too numerous to count, multifocal-to-coalescing, pale tan-to-white, slightly raised, firm coalescing nodules ranging from 1-4 millimeters in diameter. The distal 2 cm of the ileum and proximal 1 cm of the paired ceca and colon are infiltrated and effaced by a poorly demarcated, highly infiltrative neoplasm. On cut surface, the lumen of the distal ileum is severely stenotic, with loss of normal intestinal mural stratification.

**Laboratory Results:**
Repeated CBC results indicated a chronic progressive hypochromic and microcytic non- anemia.
See Table 4-1

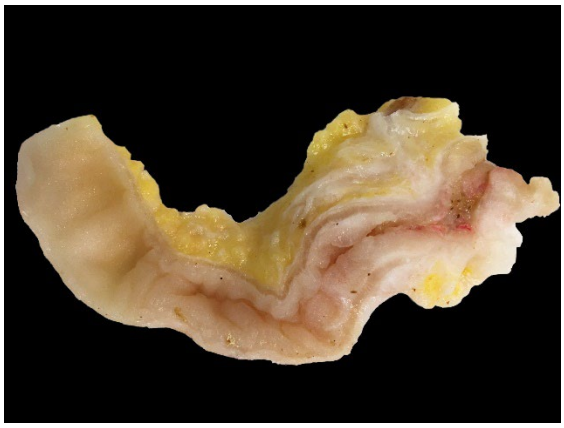

**Figure 4-1. Ileum, rhesus macaque On cut surface, the lumen of the distal ileum is severely stenotic, with loss of normal intestinal mural stratification (Photo courtesy of: Boston University School of Medicine, National Emerging Infectious Diseases Laboratory http://www.bu.edu/neidl/)**

**Microscopic Description:**
Distal ileum: In the sections submitted the submucosa, muscularis and serosa are multifocally effaced by an unencapsulated, poorly circumscribed, low-to-moderately cellular, infiltrative, highly pleomorphic epithelial neoplasm. Neoplastic cells are cuboidal-to-columnar and form both tubules and acini, with occasional formation of variably sized mucinous lakes surrounded by dense fibrous connective tissue stroma (desmoplasia). Formation of signet ring cells (epithelial cell with a large, clear cytoplasmic vacuole that peripheralizes the nucleus) is occasionally observed. Stroma is infiltrated by lymphocytes and lesser numbers of histiocytes. Neoplastic cells exhibit marked anisocytosis and anisokaryosis, have variably distinct cells borders and a moderate amount of granular, eosinophilic cytoplasm. Nuclei are round to oval with one or two distinct nucleoli. The

| CBC Parameters | | |
|---|---|---|
| WBC (K/uL) | 13.6 | 7.72–9.17 |
| RBC (M/uL) | 5.3 | 6.24–6.73 |
| HGB 9G/dL) | 5.7 | 12.03–12.95 |
| HCT (%) | 22.2 | 41.90–44.77 |
| MCV (fL) | 42 | 66.02–68.02 |
| MCH (pg) | 10.8 | 18.84–19.81 |
| MCHC (g/dL) | 25.7 | 28.32–29.29 |
| Reticulocyte (%) | 4.9 | 1.44+/-0.46 |
| Absolute Reticulocyte (K/uL) | 260 | 79.8+/-24.3 |
| Nucleated RBC (/100 WBC) | None seen | |

*Table 4-1*

**Figure 4-2. Mesentery, rhesus macaque The mesentery and abdominal visceral serosa contain too numerous to count, multifocal-to-coalescing, pale tan-to-white, slightly raised, firm coalescing nodules ranging from 1-4 millimeters in diameter. (Photo courtesy of: Boston University School of Medicine, National Emerging Infectious Diseases Laboratory (http://www.bu.edu/neidl/)**

mitotic rate ranges from 1-4/HPF. Transmurally lymphatics are markedly ectatic (lymphangiectasia) as indicated by large clear spaces neoplastic cells display cytoplasmic immunoreactivity to pancytokeratin supportive of epithelial origin.

Mesentery: Similar neoplastic epithelial cells as described infiltrating the wall of the ileum efface and expand the mesentery, with scattered patches of retained adipocytes and mesenteric blood vessels.

**Contributor's Morphologic Diagnosis:**
Ileocecocolic junction adenocarcinoma (scirrhous, mucus producing) with lymphangiectasia, and abdominal carcinomatosis

**Contributor's Comment:**
In humans, gastrointestinal carcinomas are relatively common, but most of these arise in the colon and rectum with only a small percentage in the small intestine and ileum.[1] Furthermore, large intestinal neoplasia in the rhesus macaque is believed to be significantly different from that in humans due to the absence of polyp formation, although there are similarities in histologic appearance and immunohistochemical characteristics.[1] In contrast, the ileocolic junction is considered a common site for intestinal adenocarcinomas in aged rhesus macaques and has also be described in the duodenum, jejunum, distal ileum, cecum, and colon.[1,5,10] Cotton-top marmosets are unique among NHPs as they often develop adenocarcinomas in response to chronic inflammation of the colon, including the cecum–colon, and rectum.[1] The most commonly reported site of metastasis of intestinal adenocarcinoma in NHPs is the regional mesentery lymph nodes, with colonic and thoracic lymph nodes, peritoneum, diaphragm, intercostal muscles, kidneys, adrenal glands, liver, lung, and spleen also having been reported.[1,5] Representative specimens of the mesentery and intestinal neoplasm were the only tissues submitted for histopathologic examination from this case and thus we cannot rule out the possibility of previously described metastatic locations.

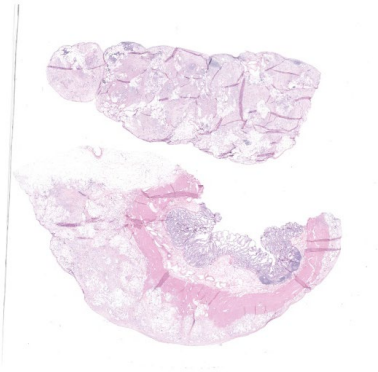

**Figure 4-3. Ileum and mesentery, rhesus macaque. A section of ileum is presented with marked expansion of the submucosa and serosa at subgross magnification. There is loss of normal mesenteric architecture as well. (HE, 0.4X)**

Surgical excision with intestinal resection and anastomosis remains the preferred treatment for intestinal adenocarcinoma in rhesus macaques. In a review article of the WNPRC breeding colony, 12% (3 of 25) of animals with surgical resection of intestinal adenocarcinomas were alive, with a mean survival time of 1.5 years.[1] The other 22 of 25 animals were euthanized due to deterioration of clinical health. Following necropsy of these animals, surgical excision was determined to be curative in 55% (12 of 22) of cases with no gross or histologic evidence of recurrence at the time of necropsy.

This case of ileocecocolonic adenocarcinoma is particularly impressive given that there was severe mesenteric and peritoneal seeding (carcinomatosis) that resulted in occlusion of lymphatics and subsequent lymphangiectasia. Neither a serum iron concentration or a fecal occult blood test were conducted in this case, but it is reasonable to attribute the chronic microcytic hypochromic anemia to a combination of G.I. hemorrhage, chronic inflammation resulting in sequestration of iron stores, as well as malabsorption due to the lymphangiectasia.

**Contributing Institution:**
Boston University School of Medicine, National Emerging Infectious Diseases Laboratory (http://www.bu.edu/neidl/)

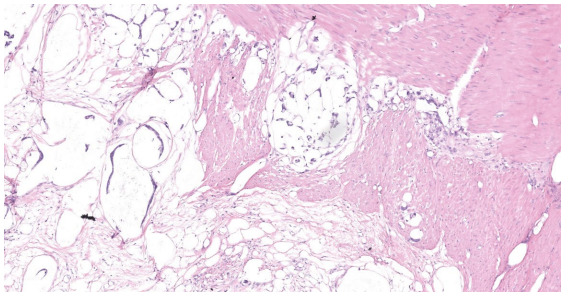

**Figure 4-4. Ileum, rhesus macaque. The wall is transmurally infiltrated in this image, the outer longitudinal layer of the muscularis and the serosa by nests of neoplastic intestinal epithelium which produce abundant mucus. (HE, 94X)**

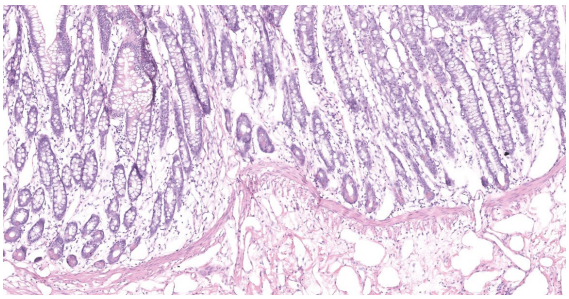

**Figure 4-5. Ileum, rhesus macaque. The lamina propria and submucosa are markedly expanded by mucus-producing neoplastic epithelium. (HE, 94X)**

**JPC Diagnoses:**
Ileocecocolic junction and mesentery: Mucinous adenocarcinoma.

**JPC Comment:**
Ileocecocolic adenocarcinoma is the most common gastrointestinal neoplasm in rhesus macaques and has also been reported in Japanese and cynomolgus macaques.[9] Clinical signs include weight loss, inappetence, bloating, hematochezia, and decreased fecal volume. Grossly, the annular appearance of intestinal adenocarcinoma may mimic chronic cicatrizing ulcerative colitis, an uncommon condition in macaques which also affects the cecum and colon and causes distension of the proximal intestinal segments.[6] These neoplasms invade transmurally and incite a pronounced desmoplastic response.[9] Prominent infiltrates of lymphocytes within and surrounding the tumor may be present.[4] In the mucinous subtype, which accounts for 25% of colonic adenocarcinomas in rhesus macaques, neoplastic cells produce abundant mucin which may impart a bubbly appearance grossly; histologically, neoplastic cells may accumulate mucin intracellularly, producing the signet ring appearance, or they may produce extracellular lakes of mucin which cause attenuation of surrounding cells.[4,6,10]

As the contributor stated, ileocecal/colonic adenocarcinomas in rhesus macaques differ from similar neoplasms in humans by the lack of polyp formation; however, a recent study suggests that at least one colony of rhesus macaques may be a suitable model for a certain type of hereditary colorectal cancer in humans.[4] Lynch syndrome, which can cause hereditary nonpolyposis colorectal cancer (HNPCC) in humans, is characterized by damage in any of the DNA mismatch repair (MMR) genes MSH2, MLH1, MSH6, or PMS2.[4] Humans with Lynch syndrome have higher risks of various neoplasms at a younger age, including neoplasms of the colon, endometrium, stomach, and small intestine.[4] Lynch syndrome can be diagnosed through identification of microsatellite instability, a phenomenon where unrepaired DNA errors occur in certain short repetitive DNA segments (microsatellites) due to MMR gene defects. Additionally, immunohistochemical staining can illustrate decreased reactivity of the MMR proteins in neoplastic cells. In a study of 60 spontaneous cases of colorectal cancer in one closed colony of rhesus macaques, 17 of 20 tested animals lacked MLH1 and PMS2 immunoreactivity, and 6 of 9 tested animals demonstrated microsatellite instability.[4] Whole genome sequencing also revealed strong association of colorectal cancer and mutations in MLH1 and MSH6 genes.[4] This study indicates that this colony of rhesus macaques could potentially supply investigative avenues for a human disease where current animal models are lacking.[4]

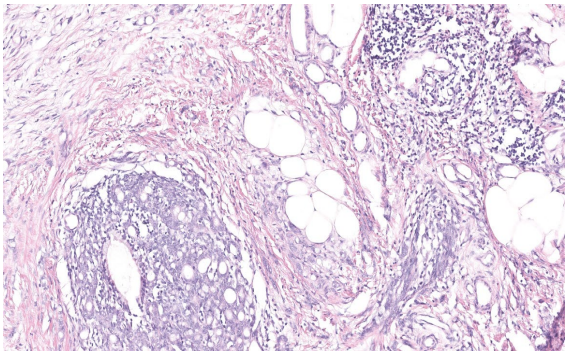

**Figure 4-6. Mesentery, rhesus macaque. The mesentery is effaced by infiltrating, mucus-producing epithelial cells. (HE, 175X)**

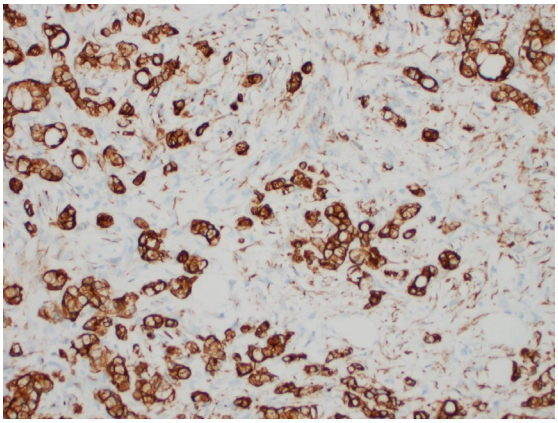

**Figure 4-7. Mesentery, rhesus macaque. Neoplastic epithelial cells are strongly immunopositive for cytokeratin. (anti AE1/AE3, 400X)**

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