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Department of Veterinary Pathology
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CASE I – 1650/02 (AFIP 2885739)

Signalment: Five-month-old male, European short-haired cat, body weight 1.9 kg.

History: Died within one hour following convulsions; no vaccinations, no history of previous illness.

Gross Pathology: An immature male short-haired cat in fair body condition. Severe pulmonary edema and acute emphysema; hyperplastic pulmonary lymph nodes; myocardial hypertrophy of the left ventricle, slight dilatation of the right ventricle; distinct lobulation of the liver.

Laboratory Results: None reported.

Contributor's Morphologic Diagnosis: Occlusive vascular endothelial proliferation in several organs (heart, intestine, liver, kidney, spleen, pancreas, lymph nodes, brain); endotheliosis; intravascular pseudoangiosarcoma.

Contributor's Comment: Provided to the conference are H & E stained paraffin sections of the myocardium.

Histological examination of the cat revealed identical unusual vascular lesions in all organs (listed above). Proliferation of cells of endothelial type filled the lumina of small arteries and veins, forming cords. Other vessels contain glomerulus-like whorls with small capillary spaces. The newly formed cells are strictly intraluminal and always in contact with endothelium. Their nuclei are dark, elongated and have

an irregular shape. Few mitoses are found. Rarely, small thrombi are in the center of the cellular proliferations.

Immunohistochemical investigation for factor VIII-related antigen proved the histogenesis of the cells as endothelial origin. Factor VIII-related antigen is an established cell marker for endothelial cells in human and animal tissues³; however, the etiopathogenesis remains unclear. It is reported that these lesions may be a neoplasm or hyperplasia of endothelial cells caused by a toxic aetiology.

AFIP Diagnosis: Heart: Reactive angioendotheliomatosis, European short hair, feline.

Conference Comment: In humans, reactive (benign) angioendotheliomatosis is a rare condition characterized by intravascular proliferation of endothelial cells that is usually limited to the skin.^{5,7} Published reports of a histologically similar lesion in animals is limited to few cases in cats,^{1,2,4} although several additional cases in cats have been identified since those initial reports (personal communication, Schulman FY).

In humans, the disease has been associated with coexistent systemic disease and patients present clinically with erythematous macules, ecchymoses, and plaques that may resolve spontaneously.⁶ In contrast, the disease in cats is multisystemic (commonly involving the heart and brain) and fatal. The pathogenesis in both humans and cats is unknown, but it is thought that immunologic factors may play a role.⁶

Immunohistochemistry performed at the Armed Forces Institute of Pathology confirmed that the lining cells in the intravascular proliferations are positive for factor VIII-related antigen, and further revealed actin-positive cells interspersed between the lining cells compatible with pericytes.

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CASE II – XN2604 (AFIP 2893499)

Signalment: 16-day-old, female, Seal-point Siamese, cat.

History: Six deaths occurred in a litter of seven Seal-point Siamese kittens born at a breeding cattery in April 2003. One kitten was stillborn, partly decomposed and reported by the owner to be malformed. Four kittens failed to feed and died within 3 days of birth; two of these were reported by the owner to have cleft palates. One kitten that died at day 16 was submitted for necropsy. One surviving kitten was reported by the owner to be 30% heavier than the other kittens.

Gross Pathology: The 16-day-old, male, Seal-point Siamese kitten weighed 133 g and had a crown-rump length of 150 mm. The carcass was pale and the blood was pale pink and “milky”. The liver was enlarged and mottled pale pink to red. The kidneys were pale pink and had multifocal ecchymotic haemorrhages, 1 to 4 mm in diameter, on the capsular surface and superficial cortex. There were pale pink streaks in the heart. Patchy atelectasis was evident in the lungs.

Laboratory Results: A cryostat section of the liver stained with oil red O had periacinar accumulation of lipid droplets.

Contributor’s Morphologic Diagnosis: Kidney: Emboli, lipid, haemorrhagic, necrotising, infarction, cortical, subcapsular, cat.

Contributor’s Comment: The kidney has multiple subcapsular vascular lipid emboli associated with haemorrhage and locally extensive necrosis of the cortical

parenchyma. In some areas there is infarction of the renal cortex. There are fine vacuoles in glomerular capillaries and other blood vessels in the kidney that represent lipid droplets circulating in the blood. Fine lipid vacuoles were also present in blood vessels in the liver, brain and other tissues in this cat. Periacinar vacuolar change of hepatocytes was evident in the liver and lipid was demonstrated in the vacuoles by staining with oil red O. Capillaries in the heart were dilated and there was intravascular and interstitial vacuolation of the myocardium. Variation in the size of lipid vacuoles within adipocytes was evident in adipose tissue at multiple sites. The pale blood, hepatic vacuolar change with periacinar lipid deposits and vascular lipid emboli in the kidneys are consistent with familial hyperlipaemia.

Familial hyperlipaemia, also known as primary hyperlipoproteinaemia or hyperchylomicronaemia, is an autosomal recessive condition in Siamese cats characterised by fasting hyperlipaemia, lipaemia retinalis, xanthomas in the skin and other tissues and peripheral neuropathy.^{1,2,3} In cats the condition is thought to be due to lipoprotein lipase deficiency and is thus analogous to type I hyperlipoproteinaemia of humans.¹ The activity of lipoprotein lipase in affected cats is reduced in comparison with control animals.³ This appears to be a primary deficiency of lipoprotein lipase, since it is not due to defective activation of lipoprotein lipase by its serum cofactor apolipoprotein C-II or by the presence in plasma of a factor that inhibits lipoprotein lipase.³ The primary gene defect, however, has not yet been determined.

Cats with familial hyperlipaemia present clinically with lethargy, inappetence, hind limb ataxia and anaemia.^{2,3} Clinical signs are ameliorated or resolve when affected cats are fed a diet low in fat. Subcutaneous plaques may be present.¹ Splenomegaly with splenic rupture has been described.¹ Thrombosis of the aorta at the level of the bifurcation of the iliac arteries has also been observed.³ Tyzzer's disease due to *Bacillus piliformis* has been identified in kittens with familial hyperlipaemia from an experimental colony.⁴ On biochemical examination, the blood of cats with familial hyperlipaemia has elevated plasma concentrations of very low density lipoprotein, cholesterol and triglycerides.^{2,3,7}

Histologically, in cases of feline hyperlipaemia, there is lipid accumulation within clear vacuoles in the liver, spleen, lymph nodes, kidney and adrenal glands, as well as other organs.⁵ Ceroid also accumulates in hepatocytes, macrophages and other cell types, mainly in older cats. Lipid emboli may be present in blood vessels, including the caudal aorta.³ There is degeneration and fibrous replacement of glomeruli and nephrons. Focal degenerative changes are evident in arteries, with haemorrhage and formation of lipid-rich granulomas (xanthomas).⁵ Degenerative lesions in peripheral nerves are due to compression by lipid granulomata.² Xanthomas are also observed in the skin.² Ultrastructurally, there are numerous

lipid vacuoles within hepatocytes, renal proximal convoluted tubular epithelial cells and macrophages in the liver, spleen and lymph nodes.⁶ Lipid emboli lodge in glomerular capillaries and interlobular blood vessels in the kidneys.⁶ There is fusion of podocyte feet and thickening of basement membranes in glomeruli, Bowman's capsule and some proximal convoluted tubules.⁶ Xanthomas were not evident in this case, probably because the age at death was too young for lipid to have accumulated in sufficient quantities in the skin and walls of blood vessels to induce granuloma formation. In this case there are multiple lipid emboli in the kidney associated with multifocal haemorrhage and necrosis. There was no evidence of aortic thrombosis.

AFIP Diagnosis: Kidney, subcapsular veins and glomerular capillaries: Fat emboli, multiple, with hemorrhage and granulomatous inflammation, Seal-point Siamese, feline.

Conference Comment: The contributor provides an excellent review of feline inherited hyperchylomicronemia. In addition to Siamese cats, this condition has been reported in domestic shorthair cats.^{1,2,4-6}

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CASE III – N53 (AFIP 2892820)

Signalment: 1 year-old male domestic rabbit (*Oryctolagus cuniculus*), lagomorph.

History: Onset of a large skin mass (4-5 cm in diameter) in the interscapular area.

Gross Pathology: Firm flattened 4-5 cm skin mass in the interscapular area.

Laboratory Results: None reported.

Contributor's Morphologic Diagnosis: Subcutis: Atypical mesenchymal cell proliferation with eosinophilic intracytoplasmic inclusions (Shope fibroma).

Etiology: Leporipoxvirus, Poxviridae.

Contributor's Comment: The lesion consists of a large subcutaneous multinodular mass that is partially delineated and encapsulated with a moderately abundant fibrous capsule and has an expansile growth towards subcutaneous skeletal muscle. It is composed of interlacing bundles and whorls of spindle cells consistent with fibroblasts remaining within a sparse collagenous stroma with multifocal areas of marked edema. The proliferation is either densely cellular or more loosely cellular with densely cellular areas predominating. Proliferating cells are spindle shaped to polygonal, large with poorly defined cell borders, abundant glassy to fibrillar eosinophilic cytoplasm and large, centrally located, ovoid hypochromatic nuclei with one to 3 round eosinophilic nucleoli. There are numerous eosinophilic intracytoplasmic inclusion bodies varying in size (1 to 4µm in diameter) and shape (round to ovoid to fusiform). There is a marked anisocytosis and anisokaryosis but the mitotic index is low (less than one mitotic figure per HPF). There are multifocal areas of necrosis associated with heterophilic infiltration and edema within the proliferation. There is also a rim of inflammatory cells at the periphery including mainly lymphocytes, plasma cells, macrophages and fewer heterophils.

The electron micrographs show fibroblasts (fibroma cells) with numerous intracytoplasmic viral inclusions that consist of masses of viral material, immature and mature poxviruses (Fig. 1). Viral material is better depicted in figure 2 (x 12000) and consists either of fibrillary, regular aggregates of a moderately electron dense material arranged in long strands or bundles, or of finely granular aggregates. Interspersed within this viral material are numerous immature virions characterized by a spherical shape (around 250 nm in diameter) with electron dense granular

content and an outer envelope. Numerous mature virions are also present showing characteristic features of poxviruses: large size (around 300 x 200 nm), ovoid shape, dumbbell-shaped finely granular electron lucent central body (nucleoid) and granular electron dense matrix of viroplasm surrounded by an outer envelope.

All these features are consistent with Shope fibroma although the interscapular localization is not the most commonly involved site. The most frequent reported sites are legs and feet and, to a lesser extent, muzzle, periorbital and perineal regions¹.

Rabbit fibroma virus is a poxvirus closely related antigenically to myxomatosis virus and to the hare and squirrel fibroma viruses. It was first isolated from a cottontail rabbit (*Sylvilagus floridanus*) in the United States in 1932. The virus is transmissible to European rabbits (*Oryctolagus cuniculus*) and cottontails. The infection is considered as a benign, self-limiting disease in the wildlife population. The virus may persist for several months within lesions and mechanical transmission by arthropod vectors appears to be the primary means of spread.¹ These pox virus-induced lesions are not neoplastic but hyperplastic³ and may regress spontaneously due to cell-mediated immunity.

Poxviruses in general have an affinity for epithelium, particularly epidermis, but leporipoxviruses produce fibroblastic nodules rather than epidermal nodules, and cytokines are probably involved in genesis of the lesion.³

In the present case, the overlying epidermis is not present but the lesions in the epidermis are commonly described as severe hyperplasia with projection of cords towards the dermis. Epithelial cells show ballooning degeneration, cytoplasmic vacuolation and presence of irregular eosinophilic intracytoplasmic inclusion bodies.² Their nuclei are often large, hypochromatic with one or several large nucleoli.

AFIP Diagnosis: Skeletal muscle and associated fibroadipose tissue, subcutis (per contributor): Atypical mesenchymal proliferation, with chronic-active inflammation and eosinophilic intracytoplasmic inclusion bodies (Shope fibroma), domestic rabbit (*Oryctolagus cuniculus*), lagomorph.

Conference Comment: There are four poxviruses that affect rabbits: myxoma virus, Shope fibroma virus, and hare fibroma virus, all in the *Leporipoxvirus* genus, and rabbitpox virus in the *Orthopoxvirus* genus. Arthropod vectors are the primary means of transmission of myxoma virus and Shope fibroma virus, whereas the

mode of transmission of hare fibroma virus is unknown. Rabbitpox is spread by nasal discharge and inhalation or ingestion of airborne droplets. Characteristic eosinophilic intracytoplasmic inclusion bodies are present in the lesions caused by viruses of the genus *Leporipoxvirus*, but are uncommon in lesions of rabbitpox.⁴

Clinical disease caused by myxoma virus varies with species susceptibility. Rabbits of the genus *Sylvilagus* (wild rabbits of the Americas) are natural hosts of the virus and relatively resistant to infection, although young rabbits may succumb to generalized disease. Rabbits of the genus *Lepus* are highly resistant, whereas infection in *Oryctolagus cuniculus* (wild European rabbits) results in severe disease and high mortality. In susceptible species, initial clinical signs include edema of the eyelids, followed by blepharoconjunctivitis, mucopurulent nasal discharge, and edema of the base of the ears, perineal region, external genitalia, and lips. The disease rapidly progresses and rabbits may die within 48 hours of initial clinical signs. If rabbits survive longer, disseminated subcutaneous gelatinous swellings develop within several days, and 99% of affected rabbits die within 12 days of infection. Histologically, these lesions are characterized by a proliferation of undifferentiated mesenchymal cells, which become large stellate (myxoma) cells surrounded by a mucinous matrix interspersed with capillaries and inflammatory cells.^{4,5} Other histologic findings may include vascular endothelial proliferation, reticuloendothelial cell proliferation, and lymphopenia.^{1,2,4}

As described by the contributor, Shope fibroma virus is a benign, self-limiting disease that causes subcutaneous, freely moveable tumors most commonly located on the legs or feet, but may also occur on the face, perineum, and elsewhere. These lesions, characterized by localized fibroblastic proliferation, can persist for several months before regressing.⁴

Hare fibroma virus is a disease of European hares (*Lepus europaeus*) and, although European rabbits (*Oryctolagus cuniculus*) are susceptible, there are no reports of natural outbreaks. The disease causes skin nodules on the face, eyelids, and around the ears with similar histopathologic features as Shope fibroma virus.⁴

Rabbitpox is a relatively rare virus that is antigenically related to vaccinia virus. The natural source of the virus has not been determined. It causes high mortality in young rabbits and pregnant or lactating females. Lesions range from localized cutaneous papules to confluent maculopapular lesions with necrosis and hemorrhage anywhere in the body, extensive facial and oral edema, orchitis, conjunctivitis, and death within 7 to 10 days of infection. Histologically, a typical nodule consists of a central zone of necrosis surrounded by mononuclear cells with edema and hemorrhage in adjacent tissues.⁴

Contributor: Pfizer Global Research and Development (PGRD), BP 109, 37401 Amboise cedex, France

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CASE IV – 03-12819 (AFIP 2890206)

Signalment: 10 year-old, female, domestic shorthair cat.

History: One eye of this cat had changed color, was painful and blind and had a severe acute onset of buphthalmos. The cat was vomiting brown fluid and had a decreased appetite. The eye was enucleated.

Gross Pathology: The globe was 2.4 cm in diameter. The posterior segment was completely filled and obliterated by white, opaque, firm and solid tissue with the presence of a small amount of brown-red mucoid material in the center.

Laboratory Results: CBC and biochemistry panels were unremarkable.

Contributor's Morphologic Diagnosis: Feline ocular sarcoma with lens rupture and chronic, severe, diffuse keratitis.

Contributor's Comment: The posterior segment of the eye is filled (predominantly peripherally) by an unencapsulated, poorly demarcated, invasive, densely cellular neoplasm which extends to the anterior chamber and the cornea. It consists of closely packed spindle cells with indistinct borders and small amount of eosinophilic amorphous cytoplasm. The cells are organized in wavy bundles and whorls supported by a moderate amount of collagenous matrix. Other areas show osseous

and chondroid differentiation. The nuclei are elongated with finely stippled chromatin. There is fourfold anisokaryosis and anisocytosis. Mitoses are rare. There are large numbers of cells undergoing necrosis. The lens is ruptured and a fragment of its capsule is coiled and embedded within the tumor. There are moderate numbers of macrophages, neutrophils, lymphocytes and plasma cells and a few multinucleated giant cells throughout and surrounding the mass. At the periphery of the globe there are lymphoid nodules. There is moderate vascularisation throughout the cornea with squamous metaplasia of the corneal epithelium.

The cat developed neurologic signs one week after enucleation and was euthanized. Necropsy was performed and histology revealed an extensive infiltration of the brain by the ocular sarcoma. The other eye had lens rupture with phacoclastic uveitis.

Ocular sarcoma is the second most common primary ocular neoplasm in cats¹ (the first being diffuse iris melanoma) and is often secondary to ocular trauma,^{2,3,4,5} but uveitis without trauma may also be a risk factor.^{3,5} Histological characteristic features include long-standing lens rupture and inflammation, and circumferential distribution of the tumor within the globe.¹ Morphologic studies showed convincing evidence of lens epithelial cell origin for this neoplasm.⁵ Ultrastructural features of ocular feline sarcoma suggesting an epithelial origin include a thick basement membrane surrounding each cells as well as visible cell junctions.⁵ A common consequence of this tumor is infiltration of the brain via invasion of the optic nerve² but local recurrence in the orbit and distant metastasis can also occur.^{1,3}

AFIP Diagnosis: Eye: Feline ocular sarcoma, with osteosarcomatous and chondrosarcomatous differentiation, domestic shorthair, feline.

Conference Comment: As mentioned by the contributor, the two important histologic features of this neoplasm are 1) evidence of long-standing lens rupture (i.e. lens capsule embedded within the sarcoma), and 2) circumferential distribution of the sarcoma within the globe. Previously, this neoplasm was termed “post traumatic sarcoma” to highlight its association with a history of trauma.² This term has fallen out of favor because a history of trauma has been documented in only half of the published cases. More recently the term “feline ocular sarcoma” has been proposed.¹

Lens epithelium is one proposed cell of origin, although an *in vitro* study⁶ raises the possibility that ciliary body epithelium may be the cell of origin. The

immunohistochemical staining pattern of these tumors are similar to those of lens epithelial cells in a traumatized globe. Neoplastic cells stain positively for vimentin, muscle-specific actin, transforming growth factor-beta (TGF-beta), and basic fibroblast growth factor (bFGF). Another morphologic feature of these tumors supporting lens epithelial origin is the presence of periodic acid-Schiff (PAS)-positive basement membrane surrounding the neoplastic spindle cells.¹

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