The Armed Forces Institute of Pathology
Department of Veterinary Pathology
WEDNESDAY SLIDE CONFERENCE
2005-2006

CONFERENCE 2
21 September 2005

Conference Moderator: Sarah Hale, DVM, Diplomate ACVP
Experimental Pathology Laboratories, Inc.
Sterling, VA 20166

CASE I –04101477 (AFIP 2985398)

Signalment: 5-month-old, Jersey bull calf, *Bos taurus*

History: The animal was sick 3 months ago with pneumonia and high fever, with clinical improvement following antibiotic therapy. The animal began exhibiting clinical signs of CNS disease 4 days ago and was treated with antibiotics and Banamine. The animal has opisthotonus, increased salivation/foaming from the nose and mouth and is ataxic with a constant 104°C temperature. No other animals on the farm are affected. The patient was euthanized for necropsy evaluation.

Gross Pathology: The animal was in good nutritional condition. Bilaterally, the hock, fetlock, and pastern joints were swollen. The cranioventral regions of the lung lobes were light yellow and distended by gas (emphysema). The caudodorsal regions were pale red/purple and palpably meaty with marked accentuation of lobular pattern by edema of interlobular septa. The cut sections were diffusely dark red and wet. The hock, fetlock, and pastern joints contained moderate quantities of thick, stringy synovial fluid often admixed with white flakes. The synovial membrane of the right fetlock joint was prominent with edema. The renal cortices were diffusely wet with slightly raised bulging margins. There were no oral lesions observed.

Laboratory Results: PCR for MCF ovine herpesvirus-2 was positive. Pseudomonas sp. was cultured from the lungs and joints.

Histopathologic Description: Brain (cerebral hemisphere, hippocampus, brain stem and cerebellum) and spinal cord**:** The most conspicuous lesion in the brain sections is a severe vasculitis affecting predominantly meningeal blood vessels, but also affecting blood vessels that are embedded within deep regions of the brain. The

vessel walls are expanded and effaced by intense infiltrates of macrophages, lymphocytes and plasma cells. The inflammatory cells are admixed with a coagulum of homogenous eosinophilic material and cellular debris that obscures recognition of the tunics of the blood vessels. The tunica intima is often indiscernible due to the intense cellular infiltrate, but when seen, the endothelium is markedly hypertrophied. Rarely there are thrombi. Occasionally, there are random aggregates of macrophages, plasma cells and lymphocytes present in the neuropil. Although the inflammation involves all regions of the brain, lesions are most severe in the cerebellum. Similar inflammatory foci are present in the spinal cord at all anatomical levels (cervical, thoracic and lumbar). The kidney, testicles and adrenal glands exhibit a severe vasculitis of similar character with inflammation extending into the surrounding parenchyma of these organs.

Contributor's Morphologic Diagnosis: Brain; Meningoencephalitis with vasculitis, necrotizing, lymphoplasmacytic, histiocytic, multifocal, chronic, severe

Contributor's Comment: The necrotizing vasculitis of predominantly medium-sized arteries of multiple organs suggested a presumptive diagnosis of malignant catarrhal fever (MCF). Other differentials included BVD and idiopathic vasculitis. The presumptive diagnosis of MCF was further confirmed by a positive PCR test for ovine herpesvirus-2.

Malignant catarrhal fever (MCF) is a highly fatal, sporadic disease affecting several ruminant species including cattle, bison and all species of Cervidae except fallow deer. There are two forms of disease, wildebeest (WA-MCF) and sheep-associated form (SA-MCF). The WA-MCF is caused by alcelaphine herpesvirus-1 (AHV-1, formerly bovine herpesvirus-3) while SA-MCF is caused by ovine herpesvirus-2. Both of these viruses are cell-associated lymphotropic viruses and belong to the subfamily gammaherpesvirinae and genus *Rhadinovirus.*

WA-MCF primarily occurs in Africa and occasionally in zoological parks while SA-MCF is seen throughout North America, Europe, and Australia. The principle reservoir for WA-MCF is the blue or white-bearded wildebeest in which AHV-1 is asymptomatic. Wildebeest calves become infected during the first 2-3 months of life and shed cell-free AHV-1 in nasal and ocular secretions. Wildebeest are infected for life and transmit AHV-1 to their calves without showing clinical signs. The mucosa of the upper respiratory tract and/or tonsils is the most likely route of entry for AHV-1. Sheep are the reservoir for OHV-2, although goats can also be affected. Clinical signs of MCF are not observed in sheep and goats under natural conditions.

Both forms of disease can be transmitted with whole blood or lymphocytes but not cell-free filtrate. Viremia in WA-MCF usually starts about 7 days before the onset of fever and persists throughout the course of the disease. Virus replication occurs primarily in the lymphocytes, and the spleen and lymph nodes have high virus titers. There is wide variation in the presenting clinical syndromes; however,

consistent signs include lymphadenomegaly with ocular and oral disease and exudative dermatitis. There is edema of the eyelids, conjunctivitis, corneal opacity with occasional hypopyon and congestion of nasal and buccal mucosa. Photophobia may be accompanied by extensive lacrimation. Nervous signs present in some cases include head pressing, hyperesthesia, trembling, nystagmus and incoordination. Gastroenteritis with and without bloody diarrhea may occur in acute cases, especially in deer. Laryngeal, pharyngeal and rarely the tracheal mucosa may develop erosions and ulcers that are also covered by pseudomembranes. Erosions and ulcers may also involve the tongue, dental pad, the tip of buccal papillae, esophagus and forestomachs. The kidneys have foci of interstitial nephritis. The meninges are wet and cloudy.

The pathogenesis of the vascular lesion is not well understood. A lack of circulating antibody and viral antigen and absence of antigen-antibody complexes and complement in the vessel walls are inconsistent with an immune-mediated pathogenesis. In one study, the vascular lesions in the brains of a cow with acute MCF demonstrated that the predominant infiltrating cell type in these lesions was CD8(+) T lymphocytes and that large numbers of these cells were infected with ovine herpesvirus 2.

Antemortem diagnosis can be done by PCR for OHV-2 on buffy coats from whole blood (EDTA). PCR is both sensitive and specific. Serological tests are not reliable because some animals fail to seroconvert before death or convert later in the disease process. Virus isolation is not routinely performed because OHV-2 does not replicate in cell culture. There is no treatment and no effective vaccine available.

AFIP Diagnoses: Meninges; cerebrum: Vasculitis and perivasculitis, lymphohistiocytic, necrotizing, subacute, severe, Jersey, bovine.

Conference Comment: The contributor provides a good review of the two forms of malignant catarrhal fever (MCF), the clinical signs associated with the disease and the typical gross findings. Conference attendees focused their discussion on the histopathologic presence of a vasculitis, predominantly within the meninges, but also within the vessels of the brain, and on developing a differential diagnosis list. Other viral diseases which cause vasculitis in cattle and wild ruminants include bovine pestivirus (Bovine Viral Diarrhea), ovine orbivirus (Bluetongue), and adenoviral hemorrhagic disease. Common bacterial diseases include salmonellosis and thrombotic meningoencephalitis (TME) caused by *Histophilus somni* (formerly *Haemophilus somnus*). The differential diagnosis for erosive and ulcerative mucosal diseases in ruminants includes bovine pestivirus, ovine orbivirus, rinderpest, foot-and-mouth disease and vesicular stomatitis. The differential diagnosis for lymphoproliferative diseases includes enzootic bovine lymphosarcoma, caused by

bovine leukemia virus, Jembrana disease in Indonesia, caused by a lentivirus, and East Coast Fever in Africa, caused by the protozoan *Theileria parva*.

Malignant catarrhal fever is characterized by lymphoproliferation, vasculitis, and erosive-ulcerative mucosal and cutaneous lesions, predominantly affecting the respiratory and gastrointestinal systems. Corneal edema and lymphocytic uveitis often occur concomitantly and can help differentiate MCF from other ulcerative mucosal diseases.

Clinically, MCF can be divided into four overlapping categories:

The **head-and-eye form** is the most common and results in pyrexia, copious serous to mucopurulent ocular and nasal secretions, an encrusted muzzle with occluded nostrils, dyspnea, oral mucosal hyperemia with erosions, sloughed buccal mucosal tips, photophobia, conjunctival hyperemia, chemosis, corneal opacity and hypopyon.

The **peracute form** results in severe oral and nasal mucosal inflammation and hemorrhagic gastroenteritis.

The **intestinal form** is characterized by pyrexia, diarrhea, hyperemic oral and nasal mucosa with profuse catarrhal and mucopurulent discharge and generalized lymphadenopathy.

The **mild form** results in mild oral and nasal mucosal erosions.

The typical light microscopic findings associated with MCF include vascular and perivascular necrosis and lymphocytic and lymphoblastic infiltrates in all tissues. Ocular lesions include corneal edema with or without vascularization, erosions, ulcerations and lymphocytic uveitis and ophthalmitis. Kidneys may have infarcts and nonsuppurative interstitial nephritis. Lymph nodes may be severely edematous with ectatic lymphatics and lymphocytic and reticuloendothelial cell proliferation. Central nervous system findings include perivascular edema, nonsuppurative meningoencephalomyelitis and lymphocytic perivascular cuffing. Gastrointestinal tract lesions include congestion, mucosal erosion, abomasal ulcers and submucosal eosinophilic inflammation. Other potential findings include lymphocytic stomatitis and pharyngitis with erosions and ulcers, cutaneous edema, and lymphocytic ulcerative dermatitis.

Other ruminants in North America which can become clinically affected include deer, elk and bison.

Contributor: Department of Veterinary Pathobiology, Center for Veterinary Health Sciences, Oklahoma State University, www.cvm.okstate.edu

References:
1. Simon S, Li H, O'Toole D, Crawford TB, Oaks JL. The vascular lesions of a cow and bison with sheep-associated malignant catarrhal fever contain ovine herpesvirus 2-infected CD8(+) T lymphocytes. J Gen Virol. 2003; 84:2009-2013.
2. Barker IK, Van Dreumel AA, Palmer NC. The Alimentary System. In: Jubb KVF, Kennedy PC, Palmer NC, eds. Pathology of domestic animals. San Diego, CA: Academic Press; 1993:163-173.
3. Collins JK, Bruns C, Vermedahl TL, Schiebel AL, Jessen MT, Schultheiss PC, Anderson GM, Dinsmore RP, Callan RJ, DeMarini JC. Malignant catarrhal fever: polymerase chain reaction survey for ovine herpesvirus 2 and other persistent herpesvirus and retrovirus infections of dairy cattle and bison. J Vet Diagn Invest. 2000; 12:406-411.
4. Callan RJ, Van Metre DC. Viral diseases of the ruminant nervous system. Vet Clin North Am Food Anim Pract. 2004; 20:327-62.

CASE II – 2004AC328 (AFIP 2986830)

Signalment: Three year old, neutered male ferret

History: A purpose-bred sable ferret, maintained in a laboratory animal facility, presented for weight loss and dehydration. Physical examination was unremarkable and the ferret was treated with fluids and nutritional supplementation. Blood glucose was slightly elevated; otherwise, serum chemical analyses were within normal limits. Hematologic evaluation revealed that the white blood cell count, hemoglobin and platelet count were slightly increased. The differential was within normal limits. The condition continued to worsen and dyspnea was noted. Radiographs revealed a diffuse pulmonary interstitial pattern. Despite treatment, the ferret's condition continued to deteriorate. The ferret was euthanized.

Gross Pathology: Extensive multifocal lesions (about 1.5 mm in diameter) affecting all lung lobes were reported. The spleen contained similar lesions.

Contributor's Morphologic Diagnosis: Lung: Extensive, marked, pyogranulomatous pneumonia with intralesional yeast, consistent with *Blastomyces dermatitidis*.

Contributor's Comment: Similar, less extensive, inflammation with yeast present was also observed in the spleen from this animal. Other tissues were unavailable for examination.

Blastomycosis commonly results from inhalation of the mycelial phase of this dimorphic fungus from infected soil of an endemic area.[1] At body temperature, the organism assumes the yeast form and may cause an asymptomatic infection, pneumonia, or disseminated disease. Cutaneous infection is also possible through wound contact with infected soil. A case of focal blastomycosis in a veterinarian, associated with necropsy of an infected dog, has been reported.[2] Although not a contagious disease, outbreaks may be associated with exposure to a common environmental source. Within North America, the organism is prevalent in the Mississippi and Ohio River valleys. It is also present in Africa and Asia. Although different serotypes exist, *B. dermatitidis* is the species unique to the genus.

B. dermatitidis may infect a wide range of species, including human beings, dogs, horses, domestic and exotic cats, wolves, dolphins, sea lions, monkeys, prairie dogs, and bats. A least one other case of blastomycosis in a ferret is documented in the literature.[3] Blastomycosis has also been described in a laboratory animal (Rhesus monkey) without recent contact with soil.[4] In that case, as in this one, subclinical infection was presumed to have occurred prior to introduction to the facility, with subsequent exacerbation.

AFIP Diagnosis: Lung: Pneumonia, pyogranulomatous, diffuse, severe, with yeast, etiology consistent with *Blastomyces dermatitidis*, ferret, mustelid.

Conference Comment: Conference attendees identified the yeast as *Blastomyces dermatitidis* by its characteristic "broad-based budding," its size of 10-20 μm diameter and its double-contoured, 1-2 μm thick wall. Discussion centered on differentiating *Blastomyces dermatitidis* from the other common fungal causes of systemic or deep mycoses. Below is a simple chart to help with identification of the common systemic mycoses.

Common Systemic (Deep) Mycoses

Yeast	Size	Wall or Capsule	Reproduction
Blastomyces dermatitidis	5-25 µm in diameter	double-contoured, refractile	Broad-base budding
Cryptococcus neoformans	5-20 µm in diameter	2-8 µm thick mucopolysaccharide carminophilic capsule	Narrow-base budding
Histoplasma capsulatum	*var. capsulatum* 2-5 µm in diameter *var. duboisii* 8-15 µm in diameter	thin cell wall; no capsule	Narrow-base budding
Coccidioides immitis	Spherules 20-200 µm in diameter	double-contoured, refractile	Endosporulation

There are three clinical forms of blastomycosis:

1. Primary **pulmonary infection** is most common.
2. The **disseminated** form can involve the eyes, bone, skin, lymph nodes, subcutaneous tissues, external nares, brain and testes.
3. Local **cutaneous infection** follows traumatic implantation.

The pulmonary form occurs when spores are inhaled and deposited in the alveoli of the host. Alveolar macrophages phagocytose the spores which develop into the yeast form and multiply. Macrophages rupture and release the yeast initially inciting a neutrophilic response which progresses to granulomatous pneumonia.

Typical clinical signs include: fever, weight loss, anorexia, dyspnea, chronic cough, ocular and nasal discharge, swollen joints and lameness, lymphadenopathy and draining lymph nodes, blindness, and enlarged testicles. Clinical pathology findings can include neutrophilic leukocytosis, nonregenerative anemia (anemia of chronic disease), lymphopenia, decreased serum albumin, increased alpha2 globulins and hypercalcemia.

Blastomycosis affects primarily dogs but has also been reported in humans, non-human primates, cats, horses, hamsters, bottlenose dolphins, sea lions, a ferret and an African lion.

Contributor: Abbott Laboratories, Department of Pathology, AP13A/R 469, 100 Abbott Park Road, Abbott Park, IL 60064

References:

1. Dungworth DL. The Respiratory System. In: Jubb KVF, Kennedy PC, Palmer N, eds. *Pathology of Domestic Animals, Volume 2.* New York, NY: Academic Press, Inc.; 1993:667.
2. Graham WR, Callaway JL. Primary inoculation blastomycosis in a veterinarian. *J Am Acad Dermatol*. 1982;7:785-786.
3. Lenhard A. Blastomycosis in a ferret. *J Am Vet Med Assoc.* 1985;186:70-72.
4. Wilkinson LM, Wallace JM, Cline JM. Disseminated blastomycosis in a Rhesus monkey (*Macaca mulatta*). 1999;36:460-462.
5. Arceneaux KA, Taboada J, Hosgood, G. Blastomycosis in dogs: 115 cases (1985-1995). *J Am Vet Med Assoc* 1998;213:658-664.
6. Legendre AM. *Infectious Diseases of the Dog and Cat*. Philadelphia, PA: WB Saunders; 1998.
7. Lopez A, Respiratory System, Thoracic Cavity, and Pleura, In: McGavin MD, Carlton WW, Zachary JF, 3rd ed. *Thomson's Special Veterinary Pathology*. St. Louis, MO: Mosby; 2001.

CASE III – 760-05 (AFIP 2985446)

Signalment: 8 year old, male castrate, Boxer dog (*Canis familiaris*).

History: This dog presented with a 4-week history of aphonia attributed to a right laryngeal mass. Physical examination revealed a laryngeal mass arising from the right larynx. Computed tomography (CT) scans revealed a contrast enhancing mass involving the right larynx that extended into the adjacent musculature laterally and craniodorsally. Regional lymph nodes appeared to be within normal limits. *En bloc* resection of the mass via laryngectomy was performed two weeks after initial presentation.

Gross Pathology: A 2.0 x 1.0 x 1.0 cm, pale tan to orange, circumscribed, smooth-surfaced, raised, ovoid mass was observed arising from the right ventrolateral surface of the right vocal fold. The mass projected into and occluded the right lateral laryngeal ventricle, and resulted in mild right lateral occlusion of the laryngeal vestibule and rima glottis (Figures 1, 2, 3 and 4).

Laboratory Results: Immunohistochemistry was performed on sections of the mass. There was strong immunoreactivity to vimentin (Figure 10) and moderate immunoreactivity to desmin (Figure 11). There was no immunoreactivity to cytokeratin AE1/AE3, pan-actin, smooth muscle actin, CD3, and CD79.

Histopathologic Description: There was a focally extensive, expansile, nonencapsulated, circumscribed mass within the right vocalis muscle (Figure 5). The mass comprised of sheets, lobules, and packets of cells supported by scant fibrovascular stroma (Figure 6). The cells were large and pleomorphic (ovoid, polygonal, spindle, strap-like) with well defined borders and moderate to large amounts of finely granular, deeply eosinophilic cytoplasm (Figure 7). A small proportion (5 to 15%) of cells contained many uniformly-sized, 1 to 4 micron diameter, clear, round intracytoplasmic vacuoles (Figure 8). PTAH-stained sections of the mass did not reveal cross-striations within the cytoplasm of the cells (not submitted). The nuclei were pleomorphic with finely stippled chromatin, single to multiple prominent basophilic nucleoli, and rare large, glassy, eosinophilic, cytoplasmic invaginations consistent with pseudoinclusions (Figure 9). Less than 1 mitosis per ten 400X fields was noted. A few cells were binucleated. There was marked anisocytosis and anisokaryosis (up to 3 fold). Moderate to large numbers of neutrophils, lymphocytes and plasma cells were scattered throughout the mass, along with moderate amounts of hemorrhage and fibrin deposition. The inflammation extended multifocally into surrounding skeletal muscle tissue and into overlying propria-submucosa, which was also mildly edematous. There was multifocal ulceration of overlying mucosa. There was moderate central osseous

metaplasia of neighboring laryngeal cartilage. The mass did not extend beyond the natural tissue planes defined by neighboring laryngeal cartilage.

Contributor's Morphologic Diagnosis: Laryngeal rhabdomyoma.

Contributor's Comment: Rhabdomyomas and rhabdomyosarcomas are neoplasms of striated muscle. In humans and domestic animals, rhabdomyomas occur less commonly than their malignant counterparts.[1] Striated muscle neoplasms can be divided into two main groups (cardiac and extra-cardiac) based on anatomical location.

Cardiac striated muscle neoplasms are rare. *Cardiac rhabdomyomas* have been reported mostly in young animals in pigs, sheep, cattle, dogs and a fallow deer.[1,2,3] There is a general consensus that cardiac rhabdomyomas represent a congenital developmental abnormality (i.e., hamartoma) of cardiac muscle.[1,2,3] *Cardiac rhabdomyosarcomas* are extremely rare, and there are only a few cases reported in dogs.[1] Since mature cardiac muscle does not retain the capacity for cell division under normal conditions, cardiac rhabdomyosarcomas are thought to arise from undifferentiated mesenchymal cells in the heart that retain the capacity to differentiate into striated muscle.[1]

Classification of extra-cardiac rhabdomyomas is similar in humans and animals, and is loosely based on age of occurrence and location[1]:

1. *Adult rhabdomyomas* occur in older individuals. In humans and animals, these tumors occur in the head or neck region as either lingual, pharyngeal, laryngeal, or subcutaneous masses.[1] There is a predisposition in males.[1] These neoplasms have been very rarely reported in dogs, cats, and horses, with the exception of laryngeal rhabdomyomas in dogs, which are relatively more common.[1]

2. *Fetal rhabdomyomas* occur in younger individuals. In humans, these tumors occur as subcutaneous masses in the head or neck.[1] There is a predisposition in males.[1] There is only one report in the veterinary literature of a congenital fetal rhabdomyoma occurred as a ventral cervical subcutaneous mass in an Appaloosa filly.[4]

3. *Genital rhabdomyomas* occur in the vagina or vulva of young to middle-aged humans.[1] Examples of this type of rhabdomyoma have not been reported in the veterinary literature.

Classification of extra-cardiac rhabdomyosarcomas is also similar in humans and animals[1]:

1. *Embryonal rhabdomyosarcoma* is the most common variant in humans and animals. Microscopically, they may present as either relatively primitive round myoblasts arranged in a compact fashion, or myotubular myoblasts embedded in myxoid matrix.[1,2] These have been reported in dogs, cats, pigs, cows, and birds, without obvious sex, age or site predilection.[1] A special variant of embryonal rhabdomyosarcoma is the *botryoid rhabdomyosarcoma*, which is a distinct entity in dogs (especially Saint Bernards) that affects the urinary bladder. [1,2] These are myotubular-type neoplasms that are grossly polypoid, botryoid ("grape-like") and exophytic masses which project into the urinary bladder lumen. [1,2] Similar botryoid rhabdomyosarcomas have been reported in two fillies, affecting the urinary bladder and the uterus respectively.[1,2]

2. *Alveolar rhabdomyosarcoma* is characterized microscopically by poorly-differentiated, round myoblasts supported by fairly dense fibrovascular septae.[1] The alveolar appearance is due to central degeneration, necrosis, and loss of the cells, resulting in a clear central area surrounded by myoblasts that line the fibrovascular septae.[1] These tumors are infrequently reported in the veterinary literature (dogs, horses and cows) without observed sex, age, or site predilection.[1]

3. *Pleomorphic rhabdomyosarcoma* is the least commonly reported variant in humans and animals, characterized microscopically by pleomorphic myoblasts without any similarities to the embryonal or alveolar variants.[1] These have been reported in dogs and horses.[1]

The diagnosis of rhabdomyomas and rhabdomyosarcomas is often difficult on light microscopy. Distinctive features of striated muscle may not be evident microscopically (i.e., cytoplasmic cross striations on H&E and PTAH stained sections); however, if present, they are reliably diagnostic. [1,2] Another feature of many tumors of myoid origin is the presence of eosinophilic granular cytoplasm, which may contain intracytoplasmic glycogen that is demonstrable on PAS staining.[1,2,3]

Transmission electron microscopy is useful for demonstrating specific ultrastructural characteristics of striated muscle, such as actin and myosin filaments that are organized into parallel myofibrils with electron dense Z-bands.[1,5,6] Other common but nonspecific ultrastructural features of striated muscle neoplasms include the presence of numerous mitochondria (often arranged between myofibrils), large euchromatic nuclei (sometimes possessing intranuclear

cytoplasmic invaginations, or "pseudoinclusions"), numerous ribosomes (many arranged as polyribosomes), and accumulation of glycogen.[1,5,6]

Immunohistochemistry is often useful in diagnosing striated muscle neoplasms, which are typically immunoreactive for vimentin, desmin, muscle specific actin, sarcomeric actin, and myoglobin, with no immunoreactivity to cytokeratin and smooth muscle actin.[1,2,6,7] However, this immunohistochemical profile is not always consistent, and is dependent on the degree of differentiation of the neoplastic cells – for example, in normal developing muscle, the order of protein expression is as follows: vimentin, desmin, myosin, and myoglobin.[1]

Canine laryngeal rhabdomyoma and rhabdomyosarcoma is a rare distinct entity in dogs. Although most are histologically benign, they may cause death or result in euthanasia due to laryngeal obstruction.[1,5,6,7] Affected dogs typically present with dysphonia, aphonia, stridor, and dyspnea.[1,5,6,7] A few cases have been reported to be locally invasive, with one case report of hepatic metastasis after surgical resection.[1] Due to the limited number of cases, age, sex and site predilection have not been recognized. Canine laryngeal rhabdomyoma and rhabdomyosarcoma have been reported as laryngeal oncocytoma in the past.[1,5,6] Although histologically similar, many of these reported cases of oncocytoma were found to be striated muscle in origin, based on immunohistochemical labeling.[1,6] This is in contrast to true oncocytes (such as those found in renal oncocytomas and salivary gland oncocytomas), which are epithelial in origin.

In this case, the dog is alive 3 months post laryngectomy with no recurrence of the laryngeal rhabdomyoma.

AFIP Diagnosis: Skeletal muscle, laryngeal: Rhabdomyosarcoma, Boxer, canine.

Conference Comment: The contributor provides a thorough review of the classification of both rhabdomyomas and rhabdomyosarcomas. There was slight variation in slides among the conference attendees with some sections demonstrating infiltration of the neoplastic cells into the adjacent laryngeal muscle and fibrous connective tissue. In some sections, neoplastic cells have atypia characterized by round nuclei, prominent nucleoli and cytoplasmic invaginations. The diagnosis of rhabdomyosarcoma is based on the atypia, infiltration at the margins, which produces islands of neoplastic cells separated from the main mass, and the fairly high (2-3/hpf) mitotic rate.

Throughout the neoplasm is an extracellular, eosinophilic, homogenous material which separates neoplastic cells and resembles amyloid, prompting a differential diagnosis among conference participants of extramedullary plasmacytoma. The material stains with Periodic Acid Schiff (PAS); however, Congo Red results are

equivocal. Interestingly, media from rhabdomyosarcoma cell cultures has stimulated *in vitro* aggregation and fibrillization of amyloid beta-protein (8).

Contributor: The Department of Pathology, The Animal Medical Center, 510 East 62nd Street, New York NY 10021, www.amcny.org

References:

1. Cooper BJ, Valentine VA. Tumors of Muscle. In: Meuten DJ, ed. *Tumors of domestic animals*. Ames, IA: Iowa State Press; 2002.
2. Hendrick MJ, Mahaffey EA, Moore FM, Vos JH, Walder EJ, eds. *Histologic classification of mesenchymal tumors of skin and soft tissues of domestic animals (Second series, Volume II).* Washington D.C: Armed Forces Institute of Pathology; 1998.
3. Kolly C, Bidaut A, Robert N. Cardiac rhabdomyoma in a juvenile fallow deer (*Dama dama*). *J Wildl Dis*. 2004;40(3):603-606.
4. Meyerrholz DK, Caston SS, Haynes JS. Congenital fetal rhabdomyoma in a foal. *Vet Pathol*. 2004;41(5):518-520.
5. Liggett AD, Weiss R, Thomas KL. Canine laryngopharyngeal rhabdomyoma resembling an oncocytoma: light microscopic, ultrastructural, and comparative studies. *Vet Pathol*. 1985;22(6):526-532.
6. Meuten DJ, Calderwood Mays MB, Dillman RC, Cooper BJ, Valentine BJ, Kuhajda FP, Pass DA. Canine laryngeal rhabdomyoma. *Vet Pathol*. 1985;22(6):533-539.
7. O'Hara AJ, McConnell M, Wyatt K, Huxtable C. Laryngeal rhabdomyoma in a dog. *Aust Vet J*. 2001;79(12):817-821.
8. Chauhan A, Chauhan VP, Rubenstein R, Wegiel J, Wisniewski HM. Media from rhabdomyosarcoma and neuroblastoma cell cultures stimulate in vitro aggregation and fibrillization of amyloid beta-protein. *Neurochem Res*. 1997; Feb;22(2):227-32.

CASE IV – CSU05-06#2 (AFIP 2985207)

Signalment: 8 month-old, male castrated, Persian, feline.

History: Cat presented with a sudden onset of neurological signs including: circling, disorientation, head pressing, muscle tremors, focal seizures and visual deficits. Blood chemistry revealed a low BUN, creatinine, total protein and albumin and increased bile acids. No shunts were identified grossly during abdominal exploratory. The cat was euthanized due to a worsening condition and poor prognosis.

Gross Pathology: Necropsy findings revealed a diffusely yellow, small and firm liver.

Laboratory Results: Brain: Predominately within the white matter, optic nerve tracts and less in the gray matter there are extensive areas of spongiform vacuolar degeneration and multifocal neuronal necrosis. Spongiform change is characterized by variably sized (7-200 micron in diameter), often coalescing, clear, distinct, round to oval vacuoles within the neuropil. Numerous blood vessels within affected areas are prominent with plump endothelial cells and are surrounded by an increased clear space that contains small amounts of eosinophilic proteinaceous fluid (edema) and variable numbers of neutrophils, lymphocytes, plasma cells and macrophages. Multifocally, within the meninges, there are variable accumulations of perivascular neutrophils with fewer numbers of lymphocytes and plasma cells.

Liver: There is a bridging midzonal pattern of hepatocytes that are expanded 2-3 times normal size by single or multiple, variably sized, clear, discrete cytoplasmic vacuoles which often peripheralize and flatten the nucleus (lipid). Diffusely sinusoids are collapsed. Portal areas contain moderate arteriolar hyperplasia with smooth muscle hypertrophy, variable biliary hyperplasia and patchy lymphoplasmacytic inflammation and scant hemorrhage.

Contributor's Morphologic Diagnosis: 1/Brain: a/White matter: Spongiform vacuolar degeneration, multifocally extensive, moderate with myelinolysis and neuronal necrosis. b/Meninges: Meningitis, suppurative, acute, patchy, moderate.

2/Liver: Hepatic lipidosis, midzonal, bridging, and moderate with arteriolar hyperplasia and smooth muscle hypertrophy.

Contributor's Comment: The histologic changes in the brain are consistent with hepatic encephalopathy. The cause of the liver failure is unknown but is most consistent with a toxic insult.

A number of theories have been proposed to explain the pathogenesis of hepatic encephalopathy. Patients develop an alteration in brain energy metabolism coupled with increased permeability of the blood brain barrier that facilitates the passage of neurotoxins into the brain. Neurotoxins include short chain fatty acids, mercaptans; false neurotransmitters such as tyramine, octopamine, and beta phenylethanolamines; ammonia and gamma-aminobutyric acid.

Hyperammonemia is a critical, although not the sole factor in the development of hepatic encephalopathy. Ammonia is produced in the gastrointestinal tract by bacterial degradation of amines, aminoacide, purines and urea. In a healthy liver, ammonia is detoxified by conversion of urea and glutamine. With liver disease, there is inefficient conversion of ammonia and

increased levels of ammonia can enter the systemic blood supply by portal shunts (1,3). In the brain, astrocytes are responsible for ammonia detoxification by conversion of glutamate to glutamine. When ammonia is high in the brain, it is thought that the accumulation of glutamine in the astrocytes causes swelling of the astrocyte (Type II astrocytosis) resulting in dysfunction of the astrocyte itself and brain edema (1,3).

Another hypothesis involves gamma-aminobutyric acid (GABA) which is a neuroinhibitory neurotransmitter produced in the gastrointestinal tract by bacteria. In liver disease there is an increase in the number of GABA complex receptors (2,3). When GABA crosses the increasingly permeable blood brain barrier it interacts with the GABA receptor complex leading to inhibitory nerve transmission. Benzodiazepines and barbiturates can bind to the GABA receptor complex and act in a similar fashion (2,3).

In liver disease, there is a shift from branched chain amino acids to aromatic amino acids (phenylalanine, tyrosine and tryptophan) which are neurotoxic, with decreased hepatic clearance. Aromatic amino acids are precursors for neurotransmitter synthesis. When levels are high within the brain, other substances such as tyramine, octopamine and phenylethanolamines are produced that act as false neurotransmitters (2,3). These substances compete with the normal neurotransmitters for the same receptor.

AFIP Diagnoses: 1. Brain, cerebral white matter: Spongiform change, multifocal, mild, Persian, feline.
2. Brain, cerebral cortex: Necrosis, multifocal, with mild gliosis, and acute meningitis.
3. Liver, hepatocytes: Degeneration, with vacuolar change (fatty type), midzonal, diffuse, moderate.
4. Liver: Portal venous hypoplasia and arteriolar reduplication, diffuse, moderate.

Conference Comment: This is a very complex case with no clear answers. The contributor provides an excellent review of the pathogenesis of hepatic encephalopathy. There was variation in brain sections among conference attendees. Some brain sections had intense perivascular neutrophilic infiltrates in both the meninges and cerebral cortex, with reactive changes in the associated vessels, all features characteristic of sepsis. Several slides had areas of liquefactive necrosis with occasional neutrophils predominantly within the grey matter of the cerebral cortex. The multifocal, and seemingly random, cerebral cortical necrosis with gliosis (predominantly gemistocytic astrocytes) could reasonably be secondary to vascular impairment. Gram stains did not identify bacteria within necrotic areas or the meninges; however, this does not eliminate sepsis as a possible cause.

The presence of Alzheimer type 2 cells are a consistent finding in human and equine patients with hepatic encephalopathy; however, they are not a consistent feature in several other species, including cats. Alzheimer type 2 cells are astrocytes with a swollen, vesicular nucleus and swollen cytoplasm caused by accumulation of ammonia or other endogenous toxins (4). Alzheimer type 2 cells were not identified in the examined sections of brain.

This cat's brain has lesions consistent with hepatic encephalopathy, such as white matter spongiosis; however, it also has lesions which are not consistent with hepatic encephalopathy, such as neutrophilic inflammation and cortical necrosis.

Midzonal fatty degeneration of the liver is uncommon in domestic animals and is most likely due to a toxin. Midzonal degeneration and necrosis has been reported in cats exposed to hexachlorophene (5). Incidentally, cats exposed to hexachlorophene have been shown to develop spongiosis of the white matter and exhibit behavioral changes (6).

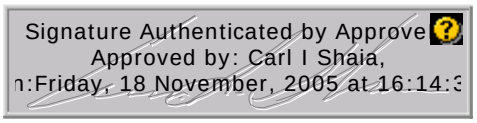
To complicate this case even further, there is arteriolar reduplication within sections of liver supporting the presence of a shunt or some form of hepatic microvascular dysplasia.

Clinical pathology and toxin screening results are not available but could help in further defining the underlying cause for this cat's interesting lesions.

Contributor: Colorado State University – Department of Microbiology, Immunology, and Pathology,1619 Campus Delivery, Fort Collins, CO 80523

References:

1. Jalan R, Shawcross D, Davies, N. The molecular pathogenesis of hepatic encephalopathy. *IJBCB.* 2003; 35: 1175-1181.
2. Katayama K. Ammonia metabolism and hepatic encephalopathy. *Hepatology Research.* 2004; 30S: S71-S78.
3. Gerber T, Schomerus H. Hepatic encephalopathy in liver cirrhosis: pathogenesis, diagnosis and management. *Drugs.* 2000; 60: 1353-1370.
4. Jubb KVF, Huxtable CR, The Nervous System. In: Jubb KVF, Kennedy PC, Palmer N, eds. *Pathology of Domestic Animals*. New York, NY: Academic Press, Inc.; 1993:305.
5. McGavin DM, Carlton WW, Zachary JF: *Thomson's Special Veterinary Pathology*, 3rd ed. pp.96-97. Mosby, 2001.
6. Thompson JP, Senior DF, Pinson DM, Moriello KA. Neurotoxicosis associated with the use of hexachlorophene in a cat. J Am Vet Med Assoc. 1987;190:1311-1312.



Carl I. Shaia, DVM
Major, Veterinary Corps, U.S. Army
Wednesday Slide Conference Coordinator
Department of Veterinary Pathology
Armed Forces Institute of Pathology
Registry of Veterinary Pathology*

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