



WEDNESDAY SLIDE CONFERENCE 2007-2008

Conference 19

5 March 2008

Moderator:

Dana Scott, DVM, DACVP

CASE I – 05-9705 (AFIP 2987057).

Signalment: 13-year-old, gelding, Quarter Horse, *Equus caballus*

History: 2 weeks prior to euthanasia, the horse exhibited signs of colic, was dehydrated and had a temperature of 102.8; CBC and serum chemistries were normal. Horse was treated with Banamine and mineral oil. His temperature and temperament returned to normal. 10 days later, the horse became anorexic, had difficulty breathing, was very weak and developed dependent ventral edema. Severe pleural effusion found on physical exam. The horse treated with Lasix. There was no improvement. On 05/23/05, one fourth of a gallon of straw colored fluid was drained from the chest. The horse was euthanized and submitted to the diagnostic laboratory. Necropsy was performed on the same day.

Gross Pathology:

Subacute, severe fibrinous serosanguinous thoracic and peritoneal effusion

Subacute, severe, proliferative, fibrinohemorrhagic pericarditis

Subacute, severe, bilateral pulmonary congestion and edema

Subacute, severe, focally extensive, ventral subcutaneous

edema

Laboratory Results: *Actinobacillus* spp. was isolated in pure culture from a swab of the pericardial sac contents.

Histopathologic Description: The epicardium is diffusely congested, hyperplastic and inflamed. The epicardial surface is covered by edematous, well vascularized fibroblastic tissue which contains a marked infiltrate of degenerative neutrophils and scattered macrophages. This proliferative tissue is covered by laminations of fibrin which contains degenerative neutrophils. Within this material scattered clusters of gram negative coccobacilli are detected in replicate tissue sections stained with Brown and Brenn.

Contributor's Morphologic Diagnosis: Subacute, severe, proliferative fibrinohemorrhagic pericarditis with intralesional bacteria.

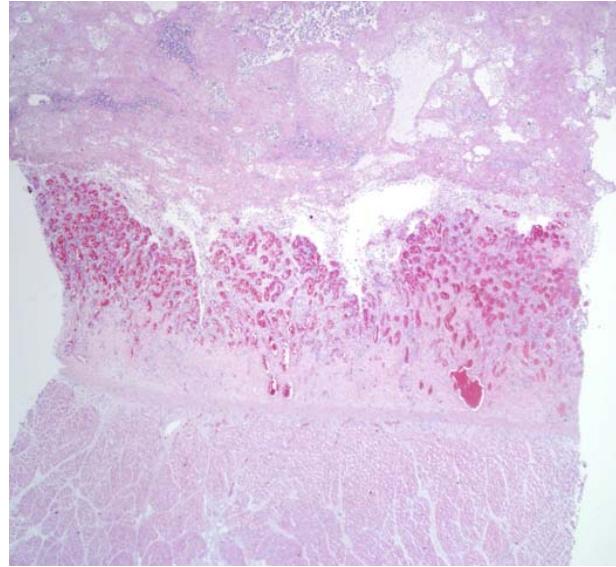
Contributor's Comment: The severe pleural effusion noted at necropsy is attributed to heart failure secondary to severe, restrictive, fibrinous pericarditis. Fibrinous pericarditis is a fairly uncommon condition in horses.³ This condition can result from hematogenous bacteria, extension of inflammation from the surrounding tissues via lymphatic spread or by direct inoculation of the pericardial sac by a puncture wound.^{3,4} Historically, strepto-

cocci have been incriminated in equine cases.⁴ However, a retrospective study of cases of terminal equine pericarditis associated with the mare reproductive loss syndrome during the spring and summer of 2001 confirmed that *Actinobacillus* species played a significant role in this disease.¹

AFIP Diagnosis: Heart, epicardium: Epicarditis, fibrous, chronic-active, diffuse, severe (**Fig. 1-1**), with abundant granulation tissue, Quarter Horse (*Equus caballus*), equine.

Conference Comment: There are three forms of pericarditis: effusive, fibrinous, and constrictive.^{6,7} Fibrinous pericarditis usually occurs via hematogenous spread of infectious agents.^{4,7} The fibrin exudate covers the epicardium and pericardium and forms gray-white shabby projections when the two are pulled apart (bread and butter pericarditis).⁴ Suppurative or purulent pericarditis occurs in the presence of pyogenic bacteria.⁴ It is seen mainly in cattle with hardware disease, and occasionally in cats and horses with pyothorax. In dogs it can be associated with migrating grass awns.⁴ Constrictive pericarditis occurs following extensive fibrous proliferation and adhesions forming between the pericardium and epicardium.⁷ Blunt dissection is usually not sufficient to break down the adhesions formed. The lesions obliterate the pericardial space and impair diastolic filling often leading to right-sided heart failure.^{4,7}

Recent articles concerning an epidemic of fibrinous pericarditis, primarily caused by *Actinobacillus* spp., indicate a strong relationship with mare reproductive loss syndrome (MRLS).^{1,2,6} MRLS is a syndrome of a abortion in horses that occurred in Kentucky in 2001 and 2002. Fea-



1-1. Heart, equine. Diffusely the epicardium is markedly expanded by variably sized blood small caliber blood vessels admixed with eosinophilic homogenous material which blends into an overlying thick fibrinous mat. (HE 20X)

tures of the syndrome include little to no signs of premonitory illness in the mare, hemorrhages in the chorion, amnion, and amniotic segment of the umbilical cord, pleura, and heart.⁵ Non-b-hemolytic *Streptococcus* spp. and/or *Actinobacillus* spp. were isolated in 50% and 20% of the cultured specimens.⁵ MRLS has been associated with the Eastern tent caterpillar (*Malacosoma americanum*), specifically the worm exoskeleton and attached

Conditions potentially associated with fibrinous pericarditis Table extracted from Maxie et al.⁴ and Van Vleet et al.⁷

Cattle: Pasteurellosis (*Mannheimia haemolytica* and *Pasteurella multocida*), blackleg (*Clostridium chauvoei*), sporadic bovine encephalomyelitis (*Chlamydophila pecorum*), contagious bovine pleuropneumonia (*Mycoplasma mycoides mycoides* small colony type), clostridial hemoglobinuria (*Clostridium haemolyticum*), neonatal coliform infections (via umbilicus)

Swine: Glasser's disease (*Haemophilus suis*), pasteurellosis (*Pasteurella multocida* and *Mannheimia haemolytica*), porcine enzootic pneumonia (*Mycoplasma hyopneumoniae* and other agents), salmonellosis, streptococcal infection of piglets

Sheep: Pasteurellosis (*Mannheimia haemolytica* and *Pasteurella trehalosi*)

Lambs: Pasteurellosis, streptococci

Horses: *Mycoplasma felis*, streptococcal polyarthritis with pericarditis, mare reproductive loss syndrome

setae.^{2,5} The exact relationship between exposure to the Eastern tent caterpillar, MRLS, and fibrinous pericarditis is not known.^{1,2,5,6}

Contributor: Tennessee Department of Agriculture, Regulatory Services
 State Veterinarian Office – C.E. Kord Laboratory
<http://www.state.tn.us/agriculture/regulate/labs/kordlab.html>

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CASE II – 07-12027 (AFIP 3075555).

Signalment: Adult, m ale, do mestic lo nghair, *Felis do mesticus*

History: The cat was ho spitalized for signs attrib utable to acute re nal failure. T he cat had eleva ted BUN a nd

creatinine levels. The cat was euthanized for acute renal failure and submitted to the diagnostic laboratory for necropsy.

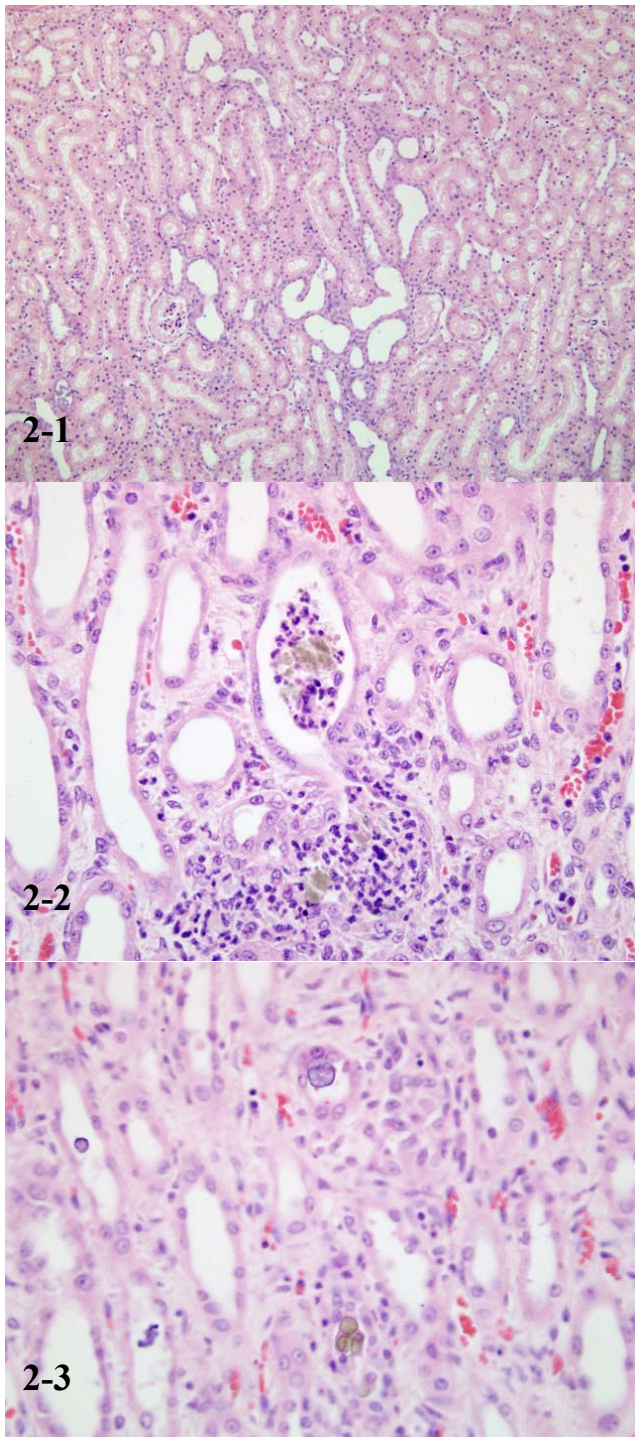
Gross Pathology: The cat was in good body condition with normal amounts of body fat and only mild postmortem autolysis. The lungs were mildly congested and edematous. The urinary bladder was empty. Cut sections of both kidneys had a diffuse lightly pale appearance in the cortices. No ot her significant gr oss changes we re ob served in the carcass.

Histopathologic Description: H&E sections of kidney were sub mitted. There is so me mild v ariability with in the slid es submit ted. Nu merous cortical an d medullary tubules are moderately dilated (**Fig. 2-1**). Tubular lining epithelium of these tubules is flatten ed and attenuated. Occasional tubules contain cl usters of necrotic epithelial cells and rare neutrophils. Rare granular casts are pre sent. Variable, but usually lo w numbers of in tratubular irregular sh aped greenish br own birefringent cr ystals (**Fig. 2-2**) that fluoresce under polarized light are present within cortical and medullary tubules. Occasional crystals also contain v ariable amounts of basophilic staining material in terpreted as partial mineralization (**Fig. 2-3**). In some sectio ns, the cortical in terstitium has multifocal mild infiltrates of lym phocytes and m acrophages with mild foci of interstitial fibrosis.

Contributor’s Mor phologic Diagn osis: Kidney, acute tubular n eerosis (n ephrosis), m ultifocal, mo derate with nephritis, interstitial, lymphohistocytic, multifocal, mild.

Contributor’s Com ment: The fi ndings i n the kidney are consiste nt with ac ute toxic t ubular necrosis (nephrosis). The history of elevated BUN and creatinine also supports the histological findings. The crystals present in scattered tubu les have a greenish brown co lor, fluoresce under polarized light and are generally less in number com pared to m ost cases of et hylene glycol (antifreeze) toxicity. The crystals do not have the typical palisading appearance as usually seen with oxalate crystals associated with ethylene glycol toxicity.

The cat had been eating one of the pet food brands (Menu foods) which had been recently recalled from the market due to suspicion of toxic compounds in the food.⁶ Current thoughts regarding etiology of this pet food toxicity are focused on melamine. Melamine has been identified as a component in the wheat gluten imported from China which was a component of the recalled pet foods. Current sp eculatio n is t hat the melamine was in tentio nally added to the wheat gluten to increase the apparent protein concentration of the produ ct. At th e tim e of this rep ort



2-1. Kidney, cat. Multifocally, within the cortex and medulla there are ectatic tubules. (HE100X).

2-2. Kidney, cat. Fragmented dense green melamine/cyanuric acid crystals often admixed with necrotic tubular epithelium and cellular debris within tubules. (HE 400X).

2-3. Kidney, cat. Variably-sized light green to slightly basophilic, round, globular crystals with radiating striations. (HE 400X).

(April, 2007), there is no standardized toxicologic test for melamine in tissue specimens.

Acute toxicity studies of melamine in mice and rats suggest that this compound is of lower toxicity and has been rated as slightly toxic in acute toxicity ratings when administered by oral route.⁷ The LD50 of this compound in mice and rats are 3.3g/kg and 3.2 g/kg respectively.^{3,7}

The pathogenesis of crystalluria and the formation of bladder stones in rodents in this syndrome is not fully understood.^{2,3} Melamine is excreted in the dog or rat partly as crystalline dimelaminemonophosphate. This can be isolated from warm urine by precipitation with oxalic acid as crystalline monomelaminemonooxalate.² In experimental studies, 60-86.5 per cent of the melamine fed to dogs was recovered in the urine in 24 hours.²

AFIP Diagnosis: Kidney, corticomedullary junction and medulla: Nephritis, tubulointerstitial, acute, multifocal, mild, with tubular necrosis and degeneration, and numerous intratubular crystals, domestic longhair, (*Felis domesticus*), feline.

Conference Comment: On March 16, 2007, Menu Foods Inc. issued a recall on more than 60 million containers of pet food that was manufactured between December 3, 2006 and March 6, 2007.⁶ This recall occurred due to numerous instances of animal deaths attributed to food related nephrotoxicosis.⁵ Over the course of several months, this recall expanded to include several major commercial pet food companies and affected large numbers of dogs and cats in the United States.¹ The toxic compounds contaminating wheat flour were isolated as melamine and cyanuric acid.^{1,4,5} Both of these compounds are considered relatively nontoxic when administered separately, but when combined, they form insoluble crystals nearly identical to the ones found in the cases of melamine associated renal failure (MARF).^{4,5}

Up to three different crystals have been identified in the kidneys of animals affected by MARF: calcium oxalate monohydrate, calcium phosphate, and melamine-containing. On H&E, melamine-containing crystals within the lumen of renal tubules are up to 80µm in diameter, birefringent, pale yellow to brown, and vary from fan-shaped to starburst radial spokes arranged in concentric

Table 2-1. Comparison of staining characteristics of melamine-containing, calcium oxalate, and calcium phosphate crystals.⁵

Stain	Melamine-Containing	Calcium Oxalate	Calcium Phosphate
Oil Red O (72 hour)	Positive	Negative	Negative
Von Kossa	Negative	Positive	Positive
Alizarin Red S (pH 4.1-4.3)	Negative	Negative	Positive
Hematoxylin and Eosin	Pale yellow-brown, radiating spokes, birefringent	Colorless, prismatic effect	Basophilic

tric circles.^{4,5} Calcium oxalate crystals are also birefringent on H&E, but have a smoother surface and a slight blue tinge due to a prismatic effect.⁵ Calcium phosphate crystals on H&E appear as non-birefringent, basophilic particles within the lumen of renal tubules as well as within the walls of blood vessels (not apparent in the present WSC case).⁵ Staining characteristics of the crystals are listed in table 2-1.

Prolonged formalin fixation results in dissolution of the melamine-containing crystals within 6 weeks.¹ Therefore, it is recommended that fixation in formalin be kept to a minimum or preserved in 100% (absolute) ethanol. Although more commonly associated with cases of ethylene glycol toxicity, the calcium oxalate crystals in cases of MARF are likely the result of a secondary oxalosis.^{1,5}

It was brought to our attention by Dr. Wayne Corapi at Texas A&M University College of Veterinary Medicine that the intratubular crystals in WSC 2004-2005, Conference 12, Case 3, are histomorphologically similar to the melamine-containing crystals recently identified in the kidneys of cats and dogs that were fed pet food on the Menu Foods recall list manufactured between December 3, 2006 and March 6, 2007. Upon reviewing the case and performing special stains, we concur with Dr. Corapi and believe it is a case of pet food-associated nephrotoxicosis with melamine-containing crystals. This association with the outbreak of renal toxicity in Asia was also reported by Puschner et al.⁴ and Brown et al.¹ Conference participants are encouraged to review the WSC 2004-2005 case and compare it with the crystals presented in the current case.

Georgia.

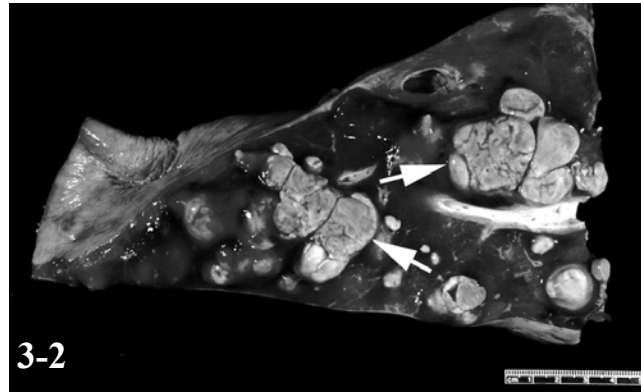
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Contributor: Tifton Veterinary Diagnostic and Investigational Laboratory, The University of Georgia, Tifton,





3-1. Lung, warmblood mare. A yellow-tan mass expands and distorts the caudal lobar bronchus.

3-2 Lung, warmblood mare. Variably-sized masses within the lung parenchyma.

Gross photographs courtesy of Eli Lilly and Company, Lilly Research Laboratories, Greenfield, IN 46140

CASE III – 2 (AFIP 2985231).

Signalment: 7-year-old, warmblood mare (*Equus caballus*).

History: The mare presented with a 6-month history of coughing. The veterinarian suspected respiratory infection and allergic pneumonitis; however, the horse did not improve with treatment. Thoracic radiography and pulmonary endoscopic examination were performed (see below).

Gross Pathology: The right lung was surgically excised. The resected lung had a large intraluminal pale yellow-to-tan firm mass expanding and distorting the right caudal lobar bronchus (**Fig. 3-1**) and had many variably-sized masses protruded into the airways and within the pulmonary parenchyma (**Fig. 3-2**).

Histopathologic Description: [Submitted tissue: Tissue from one of the lung masses fixed in glutaraldehyde]. Transmission electron micrograph. The tumor (**Fig. 3-3**) consisted of a homogenous population of neoplastic mononuclear cells. The neoplastic cells were elongate to polygonal with moderate to abundant amounts of cytoplasm, thin elongate cytoplasmic extensions, irregularly shaped nuclei and small nucleoli. The cytoplasm was filled with single membrane-bound secondary lysosomes filled with slightly electron dense amorphous granular material, membranous debris, and spherical moderately electron dense material. Some of the lysosomal contents were consistent with degenerate organelles. Cell-cell junctions, basement membranes, and angulate bodies

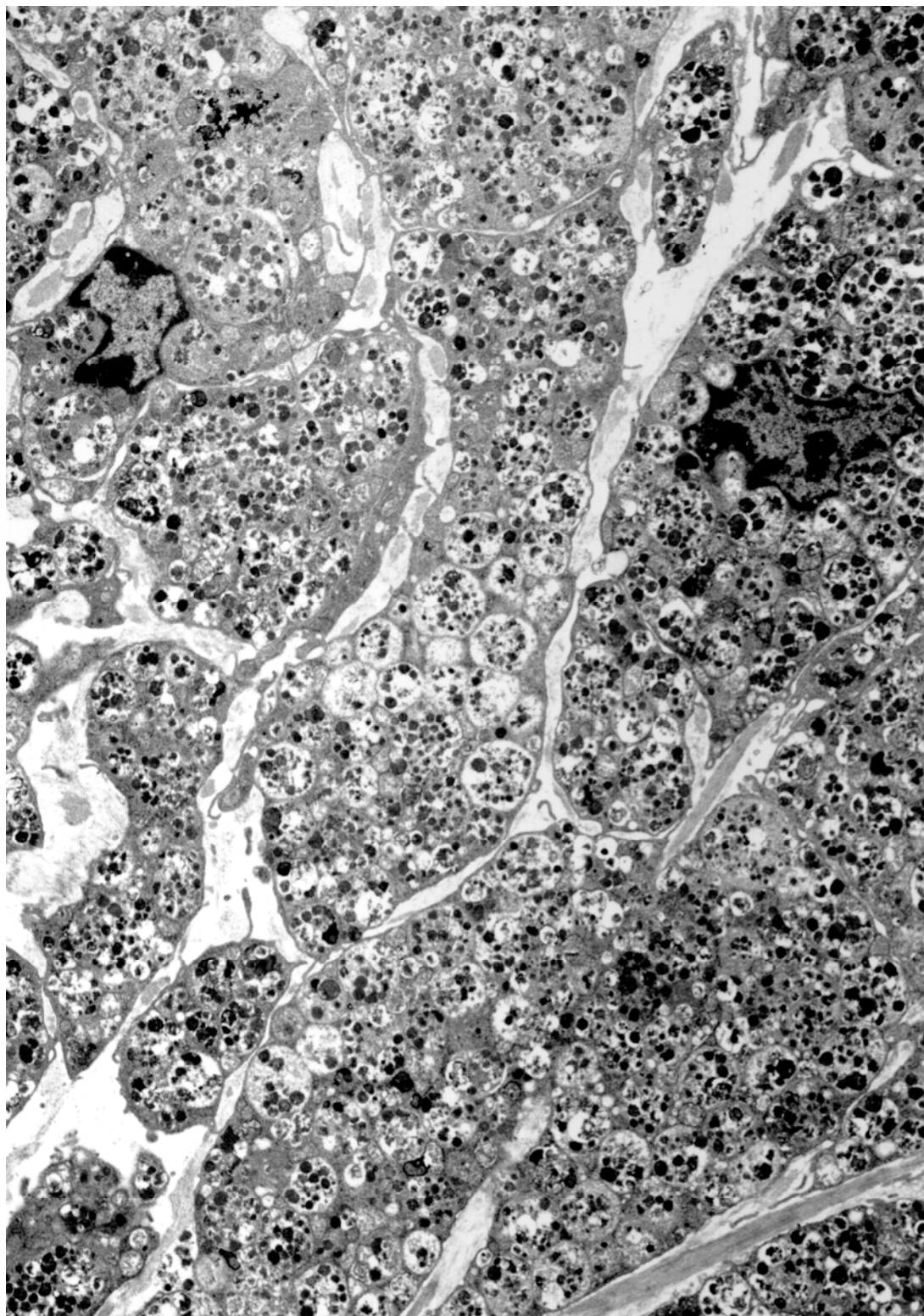
were not identified. Cytoplasmic organelles were difficult to evaluate because of the abundant number of secondary lysosomes. The neoplastic cells were separated by electron lucent spaces and extracellular bundles of fine fibrils.

Contributor's Morphologic Diagnoses: Lung mass: Granular cell tumor.

Contributor's Comment: Granular cell tumor (GCT) has been reported to occur in multiple species, including horses.^{2,6,8} In the horse GCT occurs primarily in the lungs.⁸ Similar to the horse of the current case, affected horses may be dyspneic and may be misdiagnosed with allergic airway disease. GCT in horses typically presents as single to multiple masses that may obstruct airways. Masses protruding into the airways can be visualized and sampled via endoscopic examination of the bronchial tree. The clinical course is typically benign, and in the current case surgical excision of the affected lung was curative.

The exact cell of origin of GCTs is not known.^{1,3,6,8} Morphologic and immunohistochemical analyses of a variety of GCTs in multiple species suggest that at least some GCTs may be of neural origin (Schwann cells, neuroectoderm).^{6,7} The cell of origin may depend on where in the body the tumor originated. Immunohistochemistry was not performed in the current case.

The ultrastructural features of GCT are similar across species.^{1-3,6-8} The main morphologic finding is that of neoplastic cells with abundant amounts of secondary ly-



3-3 Lung, warmblood mare. Granular cell tumor. Transmission electron micrograph courtesy of Eli Lilly and Company, Lilly Research Laboratories, Greenfield, IN 46140

osomes containing granular to membranous to amorphous material. The contents likely are remnants of degraded organelles and cell membranes (autophagosomes). In the current case a few lysosomes were found to contain degraded mitochondria. Cell-cell junctions, basal lamina, extracellular collagen, and angulate bodies are variably present in GCTs of animals and humans; however, in the current case cell-cell junctions, basal lamina, and angulate bodies were not identified. The amounts of collagen was minimal (not present in the submitted micrograph). The identity of the extracellular finely fibrillar material present in the current case is not known but may be a product of the neoplastic cells.

AFIP Diagnosis: Lung (per contributor): Granular cell tumor, Warmblood (*Equus caballus*), equine.

Conference Comment: In the horse, granular cell tumors (GCTs) are found primarily within the lower trachea and bronchi as airway associated peri- and endobronchial tumors.^{4,8} They are often slow growing, benign neoplasms that over time may result in airway obstruction.⁴ GCTs can arise in any tissue, and some are thought to be of neuroectodermal origin. They are characterized by neoplastic cells containing abundant cytoplasm with numerous small, eosinophilic, PAS positive, diastase resistant, non-argyrophilic granules identified as secondary lysosomes or phagosomes (myelin figures) on transmission electron microscopy.^{4,8} Small secondary lysosome granules have been associated with active Golgi apparatus, while larger granules are characteristic of multivesicular autophagocytic vacuoles.⁸

Although granular cell tumors have been reported to occur in many locations, in dogs they generally occur in the oral cavity, particularly the tongue, while in rats they occur within the meninges and brain.⁶ They have also been reported in the reproductive tract of rodents and a rabbit.^{6,8}

Contributor: Eli Lilly and Company, Lilly Research Laboratories, Greenfield, IN 46140

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CASE IV - EM for AFIP (AFIP 3050834).

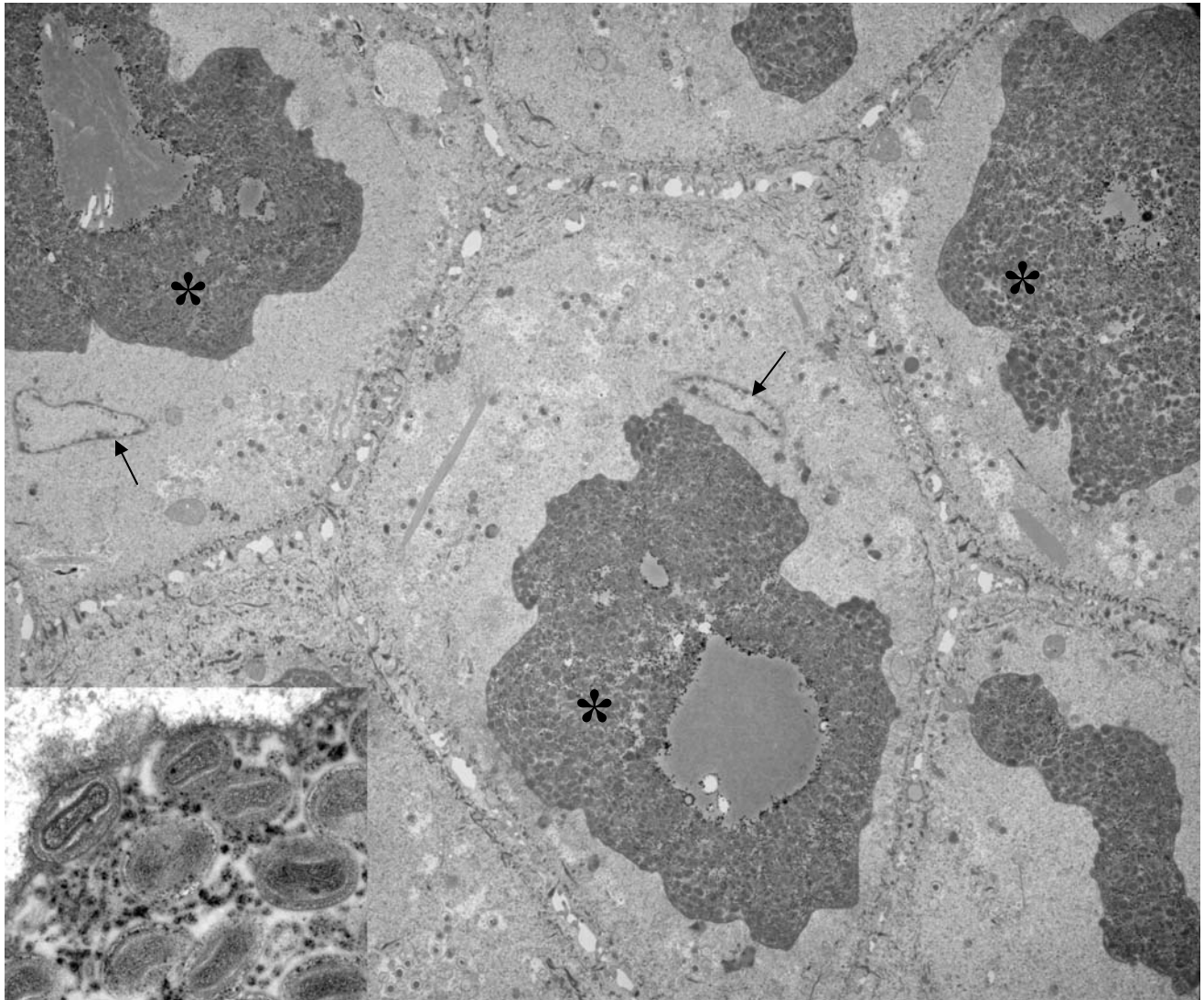
Signalment: Adult, male, rosy finch (*Leucosticte spp.*)

History: A wild-caught research flock of outdoor-housed rosy finches (*Leucosticte spp.*) captured in California and white-crowned sparrows (*Zonotrichia leucophrys*) captured in eastern Washington State presented during the winter of 2001 with history of periocular ulceration, pododermatitis and death.

Gross Pathologic Findings: Numerous birds had similar lesions that included proliferative and necrotizing palpebral dermatitis with conjunctivitis and/or fibrinonecrotic and proliferative stomatitis and glossitis. One rosy finch had a large (5-7mm) mass on the right wing. Numerous mites were noted within the feathers.

Laboratory Results (clinical pathology, microbiology, PCR, ELISA, etc.): The mites were not further characterized. *Candida albicans* and *Staphylococcus aureus* were cultured from the tongue.

Histopathologic Description: EM Skin of Wing (5,000X) (**Fig. 4-1**): Numerous polygonal cells with desmosomes, few discernable organelles consistent with



4-1. Skin, wing, rosy finch. Polygonal cells with desmosomes, few discernable organelles, and displaced and flattened nuclei (arrows). In each squamous cell, there is a large electron dense cytoplasmic inclusion body (*) that contains abundant virions.

Inset (60,000X): Enveloped virions approximately 300nm long with brick-shaped nucleocapsid and biconcave core consistent with pox virions. Transmission electron micrographs courtesy of Department of Comparative Medicine, School of Medicine, University of Washington, Seattle, WA 98195-7190

squamous epithelial cells, have displaced and flattened nuclei, loss of organelle detail, granular homogeneous cytoplasm and widened intercellular spaces. In each squamous cell, there is a large electron dense cytoplasmic inclusion body that contains abundant virions. **Fig. 4-1 Inset (60,000X):** Enveloped virions approximately 300nm long with brick-shaped nucleocapsid and biconcave core consistent with pox virions.

Contributor’s Morphologic Diagnosis:

Squamous epithelial degeneration, intra- and intercellular edema with single large intracytoplasmic inclusion bodies composed of virions consistent with pox.

Contributor’s Comment:

The gross, histological lesions are consistent with avipox infection that was confirmed by electron microscopy. Several strains of poxvirus infect a variety of avian hosts including passerines.

Transmission is via direct contact, ingestion or mechanical vectors such as mosquitoes or other insects. Pox infection results in cutaneous necroproliferative lesions (cutaneous form or dry pox) and/or fibrinonecrotic and proliferative lesions affecting the mucous membranes of the upper gastrointestinal and respiratory systems (diphtheritic form or wet pox). Both forms can cause significant morbidity by interfering with bodily functions. Secondary bacterial or fungal infections also increase morbidity and mortality. Songbirds are more commonly affected in the winter months as seen in this epornitic. Diagnosis is via gross and histological findings, electron microscopy, viral isolation serology and PCR. Distinctive microscopic findings include epithelial hyperplasia and enlargement of epithelial cells with the characteristic eosinophilic intracytoplasmic inclusion bodies (Bollinger bodies). Electron microscopy can confirm diagnosis by identifying 250 x 354 nm virions with a distinctive brick or dumbbell shape. The presumptive introduction of poxvirus into this research aviary was through the recently caught white-crowned sparrows. The stress of the capture may have exacerbated the infection and the mechanical vectors such as the mites, feather dander, and mosquitoes in the environment likely resulted in the spread of the infection to the finches. Vaccination of the remainder of the flock with a canary pox vaccine has reduced incidence of new disease.

AFIP Diagnosis: Skin, epithelium (per contributor): Intracytoplasmic inclusions, with mature virions, etiology consistent with poxvirus, rosefinch (*Leucosticte spp.*), avian.

Conference Comment: The Avipoxvirus genus contains many members that are mostly species-specific, although there are some that may cross over species, genus or family barriers.¹ Avipoxvirus strains vary in virulence and protective immunity appears to be strain specific.⁴ Characteristic histopathologic lesions of avipoxvirus infection include intracytoplasmic, eosinophilic inclusion bodies (Bollinger bodies) of the epithelial cells in the integument, respiratory tract, and oral cavity.¹ Transmission occurs primarily via inoculation, primarily through mos-

quitoes, although stable flies and blowflies have also been implicated.³

Three forms of the disease have been described: cutaneous form (dry pox), diphtheroid form (wet pox), and septicemic form.^{1,4} The cutaneous form is most commonly characterized by cutaneous proliferative lesions around the eyes, beak, nares, vent, and distal to the tarsometatarsus. It is the most common form of the disease in raptors and Passeriformes, but not the Psittaciformes.^{1,4} The diphtheroid form consists of multifocal to coalescing fibrinous and caseous lesions on the mucosa of the tongue, pharynx and larynx. Grossly, these lesions are similar to lesions caused by vitamin A deficiency, infectious laryngotracheitis, *Trichomonas gallinae*, *Capillaria* sp., and *Candida albicans*.¹ The septicemic form occurs most commonly in canaries and canary finch crosses, and is characterized by small pneumonic foci and hemorrhages, with cutaneous lesions occurring only rarely.¹ All three forms may occur simultaneously in the same individual.¹

Contributor: Department of Comparative Medicine, School of Medicine, University of Washington, Seattle, WA 98195-7190

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