The Armed Forces Institute of Pathology
Department of Veterinary Pathology
WEDNESDAY SLIDE CONFERENCE
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CONFERENCE 11
3 January 2007

Conference Moderator: Dr. Brian Wilcock, DVM, PhD
Histovet Surgical Pathology
Guelph, Ontario

CASE I – 05RD1701 (AFIP 3028106).

Signalment: Mack: 11-year-old, male, neutered, Jack Russell Terrier, *Canis familiaris*, canine.

History: The following is a chronological outline of ophthalmic tissue submissions to the Comparative Ocular Pathology Laboratory of Wisconsin (C.O.P.L.O.W.) at the University of Wisconsin-Madison, School of Veterinary Medicine from the previously described canine patient. The slides that we have submitted to you are from the left eye enucleation that was performed on October 3, 2005.

May 11, 2005: Mack had a 1-month history of having a prominent nodule in/on the medial aspect of the superior cornea of the left eye, which was non-responsive to steroid treatment. The submitting DVM surgically removed and submitted the nodule to C.O.P.L.O.W.

July 6, 2005: A second nodule appeared in/on the medial aspect of the inferior cornea, near the limbus, of the left eye and a keratectomy was performed and the sample was submitted to C.O.P.L.O.W. There was no regrowth of the first nodule at the previous excision site. A lesion in the right eye was reported at this time as having regressed with topical steroids.

October 3, 2005: The left eye was enucleated and submitted to C.O.P.L.O.W. at this time there was a larger corneal mass in/on the lateral aspect of the eye. This is the specimen submitted for the AFIP WSC (05RD1707). At this time there was also neovascularization and corneal edema reported in the medial aspect of the right eye.

December 12, 2005: A keratectomy was performed on the right eye to remove a lesion that was non-responsive to steroids/cyclosporine and the sample was

submitted to C.O.P.L.O.W. The submitting DVM was at this time initiating treatment with an oral synthetic retinoid. The diagnosis in the second eye was the same as the first.

Gross Pathology: The tissue submitted is the formalin-fixed left globe and lid. The globe is distorted by an exophytic solid tan mass involving the axial cornea and extending peripherally. Gross digital images have been provided.

Histopathologic Description: Histologically, the mass is made up of an intense cellular infiltrate. Superficially, the cellular infiltrate consists of a fairly monomorphic population of lymphocytes with large nuclear to cytoplasmic ratios. In several areas, they exist as solid sheets. In other areas, they exist as aggregated clusters within the epithelium and abut on the posterior aspect of the epithelium. At the margins, there is granulation tissue and in some areas, a histiocytic inflammatory infiltrate. The rest of the cornea shows superficial corneal stromal fibrosis and vascular infiltrate but no clear evidence of neoplasia. Although there are tumor cells at the margins of the cornea, the globe was trimmed (lids removed) at the C.O.P.L.O.W. Remaining structures of the globe are within normal limits. Histologically within the lids, a severe lymphoplasmacytic inflammatory infiltrate subtends and sparsely invades the conjunctival epithelium (lids were sectioned separately and are not submitted for AFIP WSC).

The neoplastic cells within this sample are a CD3 positive, T-Cell lineage (a digital image has been provided of this special staining). There are also few, scattered HM57, B-Cells seen within the neoplastic cell population (picture not provided).

Contributor's Morphologic Diagnoses:
1. Corneal epitheliotrophic lymphoma (mycosis fungoides)
2. Lymphoplasmacytic conjunctivitis

Contributor's Comment: The nodular tissue sample removed from the left eye on May 11, 2005 was diagnosed as corneal lymphoma, with cells staining positive for both CD3 (T-cells) and HM57 (B-Cells). The corneal tissue from the keratectomy performed on July 11th, 2005, from a different corneal location in/on the left eye, was diagnosed as an epitheliotrophic lymphoma (mycosis fungoides) with dirty margins. IHC cell marker staining was not performed on this sample. The left eye was then enucleated on October 3, 2005, after Mack presented with a third and larger corneal lesion. This enucleation is the sample that has been submitted to the AFIP WSC (05RD1707). The keratectomy sample that was performed on the right eye on December 12, 2005 was diagnosed as an epitheliotrophic corneal T-cell lymphoma (mycosis fungoides).

AFIP Diagnoses:

1. Eye, limbus: Epitheliotropic lymphoma, Jack Russell Terrier, canine.
2. Eye, cornea: Keratitis, chronic-active, diffuse, moderate.

Conference Comment: This case was unique in that the cornea is an unusual location for epitheliotropic lymphoma. The moderator emphasized that tumors do not occur in the normal cornea as tissues with no mitotic activity cannot give rise to neoplasms. There must be pre-existing corneal disease, such as cutaneous metaplasia that occurs secondary to repeated trauma, to allow for tumor formation at this site.

Conference participants briefly reviewed the differential diagnosis for limbal masses in the dog to include nodular granulomatous episcleritis and amelanotic conjunctival melanoma. All other neoplasms at this site are rare in the moderator's experience.

Immunohistochemical staining performed at the AFIP revealed diffuse, strong, cytoplasmic reactivity of neoplastic cells with CD3 consistent with T cell origin.

Cutaneous epitheliotropic lymphoma (mycosis fungoides) is an uncommon, slowly progressive disease characterized by neoplastic infiltration of the epidermis and adnexal structures. In dogs, cutaneous epitheliotropic lymphoma cells are usually CD8+. These T cells display β1 and β2 integrins that help them localize to the epithelium. Epitheliotropic lymphoma is a disease of aged dogs affecting dogs older than 10 years of age and can mimic virtually any inflammatory disease of the skin. In dogs, the course of the disease varies from a few months to 2 years. Eventually, the lesions may extend to lymph nodes and, rarely, to other organs. Chemotherapeutic protocols useful for other lymphomas are of no value. Sézary syndrome rarely occurs with any cutaneous clinical presentation; circulating tumor cells (large convoluted T lymphocytes) are required for this diagnosis. [1,2,3,4,5]

Clinically, epitheliotropic lymphoma may present as generalized pruritic erythema and scaling (exfoliative erythroderma); mucocutaneous ulceration; solitary or multiple plaques or nodules; or infiltrative or ulcerative oral mucosal disease. Many consider the various clinical syndromes to be temporal stages of a progressive disease.[1,2]

The key histomorphologic feature of epitheliotropic lymphoma is the tropism of neoplastic lymphocytes for the epidermal or mucosal epithelium and adnexal structures, especially the follicular wall. The intraepithelial neoplastic lymphocytes are either diffusely distributed within the epithelium or form discrete aggregates referred to as Pautrier's microabscesses or microaggregates which are pathognomonic for epitheliotropic lymphoma. In some cases, complete obliteration of hair follicles and adnexal glands may occur. Infiltration of apocrine glands can

be striking in some cases and is highly diagnostic for epitheliotropic lymphoma since inflammatory infiltrates do not generally occur in this area. Neoplastic cells are pleomorphic often with a cerebriform nucleus (mycosis cell). Mycosis cells appear in the epithelium as individual cells with a clear halo of spongiosis.[2,4,5]

Cutaneous epitheliotropic lymphoma occurs less commonly in cats than in dogs. The clinical presentations are similar to those seen in dogs; however, feline lesions most frequently affect the face, eyelids, mucocutaneous junctions, elbows, and the trunk. Cutaneous epitheliotropic lymphoma also occurs in cattle and, rarely, in horses.[2,3]

Tumors with epithelial tropism include the following:
1. Melanoma
2. Epitheliotropic lymphoma
3. Histiocytoma

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CASE II – 05-25602 (AFIP 3024121).

Signalment: Tissue from a 7-year-old, neutered male, domestic short-hair cat, KitCat.

History: The left eye of this cat was eventually enucleated after a 19 month history of a progressive corneal lesion. When first presented, the cat had a non-healing corneal ulcer. The lesion appeared to bother the cat, and he would rub at it. There was no response to various antimicrobials, lysine or vidarbine 3%. Over time the left cornea became a mottled yellow-pink pale and granular over its entire surface. When the cat began to develop a similar lesion on the right eye, the left eye was enucleated for diagnostic purposes.

Gross Pathology: None.

Histopathologic Description: The eye is characterized by very severe corneal epithelial and stromal inflammation. The corneal epithelium varies in width and is disorganized. Individual keratinocytes have become rounded and detached, especially in the basal layer. Squamous metaplasia is observed in the outer layers and eosinophils are consistently present in the epithelium. A segment of corneal ulceration is associated with degenerate eosinophils. The irregular epithelium contains several facet-like indentations. The corneal stroma is edematous superficially, with the added presence of an inflammatory infiltrate in the superficial and middle layers, particularly the central cornea. Numerous eosinophils are present, mixed with macrophages, plasma cells and lymphocytes in the central cornea. Inflammation extends across the width of the stroma, with segmental accumulation of cells on the corneal side of Descemet's membrane. Melanosis and vascularization extend from the periphery to the center of the cornea and affect the middle to deep portions of the stroma. There is focal conjunctival ulceration, associated with mixed eosinophilic and neutrophilic infiltrates.

Contributor's Morphologic Diagnosis: OS: Eosinophilic keratoconjunctivitis, severe, with corneal ulceration, keratinocyte necrosis, melanosis and vascular proliferation.

Contributor's Comment: The case demonstrates several types of changes that interfere with corneal transparency. Any interference with corneal stromal architecture, including stromal edema, stimulates vascular growth, promotes melanosis or alters the epithelial architecture and disrupts transparency.[1] The normal cornea is transparent because of non-keratinized epithelium, an even, lamellar arrangement of dehydrated stromal collagen fibers, as maintained by functional corneal endothelium, and an absence of blood vessels and pigmentation. The pink to red lesion described grossly is consistent with stromal neovascularization and commonly occurs in eosinophilic keratitis.

Proliferative or eosinophilic keratitis/keratoconjunctivitis is a progressive corneal disease with superficial neovascularity beginning near the limbus, and stromal edema at the leading edge of the lesion. Ulceration is often present and considerable areas of the cornea may stain with fluorescene.[2] The disease progresses to become an irregular mottled mass that is often gritty. Bilateral lesions occur in about a quarter of the cases. Neutered males and domestic short-hairs are favored. Pathology is characterized by a chronic inflammatory response and vascularization. Inflammation is dominated by eosinophils, mast cells and plasma cells superficially and lymphocytes in the deeper stroma. Predominantly observed in the US and UK, this disease has also been recently reported from Europe.[3]

The etiology of this disease is unknown with certainty. There is no association with eosinophilic granuloma complex, and variable indication in 30% to 76%(PCR) of cats that feline herpesvirus 1 (FHV1) plays a role in its pathogenesis.[4,5] Response to corticosteroids is generally favorable but with a high recurrence rate.[6] Topical antivirals administered to this cat are inconsistently effective. Eosinophilic conjunctivitis may occur without keratitis in cats, but the inability to detect FHV1 suggests that it may be a different disease.[7] This inflammatory infiltrate is unique to suspected herpetic keratitis in this species. Eosinophilic keratitis also occurs in horses, also not in conjunction with dermal eosinophilic granuloma.[8,9] In that species it has been speculated to be a result of *Thelazia*, *Habronema* or *Onchocerca* infections. In humans, a similar disease, vernal conjunctivitis, is an extremely severe proliferative conjunctivitis that rarely is associated with keratitis, and has a seasonal occurrence.[10] Vernal conjunctivitis and eosinophilic responses in the conjunctiva may be linked to atopy, and humans with vernal conjunctivitis frequently have elevated IgE in tears.[11]

Other ocular manifestations attributed to feline herpesvirus 1 infection include chronic conjunctivitis, synblepharon, keratoconjunctivitis sicca, stromal keratitis and corneal sequestrum.[12] Concurrent respiratory disease may or may not be present. FHV1 is the only documented viral cause of corneal ulceration. Keratitis probably results from viral reactivation, and may affect the epithelium or stroma.

AFIP Diagnosis: Eye: Keratitis, eosinophilic and lymphoplasmacytic, chronic, diffuse, marked, with edema and superficial eosinophilic coagula, domestic short hair, feline.

Conference Comment: The contributor provides an excellent overview of the key histomorphologic features and potential etiologies of feline and equine eosinophilic keratitis/keratoconjunctivitis.

The characteristic gross appearance is a white, granular, proliferative lesion that extends inwardly along the corneal surface from the medial or lateral limbus. With time, the entire cornea may be involved. Similar lesions may be present in the adjacent conjunctiva and third eyelid. In some cases, the lesions are exclusively conjunctival. Eosinophilic keratitis typically begins as a unilateral disease that eventually involves both eyes.[4,13]

As discussed by the contributor, the superficial stroma is infiltrated by a mixed population of inflammatory cells to include eosinophils, plasma cells, mast cells, and macrophages. The percentage of each type of cell may vary depending on duration; however, eosinophils are always present and are a requirement for the diagnosis. The granular gross appearance is caused by the degranulation of eosinophils which creates a thick refractile eosinophilic coagulum along the surface of the lesion.[13]

The diagnosis is usually made on the basis of clinical appearance and the presence of eosinophils in a superficial corneal scraping. The moderator stressed that only a few eosinophils with compatible clinical signs are sufficient to make the diagnosis.[13]

There was variability among slides with some sections having multifocal corneal ulcerations. Corneal ulceration is not a typical finding but is reported in 13 to 24% of cases.[1] Some slides had sparse superficial eosinophilic coagulum.

Contributor: Veterinary Medical Diagnostic Laboratory and Department of Veterinary Pathobiology, University of Missouri, www.cvm.missouri.edu/vpbio/index.html

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CASE III – Ex57J (AFIP 3031286).

Signalment: An enucleated globe from a mature female neutered DSH.

History: Exophthalmos, corneal ulceration and ocular pain.

Gross Pathology: The anterior chamber is filled with gelatinous material. There is a central corneal ulcer.

Histopathologic Description: Over the central cornea the epithelium is absent or markedly attenuated. Primarily in the stroma subjacent to the ulcer and to a lesser degree peripherally there is neovascularization with microhemorrhages, mild neutrophilic infiltration and a small amount of necrotic cellular debris. Hemorrhage, vascular hyperplasia and mild lymphoplasmacytic and neutrophilic infiltration are present at the limbus and extend into the conjunctiva. The anterior chamber contains a large amount of proteinaceous material admixed with RBC, a small amount of neutrophils and occasional macrophages. The anterior aspect of the iris is covered by a thin layer of spindle cells (preiridal fibrovascular membrane, PIFM). In the central iris the PIFM extends into the anterior chamber as a very loose spindle cell proliferation admixed with blood and pigment-laden macrophages, some of which stain positively for iron (Fig. 1). Peripherally, the iris is flattened against the cornea by the PIFM with closure of the filtration angle. There is edema of the iridal stroma and ciliary body with scattered hemorrhages and mild multifocal lymphocytic and lesser neutrophilic infiltration. There is profound retinal atrophy.

Throughout most of its length, the retina is converted into a thin paucicellular band and remaining nuclei are either of Mueller cells or residual outer nuclear layer neurons. There is marked retinal edema with formation of cystic spaces (microcystoid retinal degeneration), retinal and subretinal hemorrhages and mutifocal retinal detachment. Scattered pigmented macrophages are present in the retina and in the subretinal spaces where some show erythrophagocytosis. The retinal pigment epithelium (RPE) is difficult to identify in many areas but occasional hypertrophic RPE cells are seen in areas of retinal detachment. Multifocally in the choroid and retina, arterioles show narrowing of the lumen and marked thickening of the wall by homogenous eosinophilic and PAS-positive extracellular material with loss of underlying structural detail (Figs. 2 and 3). The optic disk (not present in the submitted slide) was depressed (Fig. 4). In the optic nerve there was widespread axonal loss and gliosis. The lens could not be adequately evaluated for technical reasons.

Contributor's Morphologic Diagnosis: Hypertensive choroidal and retinal vasculopathy with diffuse retinal atrophy, multifocal retinal detachment, multifocal hemorrhages, mild lymphocytic and neutrophilic anterior uveitis and ulcerative keratitis.

Contributor's Comment: The degenerative changes in choroidal and retinal arterioles are typical of hypertension. Severe systemic hypertension causes damage to endothelial cells leading to arteriolar dilatation, discontinuity of the endothelial layer, increased permeability and insudation of plasma proteins into the vascular wall.[2] In other cases there may be medial hypertrophy with adventitial fibrosis ('onion-skinning').[6,7] The morphology of affected vessels is seen to advantage in PAS stain and has been referred to as fibrinoid necrosis or hyaline arteriolosclerosis.[2,6,7] Veins are usually unaffected.[2] Arterial retinal vessels are arterioles rather than arteries as, unlike arteries, they lack an internal elastic lamina and a continuous muscular coat.[2] Changes considered secondary to vascular damage include foci of retinal necrosis, exudative retinal separation and intraretinal hemosiderin deposition.[7]

In this eye there is profound retinal atrophy attributable to hypertensive vascular degeneration probably compounded by secondary glaucoma. Hypertension leads to multifocal retinal necrosis which involves the outer retinal layers, including the RPE.[2,4,7] Glaucomatous retinal atrophy is limited to loss of ganglion cells and nerve fiber layer with sustained moderate elevation of intraocular pressure but involves all retinal layers with extremely elevated pressure.[5] Staining of the retina with GFAP showed markedly increased staining in Mueller cells with the retina virtually uniformly GFAP-positive between the inner and outer limiting membranes (Fig. 5). In the normal retina positive staining is present in astrocytes at the vitreo-retinal

border (nerve fiber layer) and multifocally within Mueller cells (Fig. 6).[1] Mueller cells increase GFAP expression in response to focal or generalized retinal injury.[1] The vertebrate retina is inverted when compared to the retina of lower organisms (e.g. cephalopods). In the inverted retina the outer segments of the metabolically active photoreceptors are apposed to the RPE. Photoreceptors have a very high energy demand. Feline photoreceptors require 3 to 4 times more oxygen than other retinal and CNS neurons for glucose metabolism in the light-adapted state and twice as much in dark-adapted conditions. In order not to compromise vision, vessels are excluded from the outer half of the retina. This results in the paradox that the most energy-dependant part of the CNS is the only region that lacks intrinsic blood vessels. The energy needs of the outer retina are supplied by diffusion of glucose and oxygen from the capillaries of the choroid, collectively termed the choriocapillaris. The chorocapillaris is a thin layer of capillaries separated from the RPE by a basement membrane complex (Bruch's membrane), which is poorly developed in carnivores. The choroid has an extremely high rate of blood flow and its highly fenestrated capillaries are more permeable than those of any other tissue in the body. The outer retina is exposed to near arterial levels of oxygen.[2]

Autoregulation refers to the intrinsic ability of a tissue to maintain its blood flow during changes in perfusion pressure. It operates by altering vascular resistance mostly by modifying the size of the lumen of precapillary arterioles. Excessive perfusion pressure may lead to failure of autoregulation.[2,4] In response to increase in blood pressure retinal arterioles undergo vasoconstriction leading to hyperplasia and hypertrophy of their smooth muscle cells. With sustained vasoconstriction damage to the smooth muscle and endothelial cells ensues and manifests as the vascular changes described above. This is accompanied by leakage of blood and serum into the surrounding retinal tissue leading to edema, hemorrhage and retinal detachment - the typical ophthalmoscopic and macroscopic findings in affected cats.[2,4,7] Although the choroid is not an autoregulatory vascular bed, hypertension-induced injury to this arterial system may cause occlusion of the choriocapillaris leading to necrosis and atrophy of the RPE and outer retinal ischemia.[4]

Enucleated eyes may have other lesions that probably occur secondary to chronic retinal detachment and chronic intraocular hemorrhage. PIFM with its resultant hyphema and neovascular glaucoma are the most notable and were present in this case.[7]

In a minority of slides a moderate amount of neutrophils were present, predominantly within the exudate in the anterior chamber where they formed small groups or a single larger collection. The presence of neutrophils raised the possibility of sepsis. However, since the extent of neutrophilic infiltration was maximal in these sections and was very low in multiple sections from other levels

of the globe, and there was no macroscopic or microscopic evidence of a perforation, we consider bacterial infection unlikely.

Systemic hypertension (SHT), generally defined as systolic pressure ≥160-170mmHg is increasingly recognized in older cats.[4] It is most commonly associated with chronic renal failure but the cause and effect relationship between the two remains uncertain.[3,4,7] Many cats with SHT develop hypertensive retinopathy, and ocular lesions are the most commonly detected complication of SHT in cats.[4] Other causes of SHT include hyperthyroidism, which appears to be less commonly associated with ocular signs, diabetes mellitus, chronic anemia and high-salt diet. Primary SHT is relatively rare.[3,4]

Other causes of retinal degeneration in cats include glaucoma, nutritional deficiencies (Feline Central Retinal Degeneration caused by taurine deficiency), hereditary retinal atrophy (best studied in Abyssinian cats), inflammation, toxins (e.g. fluoroquinolone) and senile change.[7] With the exception of glaucoma, these conditions usually manifest initially as degeneration of the photoreceptor outer segments and RPE.[7]

AFIP Diagnoses:
1. Eye, retina and uvea: Vascular fibrinoid change, multifocal, with fibrin, hemorrhage, edema, mild lymphocytic uveitis, retinal atrophy, and preiridal fibrovascular membrane, domestic short hair, feline.
2. Eye, cornea: Corneal ulcer.

Conference Comment: The contributor provides an excellent summary of the histopathologic changes observed in as well as the pathophysiology of feline hypertensive retinopathy.

Hypertensive retinopathy secondary to systemic hypertension is an increasingly frequent cause of retinal and choroidal lesions and blindness in cats over 10 years of age. It is reported as a complication in 80-100% of cats with systemic hypertension. The three most common causes of hypertension are chronic renal failure, diabetes mellitus, and hyperthyroidism.[4,8]

Typical gross findings include intravitreal and intra- and subretinal hemorrhages, hyphema, retinal edema, and retinal detachment.[3,7]

Conference participants discussed the two most common causes of preiridal fibrovascular membrane (PIFM) formation to include retinal detachment and intraocular neoplasms. PIFMs are also formed following uveitis. PIFMs are simply

a layer of granulation tissue on the anterior surface of the iris that forms by budding and migration of capillaries from the iris stroma and recruitment of fibroblasts in response to cytokine mediators of wound healing, e.g., VEGF. If the PIFM migrates across the anterior face of the lens causing pupillary block or across the filtration angle creating a peripheral anterior synechia, glaucoma results. In cases of retinal detachment, separation of the retina from the choroid results in retinal ischemia. VEGF is released into the vitreous and the iris responds with PIFM formation. Ocular tumors that require a stroma, such as iridociliary adenomas, also produce VEGF. Like immature granulation tissue elsewhere in the body, PIFMs are susceptible to hemorrhage and are a frequent cause of hyphema.[9]

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CASE IV – 05M5661 D1 or D2 (AFIP 3026800).

Signalment: Domestic short haired cat, 9 years old, male, castrated (*Felis domesticus*).

History: The cat had been boarded at a veterinary clinic while the owners were away. Upon returning home, the cat collapsed and presented to the hospital in severe respiratory distress. The cat was anemic, had bilateral mydriasis with retinal hemorrhage and bilateral detached retinas. Radiographically, there was mild cardiomegaly and mild rounding of the cardiac silhouette. The cat failed to respond to treatment and the owners elected euthanasia. Prior to this episode, the cat had been apparently healthy.

Gross Pathology: There was a small amount of clear yellow-tinged free fluid within the thorax, and the lungs were diffusely edematous.

Laboratory Results:
WBC: 5.19 (normal 5.5-19.5)
RBC: 1.53 (normal 5.00-10.00)
Hemoglobin: 3.0 (normal 8.0-15.0)
Hematocrit: 11.3 (normal 30.0-45.0)
MCV: 74.0 (normal 39.0-55.0)
MCH: 19.8 (normal 12.5-17.5)
MCHC: 26.7 (normal 30.0-36.0)
Platelet: 43 (normal 300-800)
Band neutrophil: 0.77 (normal 0.0-0.3)
Lymphocyte: 1.29 (normal 1.5-7.0)

Chemistry:
Sodium: 153 (normal 155-165)
Chloride: 119 (normal 123-131)
Bicarbonate: 5.4 (normal 17.0-24.0)
Phosphorus: 10.8 (normal 4.0-7.6)
Magnesium: 3.62 (normal 1.95-3.04)
BUN: 40 (normal 15-35)
Glucose: 275 (normal 70-135)
Total protein: 5.7 (normal 6.1-8.0)
ALT: 185 (normal 20-125)
Total bilirubin: 0.66 (normal 0.01-0.50)
Hemolytic index: 104.0 (normal 0-50)
Anion gap: 33 (normal 12-16)

PT/PTT
PTT: 41.0 (normal 8.9-18.7)

Histopathologic Description: There are multifocal to coalescing intravascular cellular accumulations of bland spindle cells that partially or completely occlude approximately 75-85% of myocardial arterioles. The cells are arranged in tight to loose whorls and nests within vascular lumens. These cells have plump fusiform to oval nuclei with finely stippled and basophilic chromatin, basophilic nucleoli and scant eosinophilic cytoplasm. Nuclei of the cells lack atypia and mitotic figures are rare. Within affected vessels, there are multifocal fibrin thrombi as well as free erythrocytes within small slit-like vascular channels. Affected vessels often are thickened by proliferative adventitial fibroblasts, and are surrounded by mild accumulations of mucinous edema. In some sections, there is mild to moderate multifocal subendocardial and myocardial hemorrhage with mild lymphocytic myocarditis. Multifocal myofibers are swollen, hypereosinophilic and have varying degrees of cross-striation loss (myodegeneration).

Similar intravascular proliferative lesions were also present within the following organs (not submitted): meninges, cerebrum, cerebellum, hippocampus, bone marrow, liver, spleen, lung, pancreas, stomach, small and large intestine, kidney, and choroid of the eye.

Contributor's Morphologic Diagnoses:
1. Heart: Angioendotheliomatosis, reactive, multifocal, marked with multifocal fibrin thrombi, part of Feline Systemic Reactive Angioendotheliomatosis (FSRA) syndrome
2. Brain, bone marrow, liver, spleen, pancreas, small and large intestine, eye and kidney (not submitted): Feline systemic reactive angioendotheliomatosis (FSRA)

Contributor's Comment: The intravascular lesions present in this case closely resemble those described by Rothwell et al in 1985, Straumann et al in 1993, Dunn et al in 1997, and most recently thoroughly reviewed by Fuji et al in 2005.[1,2,3,4] This is a rare idiopathic reactive and proliferative lesion of vascular endothelial cells and pericytes. Immunohistochemical stains in our case were consistent with other previous reports and confirmed the origin of the proliferative cells in that vWF (factor VIII) and vimentin were consistently positive in all the proliferative lesions while cytokeratin, CD18, CD79 and CD3 were negative. No organisms were seen by silver staining (Warthin-Starry). Ultrastructural examination using electron microscopy by others has shown that the endothelial cells are intermixed with pericyte-like cells.[1,3]

Systemic reactive and proliferative intravascular disorders in the feline are extremely rare. Some naming confusion exists with these conditions, but briefly,

they are divided into two categories. These are intravascular angiotropic lymphoma and a variant of reactive angioendotheliomatosis (this case). One case of intravascular lymphoma has been reported in the cat, and in that case the intravascular neoplastic round cells had immunohistochemical staining properties of T lymphocytes.[5] In the present case (and in 12 other reported cases), the intravascular globoid cellular proliferations consisted of plump fusiform endothelial cells and immunohistochemically were not marked for T lymphocytes (CD3), B lymphocytes (CD79), and were positive for endothelial cells (vWF/Factor VIII).[1,2,3,4]

This unique and recently named condition in cats bears some semblance to several human disorders, but is in other ways distinctly different.[4] In humans, several cutaneous disorders characterized by proliferative and mixed endothelial cell and pericyte intravascular lesions have been described. Although various descriptive names have been given to these disorders (reactive angioendotheliomatosis (RAE), diffuse dermal angiomatosis, acroangiodermatitis (pseudo-Kaposi's sarcoma), reactive intravascular histiocytosis, glomeruloid reactive angioendotheliomatosis, angiopericytomatosis), all are thought to be variants of cutaneous angiomatoses. In humans, these conditions are thought to be caused by occlusion or inflammation of vascular lumina by a variety of causes such as arteriosclerosis, infections (*Bartonella hensalae*, human immunodeficiency virus), valvular cardiac disease, cholesterol emboli, monoclonal gammopathies, hemolymphoproliferative diseases, immune complex deposition in hypersensitivity reactions and many others, none of which were identified in our case or in previous cases.[6] In humans, these conditions are known to affect only the skin; multiple organ system lesions have not been described as in the present case and previous feline cases.[1,2,3,4] Additionally, this unique condition has not been identified in other domestic or wild animal species.

For a thorough review of comparative pathology, please see reference 4 (Fuji et al).

AFIP Diagnosis: Heart: Reactive angioendotheliomatosis, with fibrin thrombi, domestic short hair, feline.

Conference Comment: The contributor provides a thorough overview of feline systemic reactive and proliferative intravascular disorders and compares and contrasts them with similar human angioproliferative disorders.

As pointed out by the contributor, in humans reactive (benign) angioendotheliomatosis is usually limited to the skin and may resolve spontaneously. In contrast, the disease in cats is multisystemic (commonly involving the heart and brain) and fatal.[1,2,3,4,6]

Contributor: Iowa State University College of Veterinary Medicine, Department of Veterinary Pathology, http://www.vetmed.iastate.edu/departments/vetpath/

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