Joint Pathology Center
Veterinary Pathology Services

WEDNESDAY SLIDE CONFERENCE 2011-2012

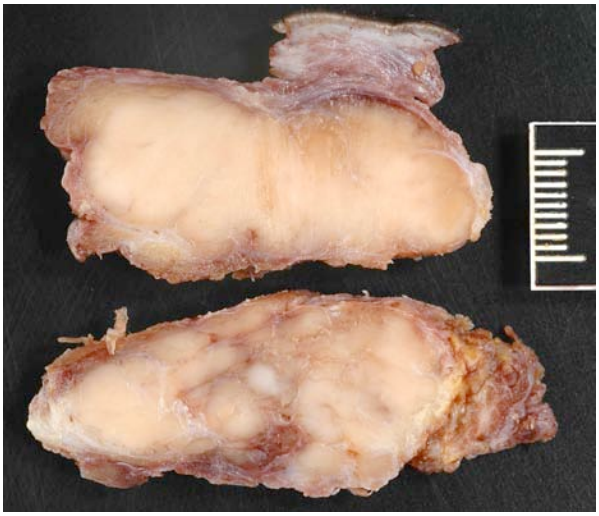
Conference 6

19 October 2011

CASE I: 08B1647 (JPC 3134348).

Signalment: 14-year-old female Dutch Warmblood horse (*Equus ferus caballus*).

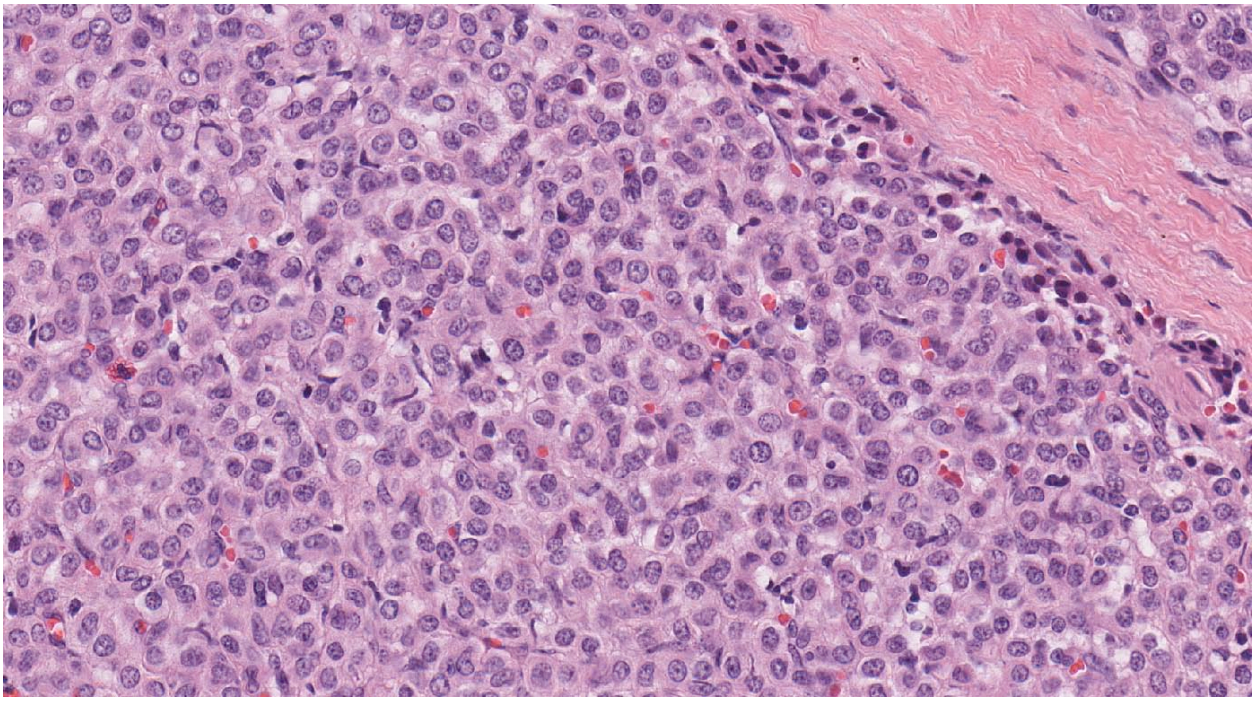
History: The horse had a history of an approximately 1 cm mass within the lower left cheek that was excised 3 months prior to presentation and diagnosed as a trichoblastoma. The mass had recurred and was rapidly enlarging at the time of presentation. On palpation, a 5 x 3 x 2 cm, bilobed, firm mass was present within the left cheek at the level of the first three mandibular cheek teeth (307 to 309). The mass elevated both the intact overlying skin and underlying intact oral mucosa. Some pain appeared to be associated with the mass, and the horse was intermittently depressed. An initial incisional biopsy was followed by complete surgical excision 12 days after presentation.



1-1. Fibrous connective tissue (cheek, per contributor), equine. Multilobulated fleshy neoplasm within subcutis and skeletal muscle. Photograph courtesy of Department of Pathology, Microbiology, and Immunology, School of Veterinary Medicine, University of California, Davis, http://www.vmth.ucdavis.edu, http://www.vetmed.ucdavis.edu/PMI.

Gross Pathology: A 5.5 x 3.0 cm by 2.5 cm thick section of skeletal muscle with an associated section of overlying skin was submitted. Within the subcutis and muscle on cut section, there was a multilobulated, pink, fleshy mass extending to the surgical margins.

Histopathologic Description: Mass, left cheek: Examined is an unencapsulated, poorly demarcated, multilobulated, densely cellular mass composed of lobules and tracts of neoplastic cells that infiltrate adjacent skeletal muscle and connective tissue and extend to the tissue margins. The cells within the bulk of the mass are arranged in sheets, cords, and packets within a moderately abundant fine fibrovascular stroma. Cells in these areas are polygonal with distinct cell borders, small amounts of wispy eosinophilic to clear cytoplasm, and large round central nuclei with finely stippled chromatin. In scattered areas (not present on every slide), the cells are pleomorphic, very large, lack distinct cell borders, and are often multinuceated and have bizarre nuclei and prominent



1-2. Fibrous connective tissue (cheek, per contributor), equine. A monomorphic population of polygonal cells are arranged in nests and packets on a fine fibrovascular stroma. (HE 320X)

nucleoli. There are 0-3 mitoses per 10 high power fields (8 per 50 high power fields) in all regions. Along the thick fibrous septae, neoplastic cells abut and bulge into large irregular, occasionally blood-filled, endothelial-lined clefts. Clusters of neoplastic cells are occasionally present within these vascular lumina.

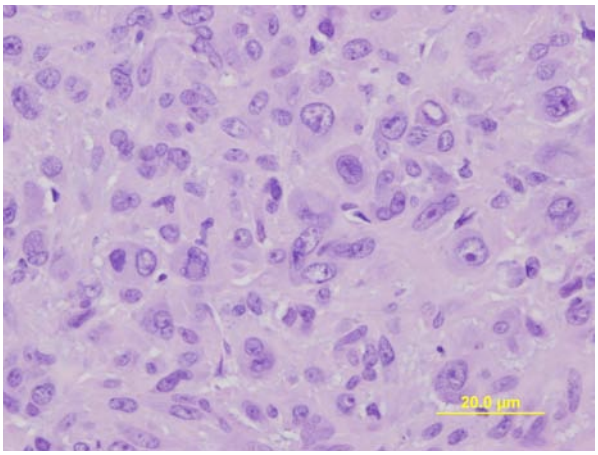
Neoplastic cells exhibited strong cytoplasmic immunoreactivity for smooth muscle actin and vimentin and variable to strong cytoplasmic immunoreactivity for desmin. A well-defined basal lamina surrounding the individual tumor cells was demonstrated by positive immunoreactivity for laminin outlining the cytoplasmic border of each cell. Neoplastic cells were diffusely negative for pan-cytokeratin, cytokeratin 14, synaptophysin, CD11c, skeletal myosin, factor VIII-ra, and S100 α and β. With factor VIII-ra, a single layer of endothelium could be variably demonstrated separating the tumor from the lumina of vessels and clefts. With S100, several immunoreactive nerves were present within the tumor.

Contributor's Morphologic Diagnosis: Mass, left cheek: Malignant glomus tumor (glomangiosarcoma).

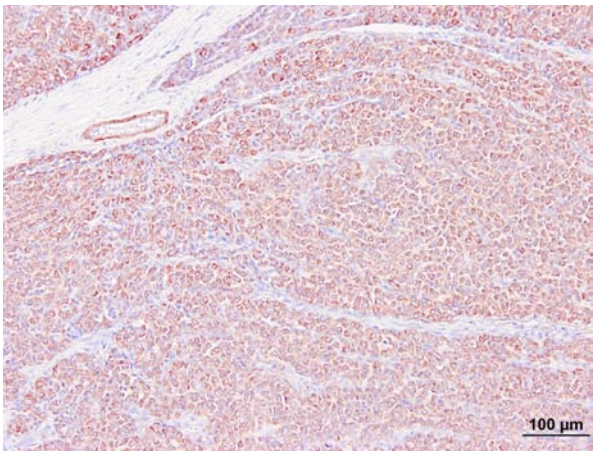
Contributor's Comment: Glomus tumors are thought to arise from modified smooth muscle cells of the glomus body, a type of arteriovenous anastomosis or shunt which is involved in regulating temperature.[6,10] Glomus bodies are composed of an afferent arteriole and small venules connected by a series of small channels (Sucquet-Hoyer canals), surrounded by dense collagenous tissue, and closely associated with small nerve branches. Within the walls of the anastomosing canals are epithelioid cells with ultrastructural and immunocytologic features similar to smooth muscle cells, called glomus cells, which are thought to be the cell of origin for glomus tumors.[4,10]

Glomus tumors have best been characterized in humans where their locations correspond to the most common sites for glomus bodies, i.e. subungual regions and skin of the extremities. Other reported sites of glomus tumors in humans include dermis, subcutis and soft tissues in other locations, as well as bone, nerve, stomach, colon, nasal cavity, and trachea.[6,10] Glomus tumors of the head and neck account for only approximately 6% of the cases in humans.[10] A similar distribution has been seen in dogs and cats, with most of the few reported cases occurring in the digits.[2,3,7,9] Of the 3 known cases of glomus tumors in horses, one occurred as an osteolytic lesion within the third phalanx deep to the hoof wall, a presentation very similar to that seen in humans,[1] while two others, this and another unpublished case from UC Davis, occurred in the cheek and skin of the neck, respectively. The distribution of normal glomus bodies in horses has not been well characterized, although they occur frequently in the skin of the mammary gland.[4]

A feature of glomus tumors of the subungual region in humans, and less commonly of these tumors in other



1-3. Fibrous connective tissue (cheek, per contributor), equine. Focus of cellular atypia with karyomegaly and prominent nucleoli. Photograph courtesy of Department of Pathology, Microbiology, and Immunology, School of Veterinary Medicine, University of California, Davis, http://www.vmth.ucdavis.edu, http://www.vetmed.ucdavis.edu/PMI (HE 400X).



1-4. Fibrous connective tissue (cheek, per contributor), equine. Diffuse strong immunopositivity for smooth muscle actin. Photograph courtesy of Department of Pathology, Microbiology, and Immunology, School of Veterinary Medicine, University of California, Davis, http://www.vmth.ucdavis.edu, http://www.vetmed.ucdavis.edu/PMI.

sites, is associated intense pain, presumably a result of innervation with substance P-containing nerve fibers.[6,10] In human medicine, this feature is diagnostically useful as few types of skin tumors are painful. Some degree of "soreness" was thought to be associated with this tumor, which was immediately adjacent to the facial nerve grossly and included several nerve fibers histologically. Interestingly, the other equine glomus tumor in the UC Davis case files was removed because it appeared to be painful to the horse when touched.

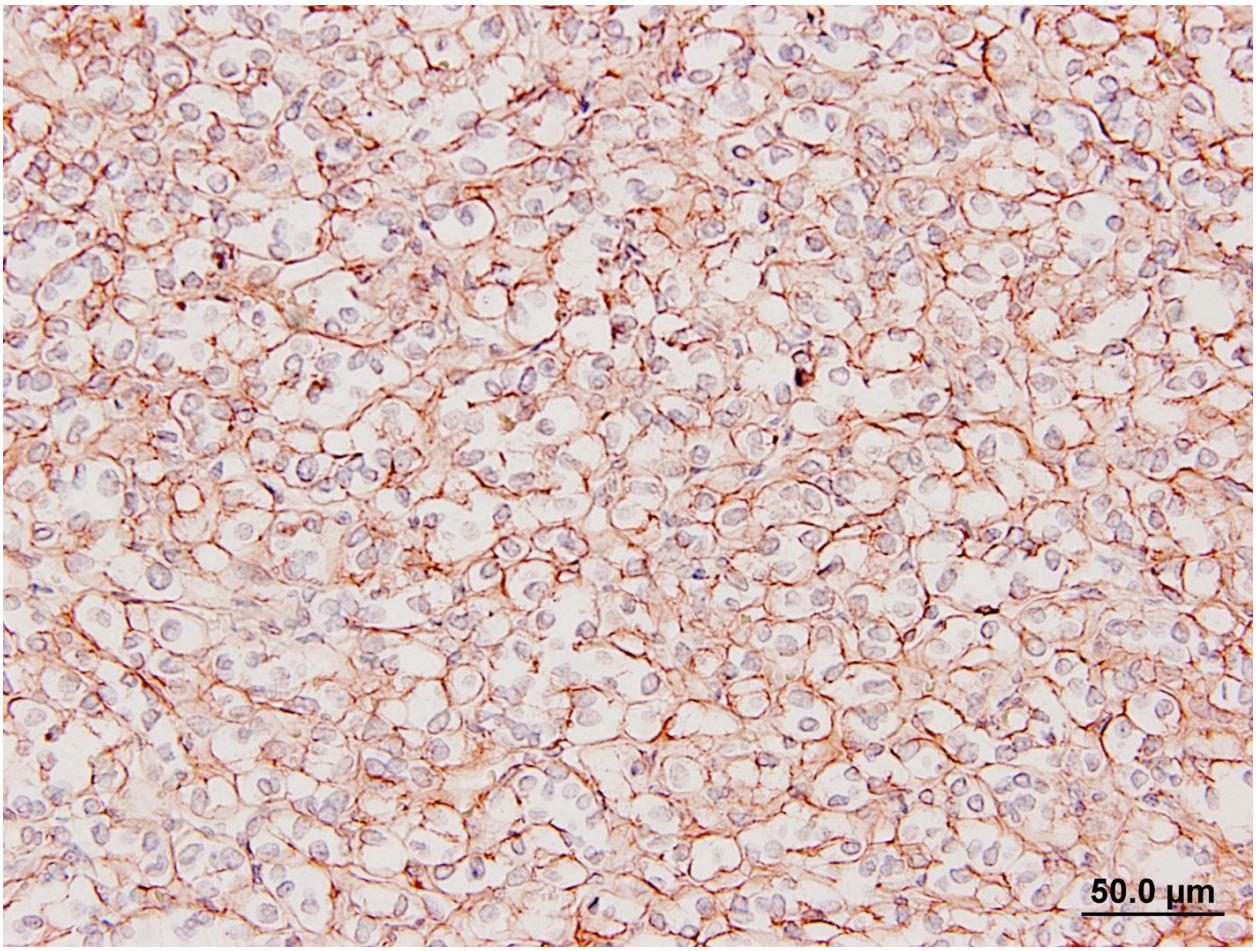
Glomus tumors in humans can be classified as solid, angiomatous, or myxoid types.[6] Except for multiple angiomatous glomus tumors in the bladder of a cow,[5] glomus tumors in animals, including this case, have generally been of the solid type.[2,3,7,9] They have several characteristic features which were seen in this case, including an intimate relationship with blood vessels, which may only be evident at the periphery, a round or cuboidal "epithelioid" cell shape with a "punched out" round nucleus and eosinophilic cytoplasm, and a network of basement membranes around each cell.[6,10] Immunohistochemistry for laminin was used in this case to demonstrate the basal lamina surrounding the neoplastic cells. Primary differential diagnoses for this tumor included trichoblastoma (the initial diagnosis), other epithelial neoplasms, or a neuroendocrine tumor, all of which were ruled out with additional immunohistochemical stains. Typical of glomus tumors, the neoplastic cells were positive for smooth muscle actin and vimentin and negative for cytokeratins, synaptophysin, factor VIII, and S100. The cells were variably positive for desmin, which has occasionally been reported in human and canine glomus tumors.[10]

In humans, malignant glomus tumors (glomangiosarcomas) are very rare, but have been defined by being larger than 2 cm with a deep location, having atypical mitotic figures, or having marked nuclear atypia and mitoses >5 per 50 high power fields (hpf). The tumor in this horse was considered to be malignant based on recurrence and rapid growth, invasiveness of deep tissues, large size, and areas of marked cellular atypia. Mitotic figures were also 8 per 50 hpf. Although clusters of neoplastic cells appeared to be present within vascular channels, true intravascular invasion was difficult to assess because of the close association of the tumor with blood vessels. No metastases were evident at presentation. The horse was treated with intralesional injections of cisplatin every 2-4 weeks post-surgery, with a total of 4 treatments planned. However, the mass recurred prior to the final injection, and the horse was euthanized (necropsy not performed at our institution).

JPC Diagnosis: Left cheek, fibrovascular tissue: Glomus tumor.

Conference Comment: Despite the history of recurrence and rapid growth, conference participants felt the tumor was a benign entity based on the section presented in conference, and a discussion on the features of malignancy ensued. Cytomorphologic features mentioned by the contributor such as areas of cellular atypia, atypical mitoses, and local invasiveness were not seen by conference participants, who felt the tumor showed no overt signs of malignancy.

The differentiation between benignancy and malignancy is one of the most important roles of the



1-5. Fibrous connective tissue (cheek, per contributor), equine. Diffuse strong membrane immunopositivity for laminin. Photograph courtesy of Department of Pathology, Microbiology, and Immunology, School of Veterinary Medicine, University of California, Davis, http://www.vmth.ucdavis.edu, http://www.vetmed.ucdavis.edu/PMI.

pathologist, and tumors can sometimes defy typical classifications, so a best effort must be made on a diagnosis. Standard features to differentiate a benign tumor from its cancerous counterpart are the amount of differentiation or presence of anaplasia, the rate of growth, and the presence of local invasion and metastasis. The moderator commented that often with a surgical biopsy, which can be accompanied by a limited or no history as was the case with conference participants, the pathologist gets no information on metastasis, and local invasion may not be observed if no adjacent normal tissue is present.[8]

Differentiation is the degree to which neoplastic cells resemble the cell or tissue of origin, both in appearance and function. Anaplasia is when the tumor is poorly differentiated, and it is believed that the undifferentiated cells with immature "stem-cell-like" properties have loss of differentiation capacity. Anaplastic tumors may also exhibit lack of cell and nuclear uniformity, or pleomorphism; abnormal nuclear morphology with hyperchromasia, high nuclear-to-cytoplasmic ratio, irregular shape, and variable nucleoli; bizarre mitoses or a high mitotic rate; loss cellular polarity with haphazard organization; tumor giant cells; and large areas of ischemic necrosis. The rate of growth in malignant tumors is often erratic, ranging from slow to rapid, and this is a difficult parameter to measure and use for the evaluation of malignancy. The local aggressiveness of a tumor is a good indicator of malignancy, as benign tumors are often expansile, while malignant tumors invade or efface the surrounding normal tissue. Malignant tumors are often poorly demarcated and lack an obvious cleavage plane. Finally, the presence of metastasis is an indisputable marker of malignancy, as benign tumors by definition to do not metastasize. Metastasis is achieved through either the seeding of body cavities and surfaces, as in carcinomatosis, or hematogenous or lymphatic spread. While generally carcinomas spread via lymphatic routes and sarcomas spread via hematogenous routes, the interconnectedness of the two vascular systems often blurs these lines. In lymphatic spread, neoplastic cells follow the natural route of lymphatic drainage. In hematogenous spread, veins are more easily penetrated

by neoplastic cells, and spread usually occurs in the closest capillary bed. However, pulmonary capillary beds or primary pulmonary tumors allow easier access to arterial spread.[8]

Despite the history of recurrence and rapid growth, conference participants felt the tumor was a benign entity based on the section presented in conference; a discussion of malignancy features followed. Cytomorphologic features of malignancy, such as areas of cellular atypia, atypical mitoses, and local invasiveness, lack of cellular differentiation, and evidence of metastasis, were not appreciated by conference participants. The moderator commented that often with a surgical biopsy, limited or no history and the relatively small amount of tissue evaluated in a single histologic slide may make the differentiation between benign and malignant tumors elusive.

The moderator offered his approach to the characteristics of malignancy in order of most reliable to least as follows: By its very definition, evidence of metastasis means that a tumor is malignant. However, this information is often not present, and the next best feature to indicate metastasis is the presence of intravasation of the neoplasm, which underscores its aggressive nature. The next most reliable feature of malignancy is focal tissue invasion, characterized by neoplastic cells breaking through basement membranes, or inciting a desmoplastic response, inflammation or other features of host reaction. The least reliable criterion of malignancy is the cytologic appearance of neoplastic cells. When evaluating malignancy based on cellular features, evidence of cell behavior is more important that their appearance, such as the presence of bizarre mitotic figures; however, this can be difficult to completely ascertain based on the two-dimensional cut through a three-dimensional nucleus.

Glomus tumors are often difficult to characterize based on histomorphology alone, and this was an excellent example, having definitive features of a glomus tumor, including characteristic bulging into vascular channels.

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CASE II: H11.0882 (JPC 4003612).

Signalment: 8-year-old male castrate mixed breed domestic dog, canine (*Canis lupis familiaris*).

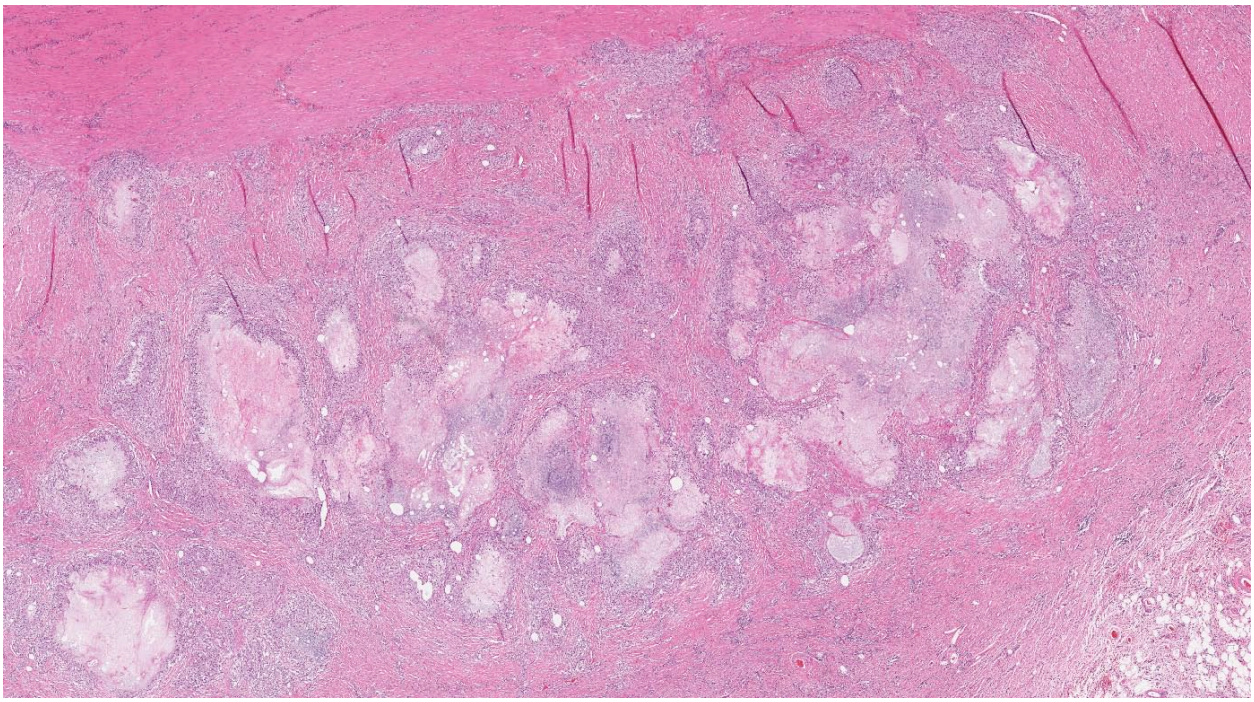
History: The animal was admitted to the Small Animal Clinic of the University of Zurich after a history of vomiting and diarrhea for two months. The animal had been operated on one year earlier because of a stenosis in the ileocecal region. The histology of the resected tissue revealed a lymphangitis and eosinophilic ileitis. Now, the small intestines were again severely dilated and congested with ingesta and a new stenosis in the mid jejunum was evident through ultrasound investigation. The animal was submitted to surgery for a second time; the stenotic intestine was resected and sent in for further histological investigation.

Gross Pathology: The wall of the jejunum and the attached mesenterium was severely thickened by firm connective tissue. Multifocal, small, round, soft, whitish nodules of up to 0,5cm in diameter could be seen between the longitudinal and circular muscle layers of the tunica muscularis. The lymphatic vessels on the mesenteric site of the intestine were severely congested with lymph.

Laboratory Results: The animal had a slightly distended abdomen with a small amount of free, accumulated fluid. The fluid was characterized by a specific gravity of 1.015, protein content of 10 g/L and nucleated cell count of 7475 Lc/µl. The leukocytes consisted mainly of viable neutrophils (95%), few lymphocytes (2%) and monocytes/macrophages (3%). No bacteria could be found within the fluid.

Histopathologic Description: Jejunum: The shortened villi are diffusely blunted and the crypts are often elongated and hypertrophied. The crypt to villus ratio is often 1:1. On the tips of the villi the enterocytes are often desquamated (autolysis). Within the lamina propria there is mild edema, slightly dilated lacteals (not visible on all slides) and on the tips of villi a mild infiltration of macrophages with foamy cytoplasm can be seen. In the mucosa, mildly increased numbers of neutrophils and eosinophils are found.

The entire wall of the small intestine is thickened by up to 3 times due to severely congested lymphatics and multifocal necrotic areas with a width of up to 0.5 cm and proliferation of granulation tissue in the lamina and tunica muscularis and the mesentery. The necrotic areas consist of a foamy, slightly granular, protein rich fluid in the center, surrounded by numerous lipid-laden macrophages (lipophages) with a foamy appearance in their cytoplasm. The periphery is marked by infiltration of moderate numbers of lymphocytes and plasma cells, few neutrophils and marked



2-1. Intestine, dog. Granulomatous inflammation centered on lymphatic vessels which markedly expands the intestinal serosa. (HE 130X)

proliferations of fibroblasts with broad collagen bundles. The collagen bundles lay perpendicular to the many newly formed capillaries (granulation tissue).

Contributor's Morphologic Diagnosis: Small intestine: Lymphangitis, lipogranulomatous, severe, multifocal with moderate granulation tissue formation. Jejunitis, neutrophilic and eosinophilic, mild diffuse.

Contributor's Comment: Protein-losing enteropathy is an idiopathic syndrome that occurs in dogs and to a lesser extent in species such as horses and cats and is characterized by weight loss, hypoproteinemia, and malabsorption. Multiple different diseases such as inflammatory infiltrates in the lamina propria, neoplasia, amyloidosis or lymphangiectasias eventually associated with villus atrophy are possible causes for this syndrome. Often a biopsy is necessary to formulate a final diagnosis.[3]

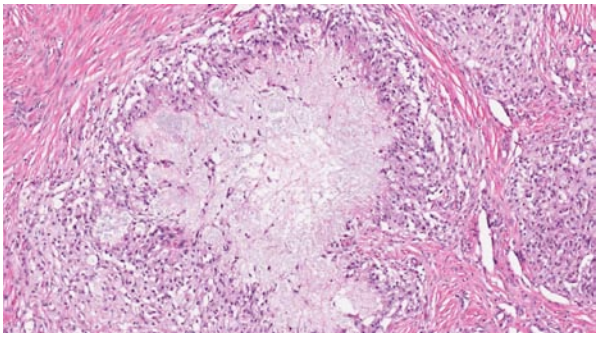
In our case, the lacteals within the villar tips are not the prominent feature, although the villi are shortened and the crypts elongated. The main feature of the lesion is the occurrence of numerous lipogranulomas in the mucosa and mesentery. These lipogranulomas occur adjacent to dilated mesenteric lymphatics, but are not usually a consistent feature of lymphangiectasia.[2,3,4,6] They are often considered as secondary lesions due to lymphatic hypertension and fat leakage and to subsequent granulomatous reponse.[3,4] Similar granulomas occurred in experimental chronic lymphatic obstruction in rats lacking in lymphatic recanalization.[4] Experimental ligation of lymph vessels in the dog did not cause an inflammatory reaction or granuloma formation.

The cause of lymphangiectasia is not always clear. Some cases appear to be acquired by a chronic inflammatory bowel disease, malignant lymphoma or granulomatous infiltrates, but in others, neither a congenital or acquired obstruction of the lymphatic system nor an increase in the inflammatory population of cells in the bowel wall can be seen. This suggests the etiology of the clinical syndrome might be more complex than simple obstruction of the lymphactics.[4] In Basenjis and Soft Coated Wheaten Terriers (SCWT), a familial predisposition for both protein-losing enteropathy (PLE) and protein-losing nephropathy (PLN) is suspected. However, Basenjis differ from SCWT in their clinical presentation. In Basenjis, PLN was not seen separately without intestinal lesions, whereas PLN occurred alone in the SCWT.[2]

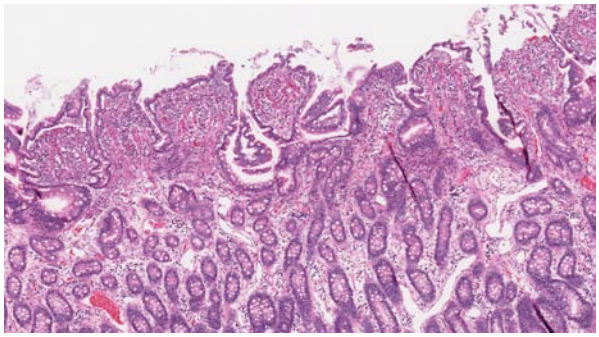
JPC Diagnosis: Small intestine and mesentery: Lymphangitis, lipogranulomatous, diffuse, severe, with mild villar blunting.

Conference Comment: Lymphangiectasia is usually caused by obstruction of lymphatic flow, most commonly due to inflammation.[5] Other underlying mechanisms include neoplastic infiltration, fibrosis, congenital malformation, or physiologic obstruction due to congestive heart failure. When the lymphatics become obstructed, Starling's law dictates the leakage of excess protein and lipid, which incites granulomatous inflammation. This exacerbates the obstruction of lymphatics, and the ensuing cycle may result in lipogranulomatous lymphangiectasia and lymphangitis as seen in this case.[1]

Clinical pathology abnormalities often associated with lymphangiectasia include panhypoproteinemia, which is seen in severe disease with failure of compensatory plasma protein production; lymphopenia, due to loss in lymphatic fluid or stress; hypocholesterolemia; and hypocalcemia. Hypocalcemia is attributed to hypoalbuminemia, and the majority of dogs have serum calcium levels in the normal reference range after correction for albumin[5]; however, some dogs develop ionized hypocalcemia, which may be the result of vitamin D malabsorption, seen commonly with lymphangiectasia.[1]



2-2. Intestine, dog. Closer view of occluded lymphatic withmineralized content, bounded by numerous epithelioid macrophages. (HE 360X)



2-3. Intestine, dog. Marked villar blunting within the overlying mucosa; lymphatics are widely dilated due to downstream occlusion. (HE 200X)

As mentioned by the contributor, the lesions in this case largely spare the mucosa and lack the dilation of lacteals classically described in lymphangiectasia-derived protein-losing enteropathy. As such, this case illustrates a major limitation of surgical mucosal biopsy, which would have failed to sample the diagnostic lesions in the submucosa and outer tunics. The conference moderator emphasized the distinction between lipogranulomatous lymphangitis and lipogranulomas. In two-dimensional cross section, an inflamed lymphatic vessel may appear as a characteristic discrete granuloma with the four typical layers (i.e. central necrosis surrounded by histiocytes, fibrosis, and lymphocytes); however, since the inflammation is actually tracking lymphatics, the term "lipogranulomatous lymphangitis" may be preferable to "lipogranuloma."

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CASE III: 1106976 (JPC 4002864).

Signalment: Tissue from yearling cattle (*Bos taurus*), breed and sex unknown.

History: Several livers were collected at slaughter from animals belonging to a single producer, and were submitted for diagnosis. The veterinarian reported that the animals had been given anthelminthics, which did not appear to be effective. There was further indication that these lesions had been seen in a few calves the previous year, but that more animals were affected this year.

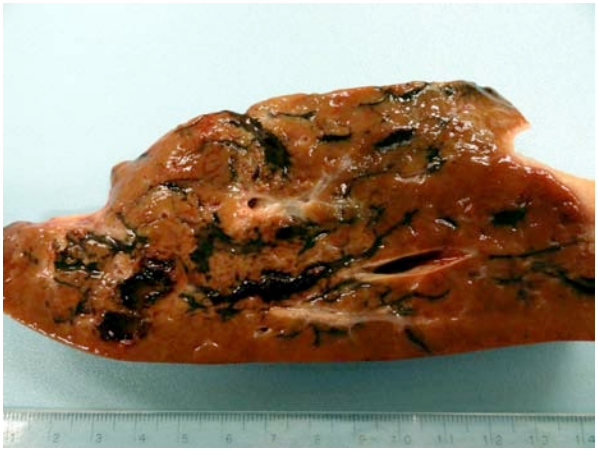
Gross Pathology: Gross findings included the presence of multiple black, irregularly sized tracts throughout the parenchyma that occasionally contained trematode parasites. Fibrosis was apparent in a minority of lesions.

Laboratory Results: Parasites were identified by a veterinary parasitologist as *Fascioloides magna.*

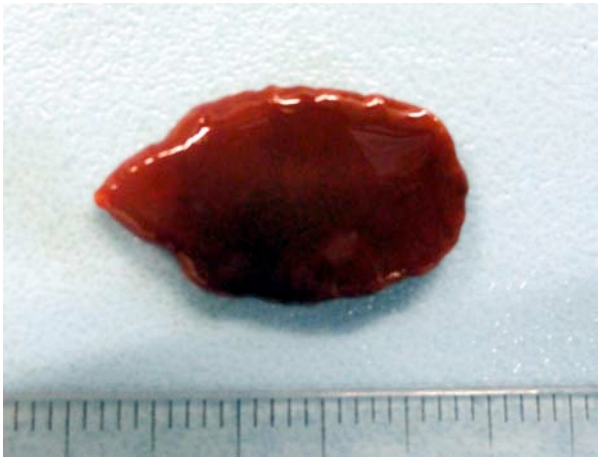
Histopathologic Description: Liver: There is some variation between slides, with some containing more acute and others more chronic lesions. However, they are characterized by periportal fibrosis and inflammation together with much larger randomly distributed tracts that may contain mixed inflammation and hemorrhage, or inflammation and fibrosis. Eosinophils, plasma cells and lymphocytes dominate periportal infiltrates with more numerous macrophages, eosinophils and a few neutrophils in migratory tracts. Many macrophages contain small, isomorphic, birefringent granules of brown cytoplasmic pigment. Acutely, hemorrhage and eosinophils predominate. Stranded in the fibrosis of chronic lesions or in hemorrhage in acute lesions are scattered operculate ova, each with a well defined yellow-brown shell and a central developing embryo. Some ova are degenerate, with neutrophils or multinucleate phagocytes occur around them. Adult trematodes are present in acute migratory tracts surrounded by hemorrhage, and are not located in bile ducts. They are characterized by an external tegument and absence of a body cavity. Muscular, external suckers are present in some sections. The body is filled by loose, pale eosinophilic parenchyma and suspended within is the intestinal tract, containing brown pigment like that seen in tissue. Vitelline bodies are also sometimes apparent. Both male and female reproductive organs can be seen in some sections. A mixture of eosinophils and lymphocytes is present in peripheral hemorrhage and in the adventitia of portal triads. In areas of acute migration, hepatocytes have undergone localized necrosis without reference of their position in the lobule. Most inflamed portal areas contain increased bile duct profiles.

Contributor's Morphologic Diagnosis: Acute to chronic multifocal hepatitis, eosinophilic to granulomatous, with hemorrhage, fibrosis pigment deposition, adult trematodes, trematode ova, and eosinophilic cholangitis with bile duct proliferation.

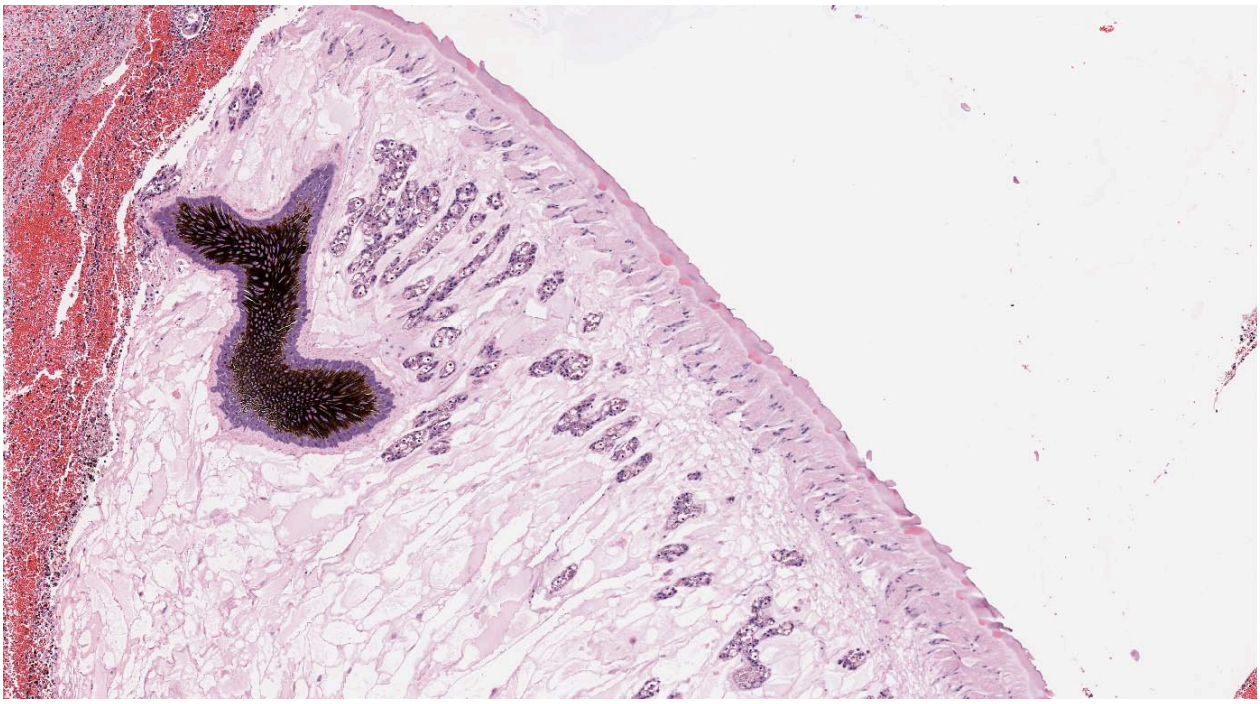
Contributor's Comment: *Fascioloides magna* is the liver fluke of white tailed deer and undergoes aberrant migration in domestic ruminants. In cattle, adults are eventually encapsulated in fibrous tissue and cease migration at that time, but in small ruminants they continue to wander, causing extensive damage and eventual death.[1,4] In cattle, cysts containing the



3-1. Liver, ox. Numerous black tracts, some containing trematodes, traverse the liver. Racts are occasionally bordered by pale hepatic parenchyma suggesting fibrosis and/or hepatic necrosis and steatosis due to hypoxia. Photograph courtesy of Veterinary Medical Diagnostic Lab, University of Missouri, http://www.cvm.missouri.edu/vpbio/index.html.



3-2. Liver, ox. Adult trematode removed from one of the tracts. Photograph courtesy of Veterinary Medical Diagnostic Lab, Univerity of Missouri, http://www.cvm.missouri.edu/vpbio/index.html.



3-3. Liver, ox. Subgross view of section showing adult trematode in cross-section within a migration tract. (HE, 100X).

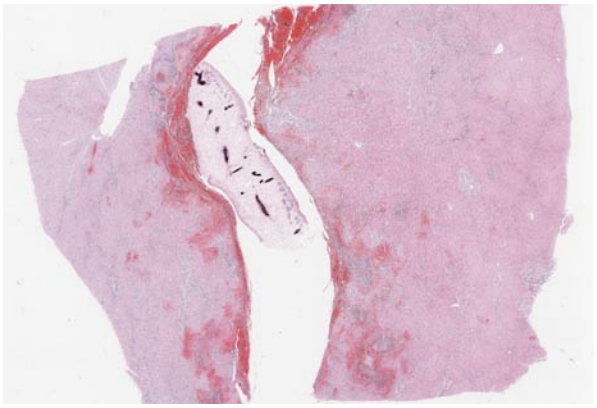
parasite do not communicate with the biliary system and ova have no access to feces; hence the life cycle is incomplete. The black pigment associated with migratory tracts is iron-porphyrin.

Other species are occasionally infected with *Fascioloides magna*. A single case has been reported in a horse[2] and it is of increasing concern to European farmed cervids, particularly red and fallow deer.[3] Because of the need of a snail intermediate, *Fascioloides magna* is not commonly observed in Missouri, although two summers of heavy rain have probably increased a normally low level of parasitism on certain farms.

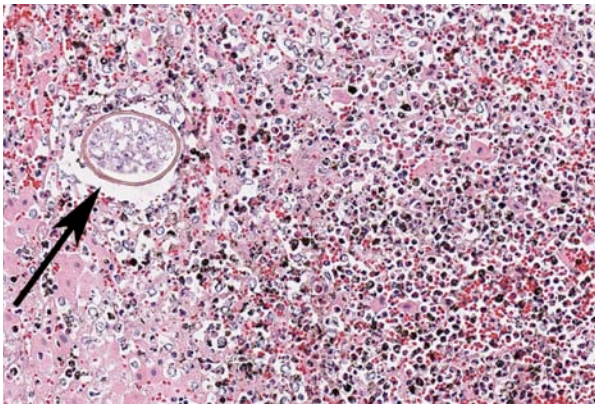
JPC Diagnosis: Liver: Necrosis and hemorrhage, focally extensive, with adult trematodes, granulomatous hepatitis, and eosinophilic portal hepatitis and cholangitis.

Conference Comment: As the contributor mentioned, there is marked variation between sections, with some characterized primarily by acute necrosis and hemorrhage associated with adult trematodes, and others with fibrosis from chronic migration tracts.

A primary differential in this case is *Fasciola hepatica*, which can be as large as *F. magna* and may appear similar histologically. In cattle, these two flukes can



3-4 Liver, ox. On cut section, easily identifiable structures include (from exterior): thick eosinophilic tegument, somatic cell nuclei, spongy body cavity, multiple vittelarian glands, and cross section of a digestive tract with black hematin fluke pigment. (320X).



3-5 Liver, ox. Migration tracts are composed of necrotic hepatocytes, abundant necrotic debris, pigment laden macrophages, lesser numbers of neutrophils and eosinophils, and trematode eggs (arrow). (HE, 400X).

be differentiated, though, by the location of the adult flukes the liver and the presence of considerable iron porphyrin pigment in *Fascioloides magna* infections. Adults of *F. hepatica* are present in bile ducts, while *F. magna* adults are distributed throughout the liver parenchyma. The migration tracts produced by larval *F. hepatica* do not generally cause sufficient damage to alter liver function in the host, as may be the case with *F. magna*. However, clinically important disease can be caused by *F. hepatica* in cattle and sheep when migrating larvae produce areas of local coagulative necrosis and lower hepatic oxygen tension. The areas of hypoxia create a favorable environment for the germination of *Clostridium noyvi* spores, resulting in a form of necrotizing hepatitis known as black disease. *C. noyvi* releases an alpha toxin and the necrotizing and hemolytic beta toxin, lecithinase. In Western and Eastern Europe, black disease may be incited by *Dicrocoelium dendriticum*. Bacillary hemoglobinuria, caused by the closely related *C. haemolyticum*, may also occur secondary to *F. hepatica* migration and has a similar pathogenesis to that of black disease.[4]

When *Fascioloides magna* encysts in the liver, the resulting 2-5 cm diameter encapsulated, pigmented cysts may grossly resemble melanocytic tumors.

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CASE IV: N10-0920 (JPC 4003271).

Signalment: 7-week-old intact male Burmese cat.

History: The animal presented to the UW VMTH emergency service for acute respiratory distress following 5 days of lethargy, anorexia and decreased activity with occasional sneezing. On presentation the animal was quiet, alert and responsive, tachypnic at 92 breaths per minute, with increased respiratory effort, and harsh lung sounds bilaterally. He was tachycardic at 260 beats per minute. There was mild ocular discharge OU. Thoracic radiographs revealed a marked alveolar pattern in the cranioventral portion of the left and right-sided lung lobes, markedly dilated and cylindrical air bronchograms that failed to taper towards the periphery. He declined on overnight supportive oxygen and fluid therapy. Approximately forty minutes after initiation of mechanical ventilation he went into cardiac arrest. Cardiopulmonary resuscitation was unsuccessful and he was presented for necropsy.

Gross Pathology: Gross pathology is limited to the respiratory tract with no ocular discharge noted. A focal 2 x 2 x 1.5 cm region at the caudal tip of the right caudal lobe contains appreciable air. Remaining lung lobes are diffusely mottled and firm. The tracheobronchial lymph nodes are enlarged, with the left measuring 13 x 3 x 3 mm and the right measuring 9 x 6 x 3 mm.

Laboratory Results: Clinical tracheal wash cytology:

- Highly cellular, numerous nondegenerate neutrophils, few macrophages and rare well-differentiated anucleated squamous cells.

- Heterogenous population of extracellular bacteria, including diplococci, rods, small rods in chains, and possibly *Mycoplasma* organisms, is noted.

- Interpretation: Marked neutrophilic inflammation

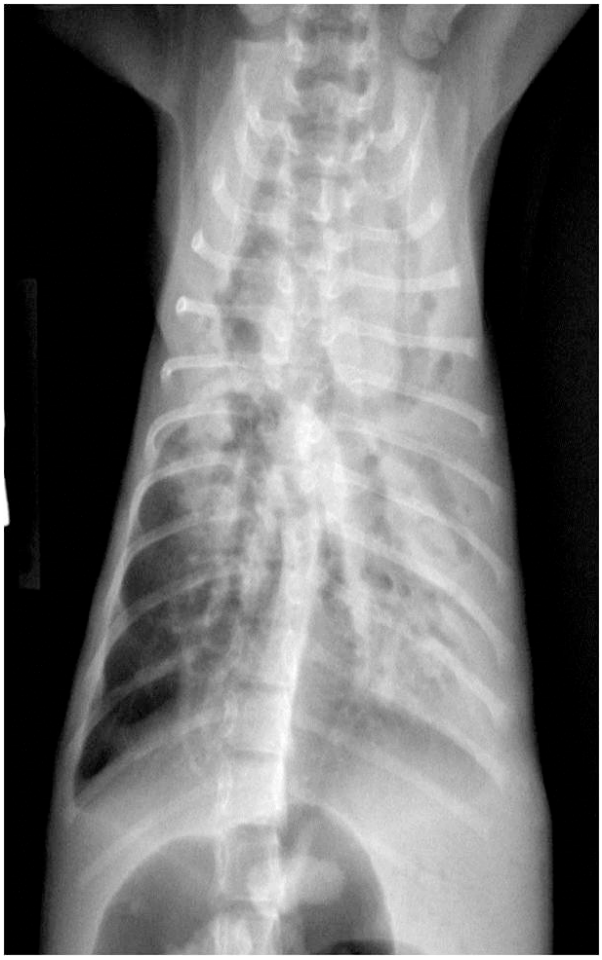
Clinical tracheal wash culture: moderate mixed growth of oral flora

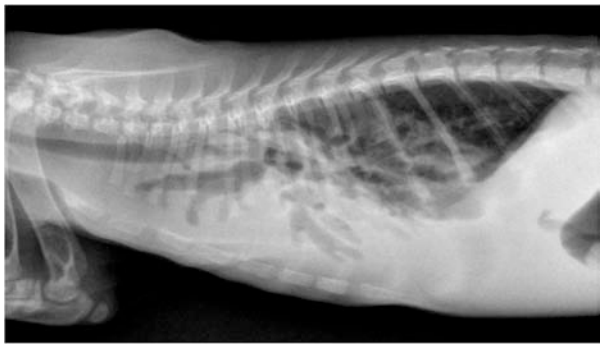
Blood chemistry:

- PCV/TP - 35%/7.4 g/dL
- Blood glucose - 89 mg/dL
- BUN (azo) 5-15

Post-mortem aerobic culture of lung tissue: heavy growth *Mycoplasma* sp. (not speciated)

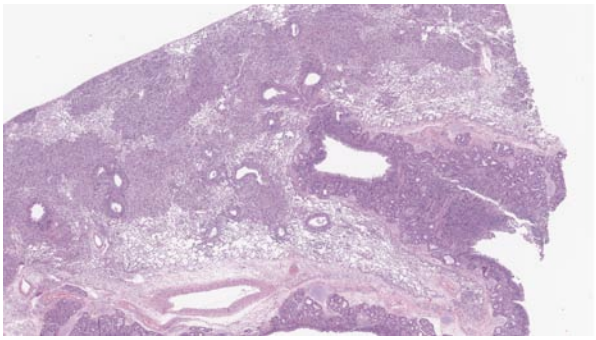
Viral PCR on lung tissue:



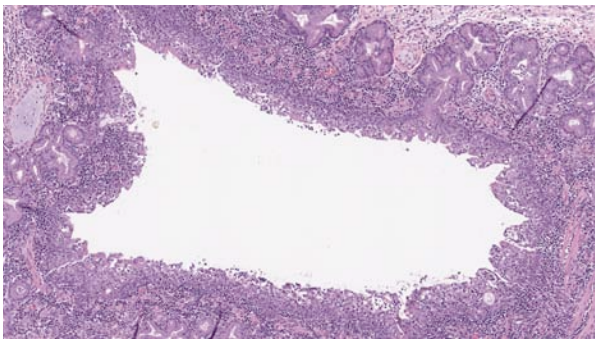


4-1, 4-2. Radiographs, lateral and dorsoventral views, cat. Both views show markedly ectatic airways against a marked bilateral alveolar pattern. Radiographs courtesy of the Department of Pathobiological Sciences, Univ. of Wisconsin School of Veterinary Medicine, http://www.vetmed.wisc.edu/home/.

- Negative for Chlamydia, feline herpes virus, influenza A
- Weakly positive for feline corona virus (CT value 29)
- Weakly positive for feline calici virus (CT value 38)



4-3. Lung, cat. The inflammation is centered upon airways throughout the section. (HE 15X)



4-4. Lung, cat. Affected bronchiole is markedly ectatic, with profound hyperplasia of bronchiolar epithelium and an infiltrate of large numbers of lymphocytes, histiocytes, and neutrophils which througout all layers of the bronchiolar wall. (HE 300X)

Histopathologic Description: Lung: All lung lobes, with the exception of the caudal margin of the right caudal lung, are diffusely and severely affected. There is near complete effacement of alveolar spaces by neutrophils and macrophages with fewer lymphocytes and plasma cells. Alveolar septae are infiltrated and distended by macrophages and neutrophils and in some areas are completely obliterated. Some alveoli are lined by plump cuboidal epithelium (type II pneumocyte hyperplasia). A suppurative exudate fills distal airways making it difficult to distinguish lining epithelial cells. The larger airways are markedly dilated and filled with moderate amounts of neutrophils, macrophages and red blood cells. There is marked hyperplasia of the respiratory epithelium and exocytosis of intraepithelial neutrophils. There are minute, round, basophilic bacteria present on the cilia of bronchiolar epithelial cells (not present in all slides).

A moderate lymphoplasmacytic infiltrate is present in the submucosa of the bronchi and trachea, which is further expanded by edema. Multifocally there is erosion and ulceration of the epithelium covered by a thick layer of fibrin admixed with degenerate neutrophils.

Right caudal lobe (not submitted with case material): The section examined is nearly free of pathology with delicate alveolar walls and normal bronchioles. Multifocally there are small aggregates of neutrophils in alveolar and perivascular spaces. Scarce neutrophils and macrophages are present in alveolar spaces.

Tracheobronchial lymph node (slide 11, not present on all slides): Medullary sinuses and cords are expanded by numerous histiocytes. Multifocally there are discrete clear spaces containing tingible body macrophages. Numerous lymphocytes have pyknotic and fragmented nuclei (lymphocytolysis).

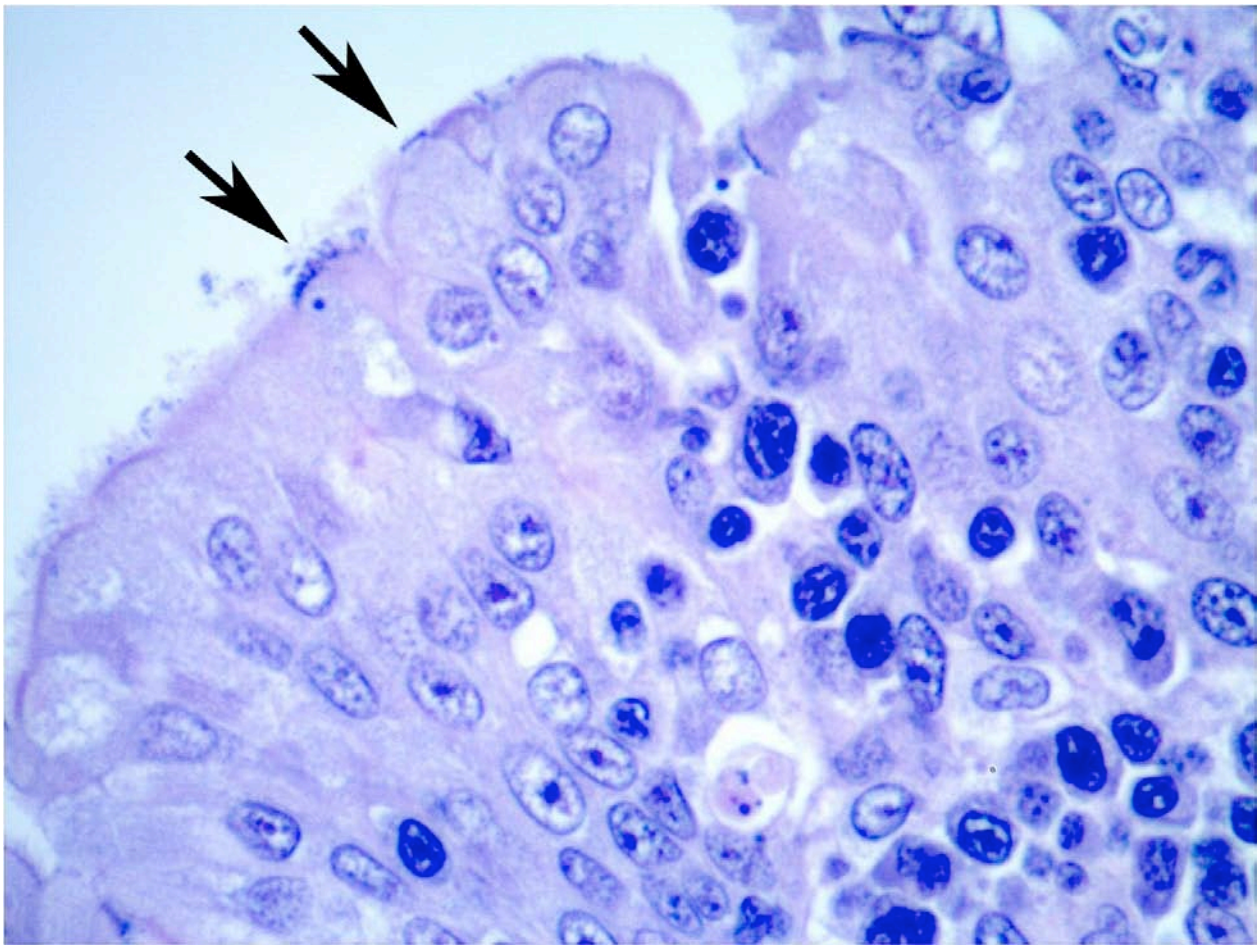
Contributor's Morphologic Diagnosis: Lung: bronchointerstitial pneumonia, pyogranulomatous, diffuse, subacute, severe, with bronchiectasis, localized necrosis and minute supraciliary bacteria.

Trachea: tracheitis, lymphoplasmacytic, necrosuppurative and ulcerative, diffuse, subacute, moderate.

Tracheobronchial lymph node: histiocytosis with lympholysis, diffuse, severe, subacute.

Contributor's Comment: Clinical signs in this case are attributed to co-infection with feline calicivirus and *Mycoplasma sp*. *Mycoplasma* species are common contributors to lower respiratory disease as single or contributory agents in pigs, cattle, and humans. In cats, *Mycoplasma* spp. are considered by many to be normal flora of the upper respiratory tract that can contribute to upper respiratory signs and ocular diseases. A single case report of a cat with primary, culminant pneumonia requiring mechanical ventilation is reported.[9] Three cats are included in a retrospective review of 17 cases of *Mycoplasma* respiratory infections in small animals at Colorado State.[5] In a retrospective study of lower respiratory infections in cats, 11 of 18 were attributed to primary *Mycoplasma* infection, another case was attributed to *Mycoplasma* and *Pasteurella multocida* coinfection, and the remaining 6 individual cases were attributed to various non- *Mycoplasma* bacterial, fungal and parasitic causes.[5]

Feline calicivirus is a common cause of both upper and lower respiratory disease in cats. Pneumonia is not uncommon and most cats recover. Classically described histologic lesions include hyaline membranes and neutrophilic and serofibrinous exudate in alveoli, not seen in this case. Additional gross findings including mucosal vesicles and ulceration were not seen in this case.[1] The vaccination status in this case is unclear, and the low CT value in this case could represent vaccine exposure rather than natural infection.



4-5. Lung cat. Small round basophilic bacilli within the cilia of bronchiolar epithelial cells. Photograph courtesy of the Department of Pathobiological Sciences, Univ. of Wisconsin School of Veterinary Medicine, http://www.vetmed.wisc.edu/home/.

Bronchiectasis in cats is usually attributed to chronic bronchitis, bronchopneumonia, or pulmonary neoplasia.[2] A case series in 2000 reported chronic bronchitis and bronchiolitis, neoplasia, bronchopneumonia, endogenous lipid pneumonia and emphysema as the etiology in 12 adult cats.[7] The age of this cat could suggest a congenital ciliary dyskinesia. Diagnostic modality to examine ciliary function or ultrastructure are not routinely available as part of our diagnostic workup. In this case, the functional obstruction due to marked inflammatory infiltrate was interpreted as sufficient to explain the bronchiectasis.

Absent vascular or gastrointestinal lesions, the positive PCR finding for feline coronavirus is interpreted clinically insignificant.

Although this kitten was the only one of three kittens in the litter affected, a second kitten born to the same dam in a subsequent litter presented with similar clinical signs and gross pathology. In addition to similar lung findings, this 7-week-old male kitten presented a mediastinal, purulent abscess. Histology, microbiology and viral PCR on the second kitten are pending at the time of press.

JPC Diagnosis: 1. Lung: Pneumonia, bronchointerstitial and proliferative, neutrophilic and histiocytic, diffuse, marked with neutrophilic and lymphoplasmacytic bronchitis, bronchiolitis, bronchiectasis, and lymphoid hyperplasia.
2. Lymph node: Reactive hyperplasia, diffuse, moderate.

Conference Comment: This case demonstrates a combination of pneumonia patterns, which help elucidate the underlying etiologies. One pattern is centered on airways and is caused by *Mycoplasma sp.,* and the other is an interstitial pattern caused by feline calicicvirus. Mycoplasmas colonize the upper respiratory tract and are not thought to be a primary cause of disease; however, colonization of the respiratory epithelium results in degeneration of cilia and ciliostasis, impedance of the mucocilary escalator and impaired clearance of microorganisms in the mucous blanket. Aerosolized feline calicivirus also causes upper respiratory disease as well as interstitial

pneumonia and, in this case, impaired respiratory clearance secondary to mycoplasmal infection may have contributed to viral infection. Typically, acute infection with feline calicivirus results in type I pneumocyte lysis and the formation of hyaline membranes and, with chronicity, type II pneumocyte hyperplasia, fibrosis and increased numbers of lymphocytes and plasma cells within the alveolar interstitium, as is seen in this case.[1]

Mycoplasma cell membranes contain superantigens, which bind multiple T-cell receptors (TCR) and non-specifically stimulate the activation of large numbers of T-cells, resulting in lymphoid hyperplasia of the bronchiolar-associated lymphoid tissue (BALT), as is seen in this case. The subsequent massive immune response, which is not specific to any epitope, undermines the ability of the adaptive immune system to target antigens with a high degree of specificity. There is also a massive release of cytokines and resultant inflammatory response, resulting in further tissue damage.[8]

The moderator discussed how bronchiectasis, likely caused by inflammatory obstruction, predisposes the lung to secondary infections. Ectatic airways result in decreased airflow, which allows the settling of particulates and the deposition of microorganisms. Subsequent inflammation and hypoxia further exacerbates the bronchiectasis, continuing the cycle.

Conference participants also discussed the histologic difference between active bronchiolitis and the presence of a retrograde alveolar exudate. Active bronchiolitis is the observance of active inflammation at the level of the bronchiole, as well as corroborating evidence such as epithelial proliferation, inflammation in the adjacent interstium, and leukocyte transmigration. A retrograde alveolar exudate is simply the presence of an exudate within the bronchiole, likely an extension of an alveolar exudate, without any corroborating evidence of bronchiolar disease.

Some slides included sections of tracheobronchial lymph node with lymphocytolytic debris, likely caused either by stress or viral infection.

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