Conference 3
17 September 2008

Conference Coordinator:
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Wednesday Slide Conference

Moderator:

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CASE I – AFIP Case 2 (AFIP 3103341)

Signalment: Tissues are from a 6-week-old, intact female, Weimaraner dog (*Canis familiaris*)

History: This has been going on in my kennel for about 1 year. Puppies will die sometimes with symptoms of URI and occasionally matted eyes. They have loss of appetite and thirst. For no apparent reason, it will stop and no puppies will die for several weeks. It then starts again with a lot of deaths. Adults are now vaccinated every 6 months. Puppies get Bordetella (4 wks), BA2MP (5wks), Parvo (6wks), DA2PP (7wks). It is not affecting adults, only puppies, usually between 5-7 weeks old.

Gross Pathology: The patient is in relatively good body condition. The eyes are markedly sunken into the orbits. There is a small amount of vomitus matted in the hair around the nose. Scattered along the ventral margins of all lung lobes are multiple to

Laboratory Results, Case 1.

Bacteriology Results

Tissue: Lung	Organism ID:	*Streptococcus canis*
Organism	ID:	*Pseudomonas aeruginosa*

Virology Results

Tissue:	Lung		
	Canine Adenovirus PCR	Positive	Canine adenovirus type 2
	Canine Distemper Virus PCR	Positive	Canine distemper virus

Fluorescent Antibody Staining

Tissue:	Lung	Positive	Canine distemper virus
Tissue:	Intestines	Negative	Canine parvovirus
Tissue:	Lung	Negative	TGE
Tissue:	Intestines	Negative	Coronavirus
Tissue:	Lung	Negative	Herpesvirus
Tissue:	Lung	Positive	Adenovirus

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

locally extensive, 2 mm to 2 cm in diameter dark red foci. These foci are slightly firm, fail to collapse and extend into the parenchyma on cross-section.

Histopathologic Description: Lung: The normal alveolar architecture is multifocally effaced by areas of necrosis and inflammation with bacterial cocci, viral syncytia, and viral inclusions. Within affected areas, there are coalescing aggregates of necrotic cellular debris with numerous foamy macrophages. Frequently, the macrophages contain large 7-10um diameter basophilic intranuclear inclusions and few 2-5um diameter eosinophilic intracytoplasmic inclusions. There are frequent syncytial cells that contain up to 5 nuclei. There are scattered lesser numbers of lymphocytes and neutrophils. The bacterial cocci are 1-2um in diameter and form small clusters within the area of more intense inflammation. The inflammation occasionally extends into the lumens of the adjacent bronchioles. The affected bronchioles are often lined by attenuated, ragged epithelium. Within the bronchi, the luminal epithelium is multifocally attenuated. Bronchial epithelial cells occasionally contain 5-7um in diameter oval eosinophilic intranuclear inclusion bodies. Bacterial cocci are occasionally clumped along the luminal surface. Within the less affected areas, the alveoli are flooded with small amounts of fibrin and proteinaceous fluid.

Contributor's Morphologic Diagnosis: Lung: Severe, multifocal to coalescing histiocytic necrotizing pneumonia with syncytial cells, intranuclear and intracytoplasmic viral inclusion bodies and bacterial cocci

Contributor's Comment: The cause of death of this puppy is related to respiratory failure secondary to the severe pneumonia. There is evidence of concurrent viral and bacterial infections. Most sections exhibit colonies of bacterial cocci consistent with *Streptococcus canis*, which was cultured from lung tissue collected at necropsy. The presence of intranuclear and intracytoplasmic inclusions in addition to syncytial formation is diagnostic for canine distemper virus. Morphologically, the character of some of the intranuclear inclusions was more consistent with adenovirus; additional ancillary testing confirmed a concurrent adenovirus infection in this puppy.

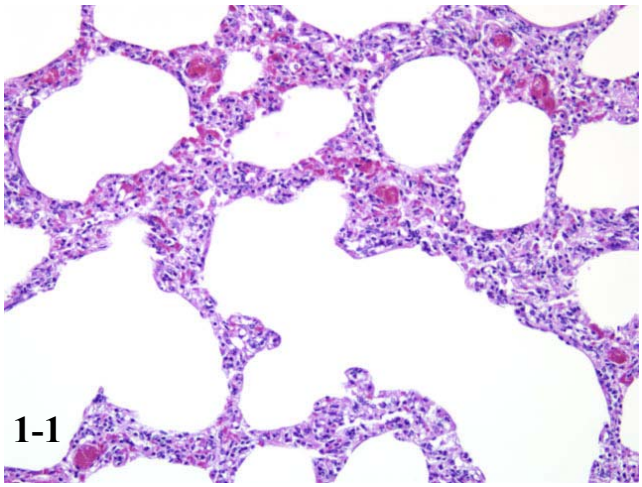
Individually, canine distemper virus (CDV) is responsible for clinical disease from infection of the respiratory, gastrointestinal and central nervous systems. In uncomplicated cases, pathogenic strains cause bronchointerstitial pneumonia, gastroenteritis that can result in vomiting and diarrhea, and a non-suppurative encephalomyelitis with demyelination. The virus has a worldwide distribution and is particularly prevalent (and generally fatal) in areas where vaccination is not practiced (4). In contrast, uncomplicated canine adenovirus-2 (CAV-2) infections are seldom fatal. CAV-2 is highly contagious and in uncomplicated cases results in transient respiratory infections characterized by high morbidity and low mortality. CAV-2 most important role from a pathogen standpoint is to predispose the patient to bacterial infection, thus CAV-2 is an important etiological factor in the canine respiratory syndrome of "kennel cough"(4).

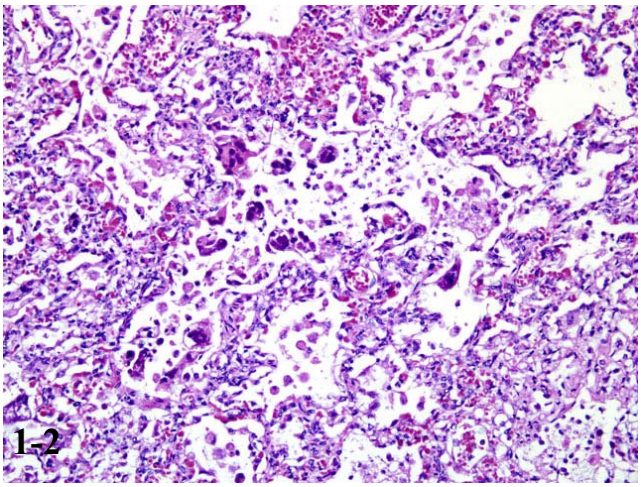
Co-infections with CDV and CAV-2 have been reported previously(2,3,4). In fact, one retrospective study suggests that co-infections occur more frequently than were previously recognized(3). The same study also indicated that histological examination alone is not as reliable for diagnosis of CDV and CAV-2 infections compared to coupling with ancillary virological testing, primarily because viral inclusions bodies cannot be demonstrated in all cases(3).

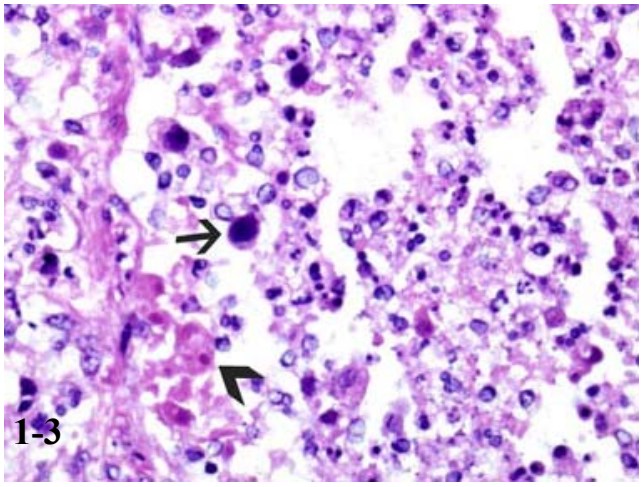
Interestingly, this puppy as well as the subjects of the previous case reports (2,4) had all been vaccinated for CDV and CAV. The development of infection and disease in the vaccinated dog may be related to vaccine failure, reversion of the vaccine strain, immune incompetence to respond to the vaccine, or perhaps infection occurred prior to vaccination(2).

AFIP Diagnosis: Lung: Pneumonia, bronchointerstitial (**Fig. 1-1**), necrotizing, multifocal to coalescing, severe, with syncytia (**Fig. 1-2**), occasional colonies of coccobacilli, and eosinophilic intranuclear and intracytoplasmic inclusion bodies and large basophilic intranuclear inclusion bodies, etiologies consistent with canine morbillivirus and canine adenovirus type 2 (**Fig. 1-3**)

Conference Comment: Canine distemper virus, from the genus *Morbillivirus* in the family Paramyxoviridae, infects a wide range of species including canids, felids, procyonids, and mustelids, with ferrets being exquisitely sensitive to this virus. Canine Distemper Virus (CDV) is transmitted via inhalation of infected aerosols, and the virus enters macrophages within the respiratory tract within the first day of infection. The virus spreads to local lymph nodes and other lymphoid organs within 2-5 days post infection, and from there the virus uses the bloodstream to gain full access to its host. This stage of infection is critical in the development of CDV. If a strong cell mediated and humoral immune response is mounted, the virus is cleared by 14 days post infection







1-1. Lung, Weimaraner. Alveolar septa are variably thicken by a cellular infiltrate and are congested. (HE 200X).
1-2. Lung, Weimaraner. Low numbers of syncytial cells within the necrotic alveoli. (HE 200X).
1-3. Lung, Weimaraner. Within necrotic debris there are epithelial cells that contain large, 10-15 micron diameter, deeply basophilic intranuclear inclusion bodies (arrow). Rarely, within necrotic epithelial cells there are 6-8 micron diameter, eosinophilic intracytoplasmic inclusion bodies (arrowhead). (HE 400X).

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with minimal to no viral shedding. If a partial immune response is mounted, the virus spreads to the respiratory and neurologic systems. Clinical signs may be minimal, but viral shedding due to infection of the epithelium of the respiratory tract are a sequelae. There may also be neurologic manifestations in dogs that mount a partial immune response. In dogs that mount a poor immune response, gastrointestinal, respiratory, and neurologic disease are the result with copious secretion of virus in feces, urine, and respiratory secretions(1).

CDV is a unique virus because it is one of the few viruses that cause intranuclear and intracytoplasmic inclusions. Inclusion bodies within the central nervous system are eosinophilic and intranuclear. In other infected tissues, inclusions are usually intracytoplasmic. Inclusions are most obvious at 10-14 days post infection with waning visibility by 5-6 weeks post infection. Inclusions normally can be seen within the central nervous system after this initial 5-6 week period. Within infected cells of the respiratory tract, inclusions are most easily seen within bronchial and bronchiolar epithelial cells. Syncytia, if present, are a key diagnostic feature within affected epithelium. In acute disease, inclusions are often seen within the urinary bladder and renal pelvis transitional epithelium(1).

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CASE II – 47508 (AFIP3103923)

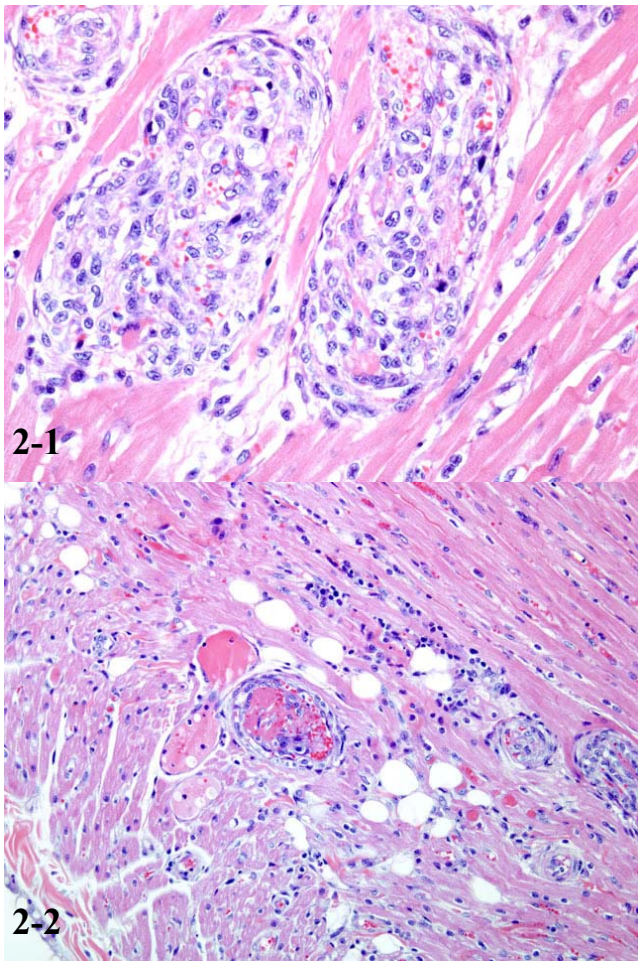
Signalment: 2-year-old, castrated male, Abyssinian cat (*Felis catus*)

History: The cat presented with a 2-week history of lethargy and anorexia. Echocardiography revealed pericardial effusion. The heart appeared normal. Pericardiocentesis was performed. The cat recovered normally from the procedure, but died shortly after.

Gross Pathology: The cat was in good nutritional condition. The pericardium contained approximately 2 ml of serosanguineous fluid with a moderate amount of fibrin loosely adhered to the epicardial surface. There was approximately 30 ml of serosanguineous pleural effusion. The abdomen contained approximately 60 ml of partially clotted blood, with blood clots adhered to a 5 x 20 mm rupture of the hepatic capsule (caused by resuscitation attempt). The spleen was enlarged, had a meaty consistency, and the cut surface showed numerous small pale grey foci, < 1 mm diameter. Mesenteric and ileocecocolic lymph nodes were moderately enlarged.

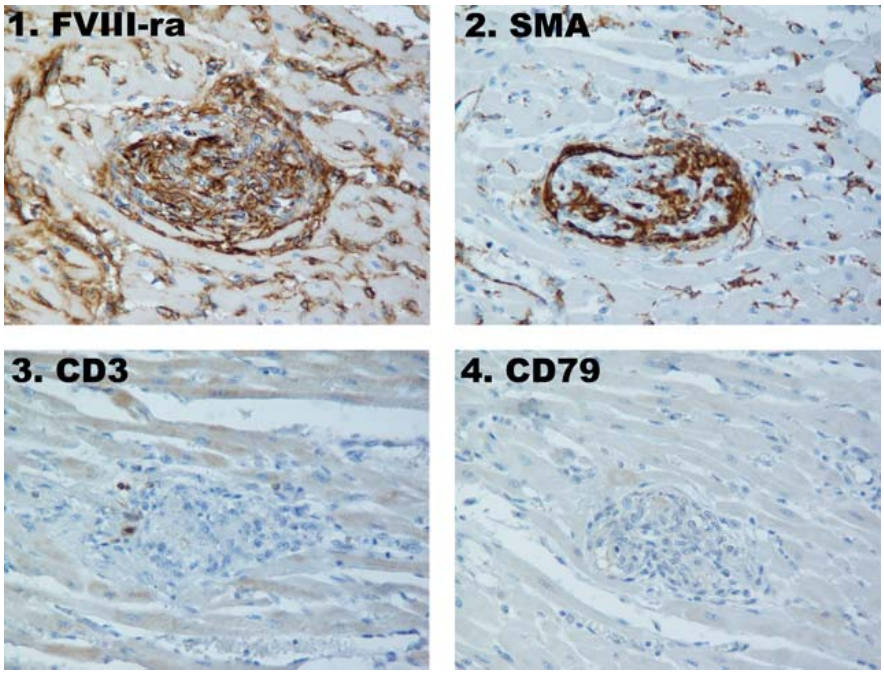
Laboratory Results: Analysis of the pericardial effusion revealed a nucleated cell count of less than 500 cells/ml. The cells were predominantly activated macrophages and nondegenerate neutrophils, with fewer mesothelial cells and small lymphocytes. Protein concentration was 4.8 g/dl. Based on these results the fluid was interpreted as a modified transudate.

Histopathologic Description: Heart. Marked vascular lesions are present in numerous small blood vessels of the left and right ventricular walls, and interventricular septum. In the free walls, the vascular changes are most prominent in the outer half of the myocardium. The vascular lesions are characterized by marked proliferation of plump spindle cells, resulting in mural thickening and luminal occlusion (**Fig. 2-1**). Small clefts containing erythrocytes are present between the spindle cells. The



2-1. Heart, Abyssinian, cat. Proliferations of spindle cells filling the lumina of small caliber arterioles Within the proliferation there are small slits and channels that contain few erythrocytes. (HE 400 X).
2-2. Heart, Abyssinian, cat. Microthrombi partially or completely occlude the lumina. (HE 400X).

spindle cells have indistinct borders and a small to moderate amount of pale eosinophilic cytoplasm. They have oval nuclei with finely stippled chromatin and one to two medium nucleoli. Mitoses are occasionally observed but are uncommon (less than 1 per 400x field). Cellular atypia is not observed. The affected vessels show occasional thrombosis (**Fig. 2-2**) and mild perivascular hemorrhages. There is mild multifocal degeneration and necrosis of myofibers, characterized by cytoplasmic hypereosinophilia and pyknosis. The epicardium is multifocally infiltrated by small numbers of lymphocytes and plasma cells, occasional siderophages, and rare neutrophils. There is hyperplasia



2-3. Heart, Abyssinian, cat. The spindle cell population is immunohistochemically positive for factor VIII-ra and smooth muscle actin, but negative for CD3 and CD79.

Photomicrographs courtesy of Department of Pathology, The Animal Medical Center, New York, NY www.amcny.org

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and hypertrophy of mesothelial cells, and a small amount of fibrin is adhered to the epicardial surface multifocally.

Similar vascular lesions were present in the kidneys, lungs, pancreas, duodenum, diaphragm, cervical soft tissues, and leptomeninges. Sections from the enlarged spleen and lymph nodes revealed lymphoid hyperplasia.

Immunohistochemistry was performed on heart sections (**Fig. 2- 3**). Most spindle cells in the affected vessels showed membrane-associated expression of factor VIII-related antigen (FVIII-ra). Fewer spindle cells showed cytoplasmic expression of smooth muscle actin (SMA). The cells did not show expression of CD3 and CD79.

Contributor's Morphologic Diagnosis: Heart, ventricular myocardium, small blood vessels: Atypical mural and occlusive spindle cell proliferation, with mild multifocal thrombosis, hemorrhage, and myocardial necrosis

Contributor's Comment: Histologic lesions and immunohistochemistry results are consistent with the condition recently described as feline systemic reactive angioendotheliomatosis (FSRA).

Fourteen cases of FSRA have been described, and this appears to be a rare condition affecting exclusively domestic cats.(2,3,4,5) Similar multisystemic vascular lesions have not been described in other animal species. In all reported cases the diagnosis was obtained on post-mortem examination, after the cat died or was euthanized, usually following an acute illness. Affected cats were predominantly young adults, and males appeared more commonly affected. The clinical signs were variable, but most commonly included dyspnea, lethargy and anorexia. Gross lesions were also variable and nonspecific, but included pericardial and pleural effusion, pulmonary edema, and multifocal petechial and ecchymotic hemorrhages of various tissues. An atypical spindle cell proliferation affecting small blood vessels was always observed in the heart. Other commonly affected tissues included kidneys, spleen, lymph nodes, gastrointestinal tract, brain, meninges, eyes, and pancreas. The vascular histologic lesions described in the present case, and the immunohistochemical findings, are similar to those described in the published cases. Ultrastructural examination was described in two cats, and revealed a mixture of two distinct types of spindle cells, consistent with endothelial cells and pericytes.(4,5) The expression of FVIII-ra and SMA is also compatible with a mixed population composed of endothelial cells and pericytes. Based on the presence of two cell types and the lack of cellular atypia, FSRA is believed to represent a reactive proliferative process; it does not appear to be a neoplasm. While the exact cause of death was not clear in most cases, it has been suggested that heart failure probably occurs based on the consistent involvement of the heart, the evidence of perivascular ischemic myocardial necrosis, and the presence of pleural and pericardial effusion, and pulmonary edema with alveolar histiocytosis in many cases.(4)

Histologically and immunohistochemically, FSRA is most similar to reactive angioendotheliomatosis (RAE), a rare human condition.(4) However, RAE in humans is a self-limiting lesion confined to the skin, while FSRA in cats is a multisystemic condition which has been

associated with sev ere illness and d eath. No similar multisystemic di sease has been described i n humans. Other hum an vasc ular di sorders characterized by mixed endothelial cell an d pericyte p roliferation i nclude intravascular p apillary en dothelial h yperplasia, acroangiodermatitis (ps eudo-Kaposi's sarc oma) glomeruloid hemangioma (POEMS syndrome), and some cases of c hronic disseminate d in travascular co agulation and t hrombotic t hrombocytopenic p urpura.(4) Th e pathogenesis o f t hese l esions i s c omplex a nd s omewhat distinct for e ach diseas e, but po ssible m echanisms include an ex aggerated resp onse to thro mbosis, an unusual resi duum o f immune-mediated vasculitis, and an exuberant angio genesis possibly r elated t o ang iogenic cytokines and a d ysfunctional en dothelial regulation of coagulation a nd fibrinolysis.(4) In one ca se o f FSR A, hematologic eval uation s howed e vidence of t hrombotic thrombocytopenic pur pura(2), bu t it r emains unclear if this is a si gnificant cause or m echanism i n other feline cases. Some p roliferative en dothelial lesio ns in human are associated with specific infectious agents, particularly in AI DS patients.(4) Ka posi's sarc oma is cause d by human herpesvirus-8, and bacillary ang iomatosis is caused by *Bartonella he nselae* and *B. quintana*. I n the FSRA cases reported, serologic results were described for only two cats, and there was no evidence of infection by FIV, FeLV, or FIP vi rus. Silve r stains and electro n microscopy pe rformed on t he l esions f rom t wo cat s di d not sh ow e vidence of *Bartonella* sp p. or any other infectious organisms.(4,5) The etiology and pathogenesis of FSRA remains unclear.

The t erm m alignant an gioendotheliomatosis has bee n used t o de scribe i ntravascular a ngiotropic l ymphoma i n humans a nd a nimals. In humans, RAE has historically been confu sed with i ntravascular lym phoma. Th is case was not c onsistent wi th lymphoma based on cel l morphology, and th is was con firmed by th e lack of expression of CD3 and CD79.

AFIP Diagn osis: Heart: Atyp ical en dothelial proliferation (an gioendotheliomatosis), multifocal, moderate, with fe w fibrin t hrombi, rare myocardiocyte degeneration and ne crosis, a nd minimal lymphoplasmacytic myocarditis

Conference Com ment: The contributor's comments accurately and concisely describe t he e ntity known as feline sy stemic react ive a ngioendotheliomatosis. A recent article in *Veterinary Pat hology* described si milar lesions in a C orriente steer t hat was persistently in fected with bovine pestivirus (BVDV).(1) In this case, vascular lesions were seen in th e heart, liv er, l ung, lymph n odes, kidney, adr enal g land, and br ain, and consisted of glomeruloid sp indle cell pro liferations within arterio lar lumens. Spindle cells we re immunopositive for sm ooth muscle act in and von-Willebrand factor and n egative for CD3 and CD79a, consistent with FSRA.(1)

The p athogenesis o f FSRA is stil l u nknown, but it is hypothesized that a reactiv e res ponse t o t hrombosis, vasculitits, or an infectious agent is the cause.(1)

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CASE III – 06-47-18 (AFIP 3102492)

Signalment: Fi ngerlings (0 +) (12.1 cm; 21.8 g) o f Rainbow trout (*Oncorhynchus mykiss*)

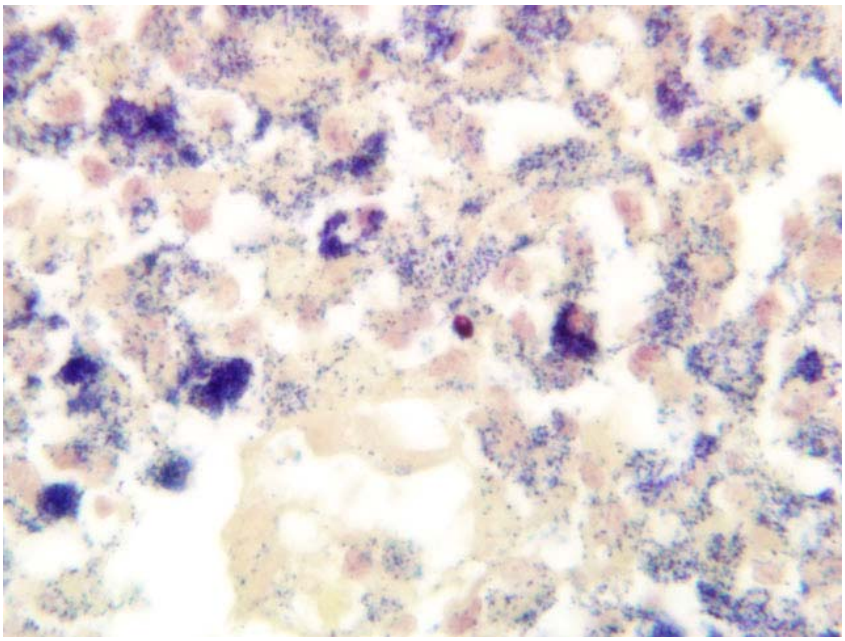
History: Recorded m ortality in p revious 3 m onths: 7.9%, 2 0.7% an d 4 .3%. C linical s igns re ported (variable): exophthalmos, cutaneous ulcers and pale gills. No t reatment at tempted. Tw elve fi ngerlings s ubmitted alive for necropsy.

Gross Pa thology: Exopthalmos, cutane ous ulcers and kidneys with multiple pale nodules (granulomas)

Laboratory Results: Routine bacteriology (trypticase soy) on kidneys: negative.
Numerous small Gram-positive rods observed in tissue smears.

Histopathologic Description: A large portion of the posterior kidney parenchyma is effaced by a granulomatous infiltrate with areas of necrosis. There is loss of epithelial and hematopoietic elements. Myriads of small bacilli can be seen in macrophages, but are better seen in Gram-stained sections. The bacilli are Gram-positive (**Fig. 3- 1**) and non-acid-Fast (Ziehl-Neelsen and Fite-Faraco).

Contributor's Morphologic Diagnosis: Kidney: Granulomatous nephritis with myriads of intra-histiocytic Gram-positive bacilli, compatible with *Renibacterium salmoninarum* (bacterial kidney disease / BKD)



3-1. Kidney, rainbow trout. Numerous 0.5-1 micron diameter gram positive cocci within histiocytes and extracellularly. (B&B 600X).

Contributor's Comment: Based on the typical lesions and absence of growth in routine bacteriology of kidneys, bacterial kidney disease (BKD) was diagnosed. Confirmation by bacteriology (special medium) FA or ELISA was not done in this case since *Renibacterium salmoninarum* was previously identified in this particular facility; furthermore, histopathology coupled with negative results on routine bacteriology is almost pathognomonic for BKD. The two bacterium that could be confused with *R. salmoninarum* are *Carnobacterium (Lactobacillus) piscicola*, the agent of pseudokidney disease (1, 2), and atypical mycobacteria. *Carnobacterium piscicola* rapidly grows at 30°C on trypticase soy or brain-heart infusion agar (1, 2), and the atypical mycobacteria are acid-fast and unevenly Gram-positive.

Renibacterium salmoninarum, the etiologic agent of bacterial kidney disease (BKD) is an important pathogen of salmonids, including rainbow trout. Horizontal and vertical transmission occurs. BKD is a chronic infection but stress can result in acute mortalities. There is no proven effective treatment. Prevention relies on identification of infected brood stock (asymptomatic carriers).(1,2)

Gross lesions include dark discoloration of fish, exophthalmoses, pale gills, abdominal distension and cutaneous vesicles/ulcers, but the most consistent and typical lesion is the presence of multiple whitish nodules in the kidney (and occasionally in other viscera). Fibrinous pericarditis and large cavitations in muscle can also be seen.(2) The typical microscopic lesion is pyogranulomatous to granulomatous inflammation in the affected organ/tissue, with variable numbers of intra-histiocytic small Gram-positive rods; necrosis can be seen, and is sometimes prominent. While histopathology gives a strong presumptive diagnosis, confirmation relies on bacteriology, FA or ELISA. Bacteriology is not very practical, as *R. salmoninarum* is fastidious, very slow-growing and requires a non-commercially available medium. As mentioned previously, the only differential diagnosis is pseudokidney disease caused by *Carnobacterium (Lactobacillus) piscicola* (1); this bacterium can be grown using routine bacteriologic techniques.

AFIP Diagnosis: Kidney, posterior: Nephritis, necrotizing, granulomatous, diffuse, severe, with myriad intrahistiocytic bacteria, Rainbow trout (*Oncorhynchus mykiss*), piscine

Conference Comment: The contributor gives an excellent overview of *Renibacterium salmoniarum* infection. *Renibacterium salmoninarum* is a gram-positive, nonmotile, non-acid-fast aerobic rod which is frequently seen in pairs. This disease has only been

reported in salmonids.(1) BKD generally affects grown fish over 6 months of age, which makes it a particularly harmful and economically damaging agent.(1) Several means of transmission have been reported and include water contamination, skin abrasions, or eating of contaminated foodstuffs. Once *Renibacterium salmoninarum* gains entry into a salmonid, the bacteria are taken up by macrophages and proliferate inside their new host. It is unclear how the bacteria avoid destruction within the macrophage. Stress is thought to be a precursor to clinical disease.(1)

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CASE IV - 208 0491 (AFIP 3103337)

Signalment: 10-year-old, neutered male, orange tabby cat (*Felis catus*)

History: Generalized edema that progressed to extremities. Euthanized.

Laboratory Results: Immunohistochemistry – Greater than 90% of neoplastic cells had strong to weak, diffuse, intracytoplasmic labeling with both CD31 and Factor VIII markers.

Gross Pathology: Red to gold, serous fluid with crepitus and occasional fibrin tags extends the subcutaneous tissues of the entire body with the exception of the head. The legs and feet are edematous and swollen due to the subcutaneous fluid. The thoracic cavity contains approximately 25 ml of clear orange to pink serous fluid (specific gravity 1.022).

Histopathologic Description: Diffusely expanding the subcutis and multifocally infiltrating the musculature is a non-encapsulated, poorly demarcated, moderately cellular neoplasm that forms numerous clefts and variably formed channels supported by a collagenous and fibrous stroma (**Fig. 4- 1**). Cells have distinct cell borders, and are pleomorphic to spindloid. There is scant to moderate amounts of amphophilic, finely granular cytoplasm, round to oval basophilic nuclei, and finely stippled chromatin with an occasional single magenta nucleolus. There are rare mitotic figures. Moderate anisocytosis and anisokaryosis is present. Channels are filled with variable numbers of erythrocytes. There are scattered lymphohistiocytic infiltrates, multifocal areas of hemorrhage, edema, and myocyte degeneration.

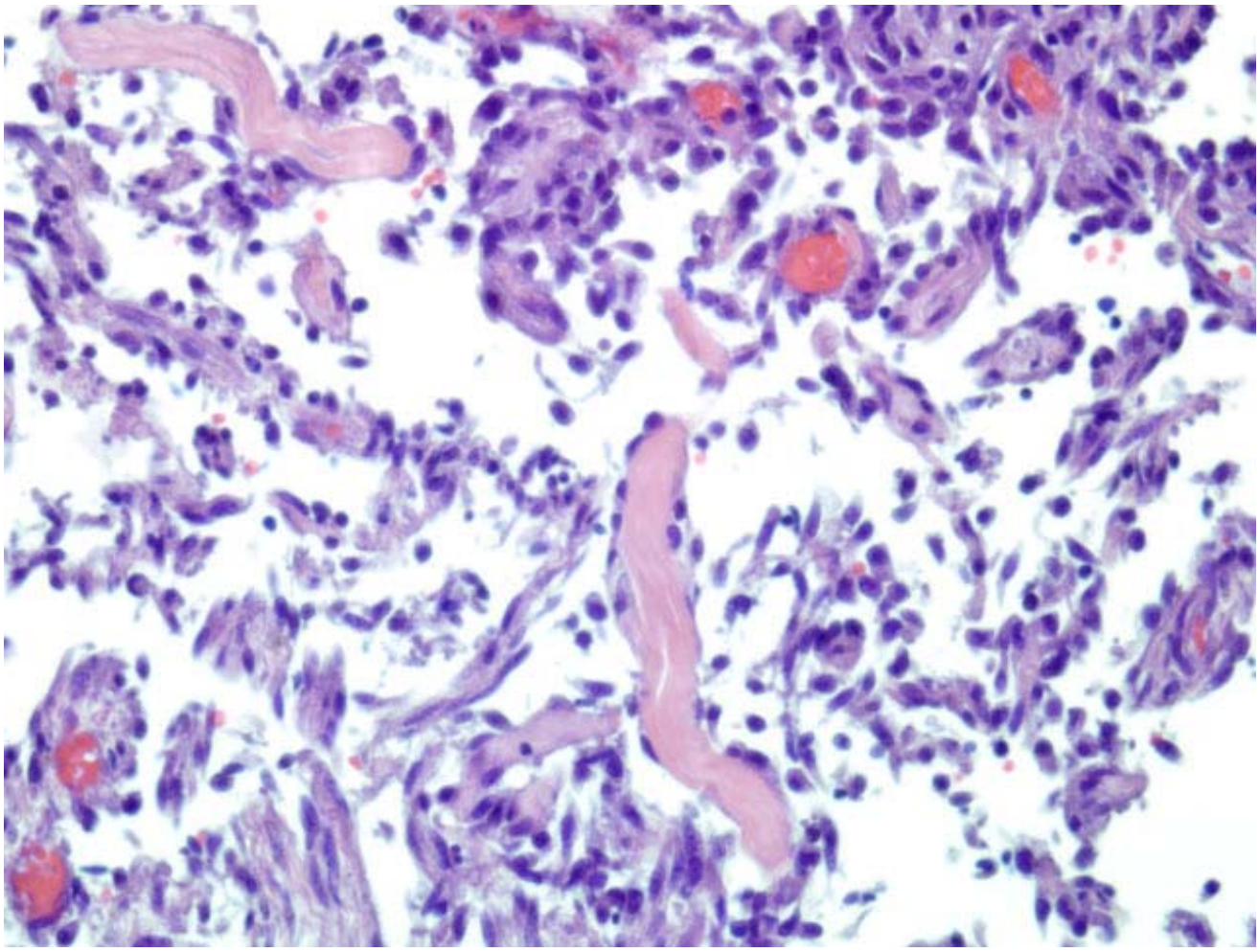
Contributor's Morphologic Diagnosis: Subcutis: Feline ventral abdominal angiosarcoma

Contributor's Comment: Feline abdominal angiosarcoma is a rare, malignant tumor of vascular endothelial origin, which typically only occurs in the dermis and subcutis of cats. Controversy exists as to whether the endothelial cell proliferation is of lymphatic or blood vessel origin.(2,3) The term angiosarcoma is used to avoid this confusion. Although a palpable distinct mass is usually not discernible, the neoplasm may vary in texture from gelatinous and soft to hard.(2,3) Grossly, the cut surface of the lesion may appear to have red or black discoloration and see pse rosanguineous fluid.(2,3) However, in this case widespread edema with occasional fibrin tags was the only clinical sign. There was no discernable mass. Typically, a preliminary diagnosis is established on anatomical location, clinical history, gross appearance, and histological features. Immunohistochemistry may be used to confirm the endothelial origin of the tumor using a CD31 and factor VIII antibody staining protocol.(3,4) Our case was positive for both CD31 and factor VIII. Although metastasis is rare, the prognosis is poor due to its extensive infiltrative growth and frequent recurrences.(2,3,6) The only recognized treatment is repeated surgical excision.(2) Hemangiosarcomas have also been reported in the cow, horse, pig, goat, and sheep.(4,8)

AFIP Diagnosis: Fibro-adipose tissue and skeletal muscle: Feline ventral abdominal angiosarcoma

Conference Comment: The contributor's comments accurately and concisely give a general overview of feline ventral abdominal angiosarcoma.

As noted by the contributor, there is controversy whether



4-1. Fibroadipose tissue and skeletal muscle, cat. Infiltrating the skeletal muscle and fibroadipose tissue is a spindle cell neoplasm that often wraps collagen bundles and forms and lines vague clefts and channels. (HE 400X).

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this neoplasm arises from blood capillary endothelium or lymphatic endothelium. Immunohistochemical staining for lymphatic vessel endothelial receptor-1 (LYVE-1), a marker unique to lymphatic endothelial cells, and the ultrastructural features are strong evidence that these neoplasms are of lymphatic origin.(1) The term 'feline abdominal lymphangiosarcoma' has been proposed.(1) These tumors form vascular clefts and cavernous channels supported by collagenous connective tissue.(5) A papilliferous growth pattern was noted in 11 of 12 cases in a retrospective study, with multifocal areas containing fusiform and polygonal cells densely packed together.(5) Differentials for this neoplasm include lymphangiomatosis and hemangiosarcoma. Pleomorphic lymphatic endothelial cells lining vascular channels as well as blinding trabeculae and a very aggressive, invasive growth pattern separate this neoplasm from lymphangiomatosis, which is considered a developmental disorder wherein the lymphatic system does not form proper communicating channels with the venous system.(3) Electron microscopy is useful in differentiating lymphangiosarcoma and hemangiosarcoma. Ultrastructurally, lymphatic vessels have a discontinuous basement membrane, while hemangiosarcomas have an uninterrupted basement membrane.(3) Useful immunohistochemical stains for lymphangiosarcoma include lymphatic vessel endothelial receptor-1 (LYVE-1), vascular endothelial growth factor receptor -3 (VEGFR-3), and podoplanin because they are purportedly markers unique for lymphatic endothelial cells.(1)

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