



WEDNESDAY SLIDE CONFERENCE 2008-2009

# Conference 24

6 May 2009

Conference Moderator:

Dr. Thomas P. Lipscomb, DVM, Diplomate ACVP

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## CASE I – 06N802 (AFIP 3105941)

**Signalment:** 3-year-old, gelding, quarter horse, (*Equus caballus*) equine

**History:** The patient presented with muscle fasciculations, hyperhidrosis, tachycardia (88 bpm) and tachypnea. The temperature was within normal limits and capillary refill time was prolonged. ECG revealed sinus tachycardia. Laboratory abnormalities included mild thrombocytopenia, azotemia (creatinine 4.8), hyperglycemia (glucose 483), hypokalemia (K 3.0), hyponatremia (Na 120), hypochloremia (Cl 81), hyperbilirubinemia (4.6) and elevated CK (5050) and AST (927).

**Gross Pathology:** An adult quarter horse gelding (500 kg) in good flesh with mild postmortem autolysis is presented for necropsy. The cranioventral lungs, representing approximately 20% of the lung parenchyma, are sharply demarcated, dark green, and consolidated with marked expansion of the interlobular spaces by edema and yellow friable material (fibrin). The trachea and bronchial airways are filled with white foam; clear fluid oozes from the cut section. The remaining lung tissue is rubbery and partially collapsed. The cranioventral pulmonary

pleura is covered by a thin layer of brown friable material (fibrin). The pericardial sac contains ~ 200 mls of dark yellow fluid. There is pale tan streaking throughout the myocardium of the ventricular free wall and the interventricular septum; the left ventricular free wall appears most severely affected. This discoloration affects greater than 40% of the myocardium. The liver is mildly firm and has an accentuated lobular pattern. There are several dozen subcapsular hemorrhages in both kidneys. Approximately 40% of the glandular stomach is thickened and hyperemic; about half of this area is covered by a fibrinous pseudomembrane. The stomach contains grain and hay/grass ingesta. The small colon contains formed feces. Urine is clear and yellow. There is mild edema of the lamina of P3 in the right front and left rear feet.

### Laboratory Results:

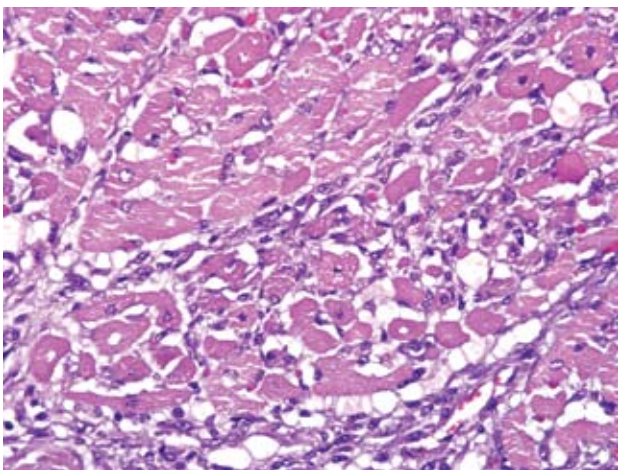
Mild thrombocytopenia  
Azotemia (creatinine 4.8)  
Hyperglycemia (glucose 483)  
Hypokalemia (K 3.0)  
Hyponatremia (Na 120)  
Hypochloremia (Cl 81)  
Hyperbilirubinemia (4.6)  
Elevated CK (5070)  
Elevated AST (927)

**Histopathologic Description:** Heart: Multifocal myocardial degeneration and necrosis are present within multiple sections of heart, affecting approximately 25% of the myocardium. The change is characterized by loss of myocardial cross striations, fragmentation, and vacuolation of myocardial cytoplasm, and nuclear pyknosis and karyolysis (**Fig. 1-1**). Sarcolemmal sheaths are collapsed, satellite cell nuclei are plump and closely arranged, and there are moderate numbers of macrophages with fewer lymphocytes and occasional neutrophils in the affected areas. Perivascular supporting tissues and tissues surrounding Purkinje cells are expanded by edema fluid or finely granular, basophilic, loose mucinous material.

**Contributor's Morphologic Diagnosis:** Heart: Myocardial degeneration and necrosis, severe, multifocal to coalescing, subacute, quarter horse, *Equus caballus*

**Contributor's Comment:** This horse is one of several that died or were euthanized after being given clenbuterol. In addition to the myocardial necrosis, the horse had varying degrees of skeletal muscle necrosis in different muscle groups. High levels of clenbuterol were found in this horse's serum the day after dosing, and clenbuterol overdose is believed to be responsible for the clinical signs of muscle fasciculation, tachycardia, and hyperhydrosis seen at presentation, as well as for the skeletal and cardiac muscle degeneration and necrosis seen grossly and histologically.

Clenbuterol is a beta-2 sympathomimetic, with most of the pharmacologic activity coming from the levo form.<sup>4</sup> The drug is used as a bronchodilator in horses and non-lactating cattle at a recommended dosage of 0.8 micrograms per



1-1. Myocardium, horse. Multifocally, cardiac myocytes are degenerative or necrotic, and are often replaced by moderate numbers of histiocytes, lymphocytes, and fibroblasts. (HE 400X)

kilogram of body weight.<sup>4</sup> Excretion is primarily via urine as unmetabolized clenbuterol. Four studies have shown that clenbuterol induces myocardial necrosis in laboratory rats<sup>1,2</sup>, although a recent study of the relative myotoxicity of clenbuterol versus other beta agonists showed that clenbuterol is less myotoxic than fenoterol, another beta-2 sympathomimetic.<sup>3</sup>

In this case, further history revealed a questionable source of clenbuterol that, when tested at the LSU Analytical Systems Laboratory, contained 67.4 times the FDA approved level of the drug. The bottle was labeled "Clenbuterol HCl, 72.5 mcg/ml, 0.5 ml/100lb," but actually contained 5.0 mg/ml instead of the labeled 72.5 mcg/ml, or 0.0725 mg/ml. The horse was given clenbuterol from this bottle five days prior to euthanasia.

**AFIP Diagnosis:** Heart, left ventricle: Myocardial degeneration and necrosis, multifocally extensive, moderate, with histiocytic and lymphocytic myocarditis and fibroplasia

**Conference Comment:** Catecholamines and catecholamine receptor agonists are believed to cause myocardial necrosis in various settings including "brain-heart syndrome," pheochromocytoma and sympathomimetic drug overdoses. Numerous toxins cause myocardial necrosis as well.

Ionophore toxicity occurs in horses and other monogastrics that are mistakenly fed coccidiostats used in ruminant and poultry feed.<sup>4</sup>

Cardiac glycosides are found in several different plants in various parts of the world, and ingestion often causes death within a few hours with little to no gross or histologic footprint.<sup>4</sup> These glycosides inhibit the sodium-potassium ATPase pump causing a disruption in ion concentration and membrane potential leading to muscle necrosis.<sup>4</sup> Diagnosis is often based on discovery of the offending plant in the gastrointestinal system or circumstantial evidence.<sup>4</sup>

Some toxic alcohols, such as gossypol and tremetol, can cause myocardial necrosis. Gossypol, often found in cottonseed meal used as a protein supplement in feed, causes myocardial necrosis in young ruminants, pigs, and dogs.<sup>4</sup> Tremetol is the toxic principal in *Eupatorium rugosum* (white snakeroot).<sup>4</sup>

Horses ingest blister beetles in dried hay, and the cantharidin present in the insects causes gastric lesions, hemorrhagic cystitis, enterocolitis, and myocardial necrosis.<sup>4</sup> Hairy vetch (*Vicia villosa*) can also cause myocardial lesions

in cattle but not horses. Histologic lesions consist of monocytes, lymphocytes, plasma cells, and giant cells. In cattle, eosinophils are also present.<sup>5</sup>

**Contributing Institution:** Louisiana State University School of Veterinary Medicine, Skip Bertman Drive, Baton Rouge, LA 70803, <http://www.vetmed.lsu.edu/>

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#### CASE II – A07-11068-4 (AFIP 3103240)

**Signalment:** 15-year-old, castrated male, mixed breed, (*Canis familiaris*) dog

**History:** A 15-year-old castrated male mongrel dog developed a mass in the left hemimandible around the first molar tooth. The owner reported that the dog pawed at its mouth. Two 1 cm x 2 cm incisional biopsy specimens from the buccal and lingual aspects of the mass were processed en toto for histologic examination by a reference laboratory; the diagnosis was osteosarcoma. One month later, the dog was admitted to the Purdue University Veterinary Teaching Hospital for total left hemimandibulectomy.

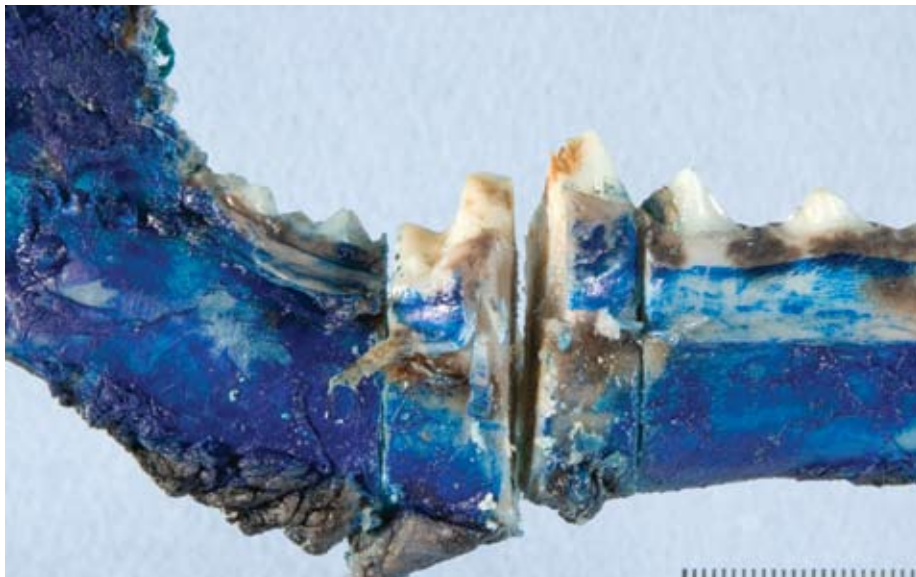
**Gross Pathology:** A left hemimandibular surgical specimen containing the entire mass had its margins painted prior to immersion in 10% neutral buffered formalin and submission to the Purdue University Animal Disease Diagnostic Laboratory (ADDL), where the specimen was transferred to a formic acid decalcifying solution. A firm to hard fibrous and bony mandibular mass surrounded the neck and roots of the first molar tooth and measured about 2.5 cm from rostral to caudal margins and 2 cm from medial to lateral aspects (**Figs. 2-1, 2-2**). The mass on cross-section consisted mostly of hard, white tissue that infiltrated alveolar and cortical bone and adjacent soft tissue (**Fig. 2-3**).

**Laboratory Results:** No abnormalities were detected in the available lateral radiographic view of the skull because of superimposition of the hemimandibles. However, in the computed tomographic (CT) scan, an expansile and lytic lesion, about 1.8 cm in width and 2 cm from rostral to caudal borders, was evident in the dorsal aspect of the left hemimandible, surrounding the neck and roots of the first molar tooth (**Fig. 2-4**). The mass destroyed alveolar and cortical bone, but had well-defined borders with a short transition zone. There was slight swelling, but no post-contrast enhancement of adjacent soft tissues. Thoracic and abdominal radiographs were within normal limits and free of evidence of metastatic neoplasia.

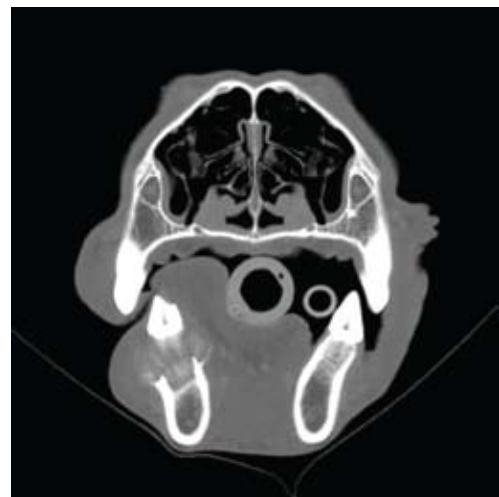
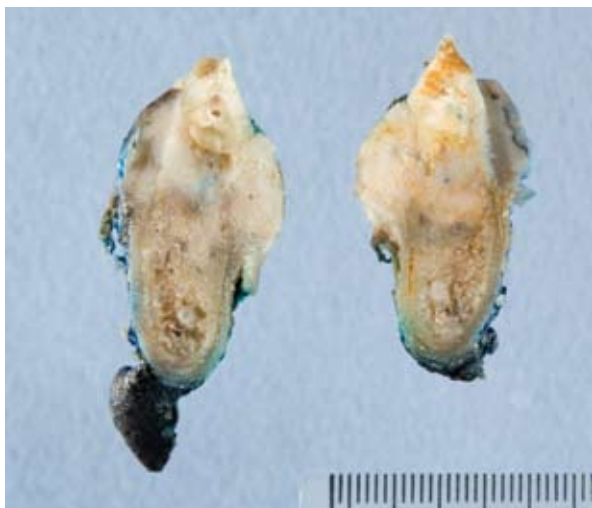
**Histopathologic Description:** The tumor consisted of a spindle-cell proliferation resembling periodontal stroma that appeared to be centered midway between the neck of the tooth and its apex. At its apparent site of origin, the tumor had provoked osteoclastic destruction of alveolar bone, adjacent cortical compacta, periodontal ligament and bone of the alveolar crest. Symmetric growth of the mass expanded the lingual and buccal borders of the hemimandible, again by stimulating osteoclastic removal of the cortical compacta at a rate that allowed development of a thin, incomplete shell of periosteal new bone that partially contained the tumor. At the gingival sulcus, the incomplete and partially resorbed periosteal shell of reactive bone nearly abutted the junctional gingival epithelium. Upward expansion of the tumor into gingival lamina propria led to ulceration and granulation tissue formation. On the buccal surface, the tumor was also partially bound by a thin periosteal shell of reactive bone that ended at the former level of the alveolar crest, which had been replaced by neoplastic tissue. Here, the tumor extended above the level of the periosteal reaction into the gingiva. Neoplastic tissue was composed of fusiform cells in scanty fibrous stroma with light but diffuse infiltration by neutrophils. The fusiform cells had an elongated oval nucleus, small nucleolus, no mitotic figures in 15 high-power fields, and scanty pale

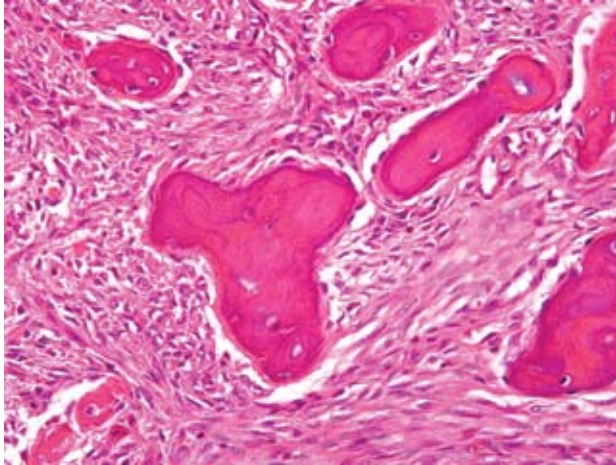


2-1, 2-2, 2-3 (From top on left). Mandible, dog. A 2.0 x 2.5 cm firm fibrous and bony mass surrounds the neck and roots of the first molar: Photographs courtesy of the Animal Disease Diagnostic Laboratory, 406 S. University Street, Purdue University, West Lafayette, IN 47907, pegmiller@purdue.edu.



2-4. Mandible, dog (Below). Effacing alveolar and cortical bone, surrounding the neck and roots of the first molar tooth, and expanding gingival soft tissues at the dorsal aspect of the left hemimandible is a well defined mass. Computed tomograph courtesy of the Animal Disease Diagnostic Laboratory, 406 S. University Street, Purdue University, West Lafayette, IN 47907, pegmiller@purdue.edu.





2-5. Mandible, dog. Ossifying fibroma. Effacing periodontal ligament and alveolar bone is a neoplasm composed of fusiform cells admixed with low numbers of neutrophils on a scant fibrous matrix. Within the neoplasm are islands of woven bone lined by a single layer of osteoblasts which are distinct from the neoplastic cell population. (HE 400X)

eosinophilic cytoplasm with indistinct cell borders (**Fig. 2-5**). The stroma was moderately vascular with numerous irregular trabeculae of osteoid and partially mineralized woven bone. Bony trabeculae were bordered by one layer of osteoblasts. A few osteoclasts were adjacent to bony spicules. There was little fibrous collagen in tumoral stroma; most of the Masson's trichrome-stained collagen was in the bony trabeculae. A preliminary diagnosis of ossifying fibroma was reported with the final diagnosis to follow examination of remaining (central) tissue.

Sections of the fully decalcified central portion of the tumor were histologically similar to the initial peripheral sections, except that 1 to 3 mitotic figures were found per ten high-power fields. Neoplastic tissue was not found in soft tissue ventral to the hemimandible or in mandibular or soft tissue caudal to the mass. Histologic impression was complete excision of an ossifying fibroma.

**Contributor's Morphologic Diagnosis:** Mandibular ossifying fibroma

**Contributor's Comment:** The case was reported as a brief communication in *Vet Pathol*.<sup>1</sup> Benign fibro-osseous proliferations of bone in veterinary species include ossifying fibroma, osteoma, and fibrous dysplasia.<sup>2,3</sup> Osteomas are typically solitary osteosclerotic lesions that arise from the surface of bones of the jaw or skull; trabeculae of woven bone constitute the bulk of the tumor, are rimmed by one layer of well-differentiated osteoblasts and, in many cases, are oriented perpendicular to the

surface of the tumor.<sup>3</sup> Fibrous dysplasia<sup>3</sup> is a tumor-like lesion that can involve one or multiple bones, often in young animals. It arises within the bone, rather than from the periosteal surface, and its ample fibrous stroma contains only thin, curved trabeculae of woven bone. The bony trabeculae are generally not rimmed by osteoblasts, which distinguishes it from ossifying fibroma or osteoma, and are regularly spaced but without orientation relative to the periosteal surface.

Ossifying fibroma has histologic features that are intermediate between those of osteoma and fibrous dysplasia, although there can be overlap among the three entities.<sup>2</sup> Ossifying fibroma is an expansile, lytic, and invasive mass that develops within the bone, particularly the mandible. Its bony trabeculae are rimmed by osteoblasts as in osteoma, but are arranged haphazardly and contribute relatively less to the fibro-osseous stroma.

Importantly, from a prognostic perspective, ossifying fibroma must be differentiated from malignant tumors, such as osteosarcoma. That distinction can be based on the lower cellularity, bland cytologic features, and low mitotic index of ossifying fibroma. Furthermore, bony trabeculae of ossifying fibroma tend to be better developed than in osteosarcoma and are bordered by a single layer of osteoblasts that are distinct from the tumor cells. However, histologic examination of excisional biopsy specimens and knowledge of the anatomic location of the tumor may be necessary for accurate diagnosis.

**AFIP Diagnosis:** Gingiva, tooth, and alveolar and cortical bone: Ossifying fibroma

**Conference Comment:** Ossifying fibromas are most commonly reported in young horses, generally less than one year of age, and usually present as a protruding mass from the rostral mandible.<sup>4</sup> There have also been reported cases in cats, dogs, and sheep.<sup>4</sup> In horses, the differential diagnosis for ossifying fibroma includes fibrous osteodystrophy, fibrous dysplasia, osteoma, and osteosarcoma.<sup>4</sup> Fibrous osteodystrophy presents as a symmetrical, bilateral lesion with numerous osteoclasts.<sup>4</sup> In fibrous dysplasia, bone spicules are not rimmed by osteoblasts and are more uniform.<sup>4</sup> Osteomas are composed of more normal appearing bone, while osteosarcomas have invasive, pleomorphic cells with a higher mitotic index.<sup>4</sup> Osteomas are most common in horses and cattle and have been reported as large as 14 cm in diameter.<sup>3</sup>

Many tumors diagnosed as osteomas in dogs are actually multilobular tumors of bone.<sup>3</sup> Histologically, the multilobular tumor of bone consists of multiple vari-shaped nodules of bone and/or cartilage at various stages of

differentiation separated by a fibrovascular stroma.<sup>2,4</sup> These tumors are slow growing but can be invasive and may metastasize.<sup>4</sup> They have been reported in dogs, cats, and horses.<sup>4</sup> Osteomas are dense masses of well-differentiated bone that protrude from bone surfaces.

**Contributing Institution:** Purdue University, Animal Disease Diagnostic Laboratory, url: <http://www.addl.purdue.edu/>; Department of Comparative Pathobiology, <http://www.vet.purdue.edu/cpb/>

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### CASE III – APO7-2381 (AFIP 3103604)

**Signalment:** 11-month-old, male castrated, dachshund, canine, (*Canis familiaris*)

**History:** This dog was presented to the North Carolina State University College of Veterinary Medicine Neurology Service for a 3-month history of stumbling and falling which had progressed to severe vestibular ataxia, nystagmus, and possible seizure activity. This dog had been treated previously with antibiotics and there was no response.

**Gross Pathology:** The necropsy was limited to the head only. Bilaterally, the meninges of the caudal part of the temporal, parietal lobe and the occipital lobe were fluctuant and markedly thickened, up to 6 mm. Serosanguinous fluid and dark red soft clots were found within the subdural space (subdural hematoma). On the

cut surface, the arachnoid space was markedly dilated due to marked cerebral atrophy which was most prominent in the left occipital lobe. The lateral ventricles were asymmetrical with the left lateral ventricle smaller than the right lateral ventricle (**Fig. 3-1**). The third ventricle was slightly enlarged ventrodorsally and the interthalamic adhesion was moderately thinned.

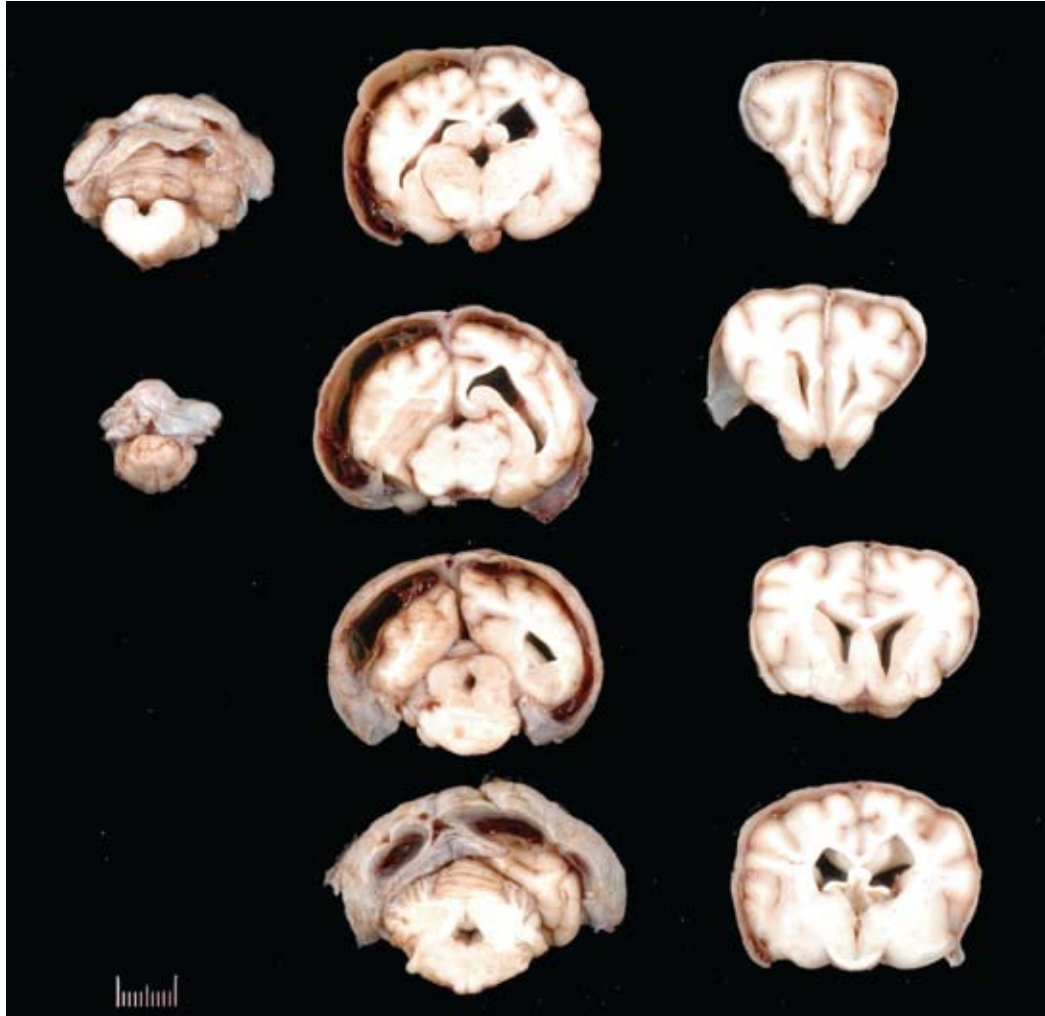
#### Laboratory Results:

##### *MRI findings*

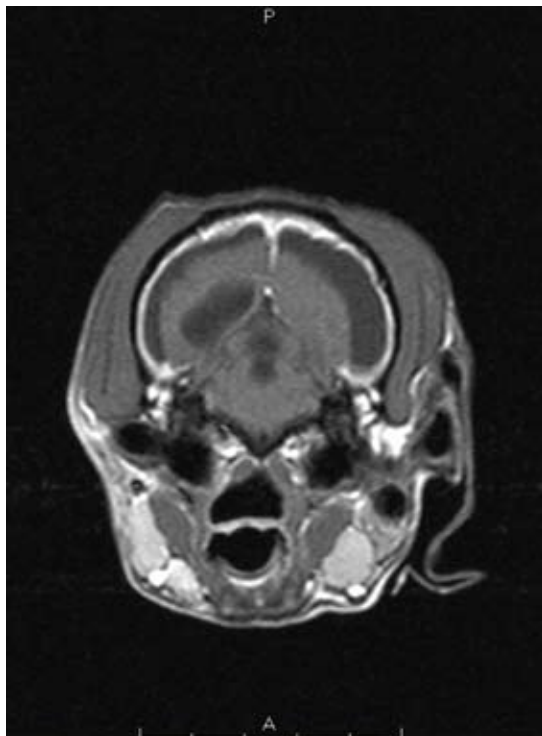
Moderate ventricular asymmetry is present with the right lateral ventricle being somewhat larger than the left. The third ventricle is also enlarged. There is a large accumulation of fluid peripheral to the cerebral cortex (extra-axial) most apparent from the level of the optic chiasm caudally (**Fig. 3-2**). This fluid accumulation does not suppress on the FLAIR sequence as does the fluid within the ventricles and is slightly T1 hyperintense relative to fluid within the ventricles. The interthalamic adhesion is noticeably small and asymmetrical. The cerebellum has an irregular margin and the folia within the cerebellum have increased conspicuity. Post contrast medium administration, there is florid enhancement of the meninges surrounding the cerebral cortex and falx. There is no abnormal parenchymal enhancement. There is no evidence of increased intracranial pressure.

**Histopathologic Description:** Cerebrum: Diffusely in the cerebral cortical gray matter, approximately 60% of the neurons contain abundant, eosinophilic to amphophilic, granular to globular, cytoplasmic pigment, which occasionally displaces the nuclei peripherally (**Fig. 3-4**). The cytoplasmic pigment stains positively with the PAS reaction and Sudan black and more obviously, but less frequently, with LFB stain (**Fig. 3-5**). Moderate numbers of neurons are shrunken, rounded or angular, and hypereosinophilic, with hyperchromatic or pyknotic nuclei, interpreted as neuronal degeneration and necrosis. The dura and arachnoid mater are markedly thickened up to 5 times normal by fibroblasts, moderate multifocal angiogenesis and additional connective tissue matrix. Multifocally, there is a moderate amount of subarachnoid hemorrhage. Under U.V. illumination the pigment is autofluorescent. Ultrastructurally, the neurons have intracytoplasmic storage bodies which consist of curvilinear forms (**Figs. 3-5, 3-6**).

Other sections examined: Cerebellum: There is moderate depletion of Purkinje cells and marked depletion of granular cells accompanied by marked narrowing of the granular layer and the molecular layer of the cerebellar cortex. Purkinje cells also contain eosinophilic cytoplasmic pigment which stains with PAS and LFB.

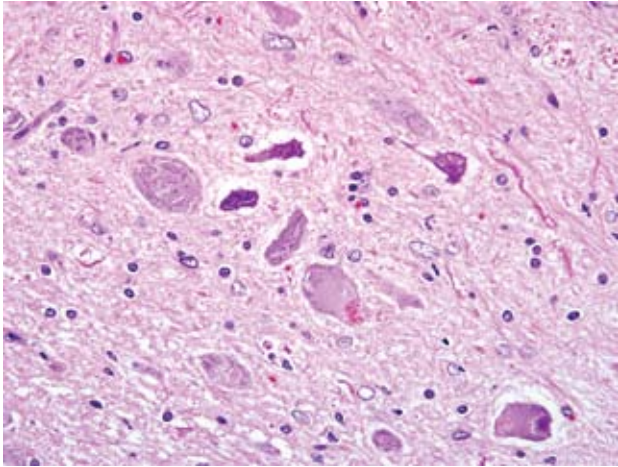


3-1. Brain, dog. Bilaterally, the meninges are thickened up to 6 mm. The subarachnoid space is markedly dilated, most notably on the left side, and the lateral ventricles are asymmetrical with the left lateral ventricle smaller than the right, and the third ventricle is mildly enlarged. Photograph courtesy of the College of Veterinary Medicine, North Carolina State University, 4700 Hillsborough Street, Raleigh, NC 27606, Sandra\_horton@ncsu.edu.

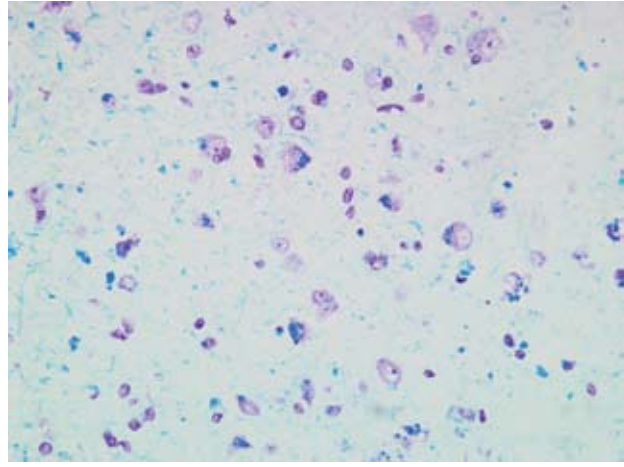


3-2. Cranium, dog. Lateral ventricles are markedly asymmetrical, with the left lateral ventricle smaller than the right, and the third ventricle is moderately enlarged. There is an accumulation of fluid peripheral to the cerebral cortex which is more prominent over the left hemisphere.

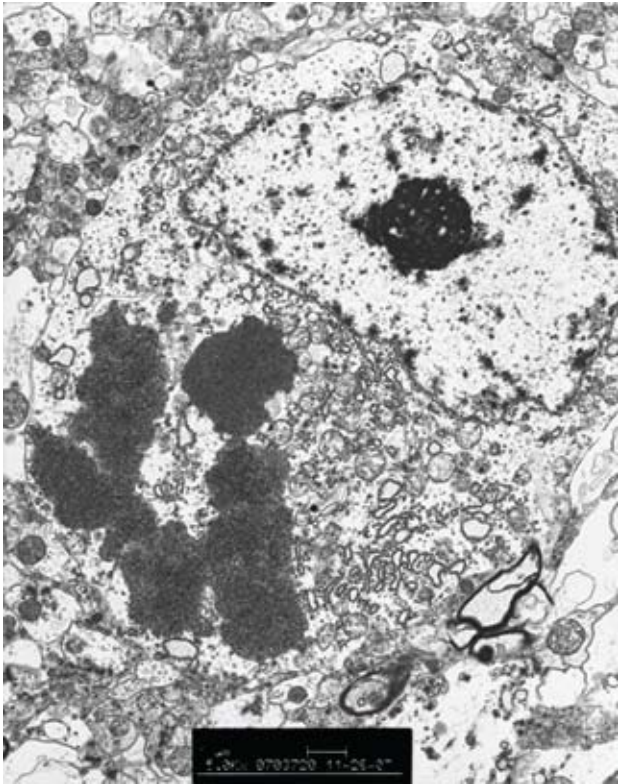
Computed tomography courtesy of the College of Veterinary Medicine, North Carolina State University, 4700 Hillsborough Street, Raleigh, NC 27606, Sandra\_horton@ncsu.edu.



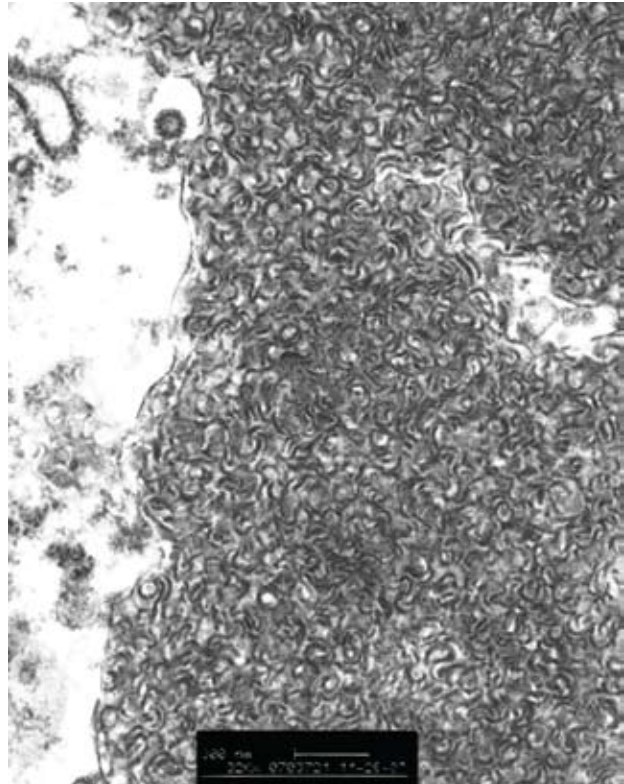
3-3. Cerebrum, dog. Multifocally within the cerebral cortical gray matter, there are low numbers of necrotic neurons, occasional satellitosis, and numerous neurons which contain globular eosinophilic cytoplasmic inclusion material. (HE 400X)



3-4. Cerebrum, dog. Neuronal inclusion material staining with luxol fast blue. (LUXOL FAST BLUE 400X)



3-5. Neuron, dog. Electron dense ceroid lipofuscin intracytoplasmic inclusions. Electron micrograph courtesy of the College of Veterinary Medicine, North Carolina State University, 4700 Hillsborough Street, Raleigh, NC 27606, Sandra\_horton@ncsu.edu.



3-6. Neuron, dog. Ceroid lipofuscin inclusions composed of many curvilinear bodies. †



Eye: Bilaterally, there is mild depletion of the ganglion cells in the retina. There are a few ganglion cells with intracytoplasmic granules which stain with LFB. There is multifocal detachment of the retina with mild hypertrophy and hyperplasia of the pigmented epithelium (tombstone change).

**Contributor's Morphologic Diagnosis:** Diffuse, moderate, neuronal degeneration and necrosis and abundant neuronal intracytoplasmic granular pigment with cerebral atrophy

**Contributor's Comment:** The neuronal ceroid lipofuscinoses (NCLs) are inherited lysosomal storage diseases characterized by progressive neuropathy and accumulation of autofluorescent lipopigment in neurons and other cells.<sup>3</sup> NCLs have been described in human beings, cattle, sheep, goats, cats and in several breeds of dogs.<sup>1,4</sup> Human NCLs are classified into several forms based on the age of clinical onset, causative gene and ultrastructure of the accumulating lysosomal storage bodies.<sup>3</sup> The causative mutations in dogs have been reported in English setters (a missense mutation in *CLN8*), border collies (a nonsense mutation in *CLN5*), bulldogs (a missense mutation in *CTSD*) and juvenile dachshund (a frame shift mutation in canine *TPP1*: the ortholog of human *CLN2*). The canine *TPP1* gene encodes a lysosomal enzyme called tripeptidyl 1 peptidase<sup>1</sup> and is known as the causative gene of infantile neuronal ceroid lipofuscinosis in humans and when mutated leads to accumulation of curvilinear-appearing cytosomes in neurons as well.<sup>3</sup>

The major accumulating protein in this breed is unknown, but subunit C of mitochondrial ATP is reported in English setters, border collies and Tibetan terriers, and sphingolipid activator proteins A and D have been identified in some types of human NCLs.<sup>1,3,4</sup> The cerebral and cerebellar cortex atrophy with cytoplasmic eosinophilic pigment, which stained with PAS and LFB stain in neurons, is consistent with ceroid lipofuscinosis. The autofluorescence and ultrastructure of the accumulating pigment in this dog are very similar to the previous reports of juvenile ceroid lipofuscinosis in this breed. The dilated subdural space is considered to be secondary to the cerebral cortical atrophy.

**AFIP Diagnosis:** Cerebrum: Neuronal degeneration, necrosis and loss, extensive, with gliosis, cerebral atrophy, meningeal fibrosis, subdural hemorrhage, and eosinophilic neuronal cytoplasmic bodies

**Conference Comment:** Neuronal ceroid-lipofuscinosis, also known as Batten disease, has been reported in several domestic species and was recently

reported in a Vietnamese pot-bellied pig.<sup>2</sup> The mode of inheritance is thought to be autosomal recessive for this type of storage disease.<sup>5</sup> Although accumulation of intracytoplasmic storage material can be found in many organs, the most prominent pathologic manifestations of these diseases are seen in the retina, cerebral cortex, and cerebellum.<sup>5</sup>

Gross lesions can vary from being nearly imperceptible to marked cerebral atrophy. The earlier the onset of the disease the more severe the brain atrophy.<sup>4</sup> Ultrastructurally, ceroid-lipofuscinosis can take on many different structural forms including curvilinear bodies, fingerprint bodies, and laminated stacks of membranes.<sup>5</sup> Areas of cerebral atrophy often appear to have a brown tinge.<sup>5</sup> The subdural hematoma in the present case is suspected to have resulted from trauma associated with motor disturbances.

Veterinary research into affected sheep resulted in a major contribution to understanding the human and animal ceroid lipofuscinoses by demonstrating that the stored material is predominantly protein (subunit C of mitochondrial ATP synthase) rather than lipid, as had been believed. Further research showed that in some forms of the disease, sphingolipid activator proteins are accumulated. Thus, "ceroid lipofuscinosis" is actually a misnomer.

**Contributing Institution:** College of Veterinary Medicine, North Carolina State University, <http://www.cvm.ncsu.edu/>

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**CASE IV – 07 0284-54 (AFIP 3065568)**

**Signalment:** Male, 8-year-old, dog, Shar Pei (*Canis familiaris*)

**History:** This dog was dysorectic for 15 days and showed poor condition and severe weight loss. Examination by clinician revealed a caudal abdominal mass, pain at palpation and corneal edema of the right eye. No micturitional troubles were reported. Prostatic abscesses were suspected. Urinary analysis revealed inflammatory cells and macrophages according to the clinician. The dog was euthanized for humane reasons.

**Gross Pathology:** Along with dramatic cachexia, the dog showed a severely enlarged (20 cm diameter), white, multilobulated and cystic prostate. Numerous white, firm, sometimes umbilicated masses were encountered in lungs, kidneys, spleen and tracheo-bronchial lymph nodes. Three ulcers were detected in proximal duodenum. Urinary bladder exhibited muscular hypertrophy.

**Laboratory Results:**

Urinary analysis

Parameter	Value
Density	1.026
Blood	+++
pH	6
Bilirubin	+
Leukocytes	+
Macrophages	+++

Blood analysis

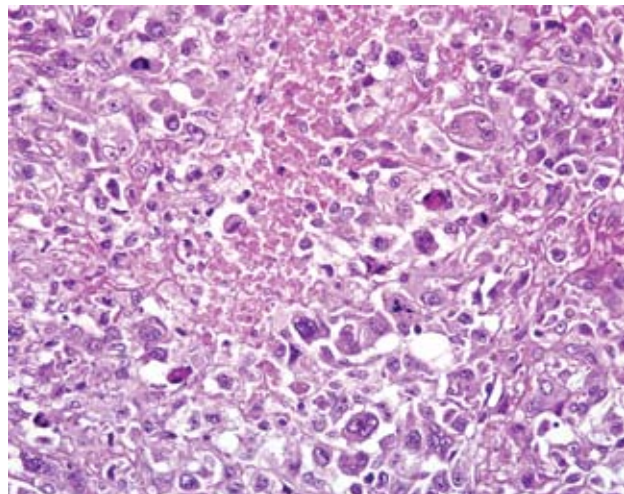
Parameter	Value	Normal value
Urea	0.64 g/L	0.2-0.6 g/L
Creat	13 mg/L	< 12 mg/L
PAL	76 UI/L	< 200 UI/L
ALAT	24 UI/L	< 80 UI/L
TP	47 g/L	55-80 g/L
Glucose	0.87 g/L	0.6-1.1 g/L
Na <sup>+</sup>	138 mmol/L	140-150 mmol/L
K <sup>+</sup>	4.4 mmol/L	3.8-5.2 mmol/L
HCO <sub>3</sub> <sup>-</sup>	22 mmol/L	25 mmol/L

**Histopathologic Description:** Prostate: Multifocal and very infiltrative cell proliferations are effacing normal prostatic architecture. They are poorly encapsulated, highly cellular and contain discrete amount of connective tissue. Cells are round-to-oval with a 15-µm diameter, not jointed, contain variable amounts of eosinophilic cytoplasm sometimes microvacuolated, have a highly vesicular and irregular nucleus showing prominent nucleoli (**Fig. 4-1**). Multinucleated cells, mitoses and abnormal mitotic figures are very frequent. Phagocytosis (erythrophagocytosis) is sometimes observed. Some areas of liquefaction necrosis are noted. Multifocal and discrete infiltrations by lymphocytes, plasma cells and neutrophils are observed. Tumoral cells can be found in the lumen of the prostatic glands. Immunohistochemical phenotype is: Vimentin-positive, cytokeratin-negative, CD3-negative, CD79a-negative.

**Contributor's Morphologic Diagnosis:**

Prostate: Malignant histiocytosis, Shar Pei, dog  
Lung, kidney, duodenum, spleen (not submitted):  
Malignant histiocytosis, Shar Pei, dog

**Contributor's Comment:** Histiocytic disorders have been reported in many species, mainly in humans, dogs and rats, rarely in cats.<sup>1,2,3,4,6</sup> They arise from the large family of antigen-presenting cells (APC) originated from the bone marrow. The different APC cell types along with their immunophenotypes are presented in **Table 1**.



4-1. Prostate gland, dog. Histiocytic sarcoma. Neoplastic cells are highly pleomorphic spindle to round cells with moderate anisocytosis and anisokaryosis, multinucleate cells, and bizarre mitoses. (HE 400X)

**Table 1: Immunophenotypes of the different antigen-presenting cells <sup>2</sup>**

Multipotent bone marrow stem cells			
CD34 + CLA +	CD34 + CLA -		CD34+ IL-3R
↓	↓		↓
Langerhans cells (epithelial dendritic cells)	Interstitial dendritic cells	Macrophages/ Histiocytes	Dendritic cells of lymphoid organs
CD1+ CD14- CD11c+ MHCII Birbeck granules+	CD1+ CD14- CD11c+ MHCII+ Thy-1+	CD1- CD14+ MHCII+ CD11c- CD11b+	IL-3R MHCII+ CD45RA+ CD4+

Origin lineage of histiocytic disorders in dogs is the subject of many debates. In humans, they tend to arise from both macrophages/histiocytes and dendritic cells whereas in rats, they are of macrophagic origin. In dogs and cats, they are believed to be mostly of dendritic origin.<sup>2</sup>

In dogs, the main histiocytic disorders are: cutaneous histiocytoma, cutaneous histiocytosis, systemic histiocytosis, histiocytic sarcoma (HS) and malignant histiocytosis (MH).<sup>4</sup> Whereas cutaneous and systemic histiocytosis are non-neoplastic proliferations of activated dendritic cells, the others are classified as true neoplasms. There is a lot of confusion concerning the terms HS and MH. HS should be used when the lesion is solitary or has metastasized. MH defines a multicentric proliferation. Thus, a disseminated histiocytic sarcoma could be undistinguishable from a malignant histiocytosis. Bernese mountain dogs (BMD) show particular susceptibility to histiocytic disorders and neoplasms.<sup>6</sup> Properties of these histiocytic disorders are summarized in **Table 2**. Concerning HS/MH, respiratory symptoms are the most

frequent cause of consultations. Anemia can be observed as part of a regenerative hemolytic process or a non-regenerative anemia caused by bone marrow invasion and erythrophagocytosis. Hypercalcemia can be observed as a paraneoplastic syndrome. On histopathologic examination, there is proliferation of round-to-oval cells with abundant eosinophilic cytoplasm, nuclear atypia, numerous mitoses, multinucleation, phagocytosis and some infiltration by lymphocytes, plasma cells and neutrophils.<sup>4</sup> On immunohistochemistry, along with markers of **Table 1**, cells are positive for lysozyme, vimentin, and negative for cytokeratin A.<sup>3</sup> Differential diagnosis includes: anaplastic carcinoma or lymphoma, rhabdomyosarcoma, and lymphomatoid granulomatosis. This case showed original features. Indeed, MH has only been reported in two Shar Peis and prostate involvement was only reported once.<sup>2</sup> Furthermore, no infiltration of the liver was observed, both at gross and microscopic examination. This feature is uncommon as the liver is one of the three most frequently involved organs.<sup>2</sup>

**Table 2: Properties of histiocytic disorders in dogs**

Diseases	Concerned breeds	Mean age	Cytonuclear atypias	Involved organs	Metastatic potential	Prognosis
Cutaneous histiocytoma	All, predisposition of Boxer, dachshund, cocker spaniel, Great Dane, Shetland	Mostly young dogs	Rare	Skin (mainly solitary lesion). Draining lymph nodes involvement is exceptional	None	Good

Cutaneous histiocytosis	All, predisposition of golden retriever and German shepherd	Mostly young dogs	Rare	Skin (multiple lesions), sometimes lymph nodes	Rare	Good
Systemic histiocytosis	BMD, golden retriever, Doberman pinscher, rottweiler	Adults Mean age is 7 for BMD	Moderate	Skin (multiple lesions), lymph nodes, sometimes ocular tissues	Moderate	Guarded
Histiocytic sarcoma		Adults Mean age is 6 for BMD	Severe	Subcutaneous tissues or internal organs	Elevated, to draining lymph nodes	Guarded
Malignant histiocytosis			Severe	Rapid multicentric dissemination (lungs, liver, spleen)	Elevated	Poor

**AFIP Diagnosis:** Prostate gland: Histiocytic sarcoma

**Conference Comment:** On additional immunohistochemical testing, the neoplastic cells were positive for CD18 and CD45 and negative for muscle actin. The diagnosis of histiocytic sarcoma was based on characteristic histopathologic and immunohistochemical findings.

Canine malignant histiocytosis/histiocytic sarcoma was first reported in Bernese mountain dogs and has since been reported in various dog breeds, cats, and other species.<sup>4</sup> Malignant histiocytosis implies multicentric origin of the neoplasm. In cases of widespread disease, it is unclear whether the neoplasm arose multicentrically or metastasized widely from a single primary site. Since conference participants were only aware of the neoplasm in the prostate, histiocytic sarcoma was considered the most appropriate diagnosis. Given the presence of widespread disease, disseminated histiocytic sarcoma is preferred. These tumors are composed of pleomorphic histiocyte-like cells that are often multinucleated or may contain phagocytized material. Two major patterns have been described: round cell predominant and spindle cell predominant.<sup>4</sup> In the round cell variant, neoplastic cells often have abundant eosinophilic cytoplasm and round to reniform nuclei.<sup>4,5</sup> The spindle cell variant is often composed of plump spindle cells and these tumors often resemble other sarcomas.<sup>4</sup> Organs most commonly affected include the liver, lung, kidney, spleen, lymph node, and bones. Almost any organ may be affected by this neoplasm.<sup>5</sup> Canine histiocytic sarcomas are of dendritic antigen presenting cell origin and express CD18, CD1, CD11c, ICAM-1 and MHC II; CD45 expression is variable. For immunohistochemistry on formalin-fixed,

paraffin-embedded tissues, CD18 positivity and negative findings for CD3 and CD79a combined with characteristic histomorphology is considered diagnostic.

A variety of other histiocytic proliferative diseases have been described in dogs. Histiocytomas generally occur in dogs four years of age or younger, are extremely common and have a predilection for the head and ears. These tumors are of Langerhans cell origin and express CD1, CD11c, MHC II, and E-cadherin.<sup>7</sup> At the subgross level, these tumors often appear dome shaped with aggregates of lymphocytes and plasma cells at the periphery. There is often superficial dermal edema, and tumor cells infiltrate the epidermis in a fashion similar to Pautrier's microabscesses of epitheliotropic lymphoma. Neoplastic cells form sheets and generally lack a discernable stroma. Neoplastic cells have oval to reniform nuclei with a moderate to abundant amount of eosinophilic cytoplasm and mitotic figures are frequent. There is little cellular atypia.<sup>5</sup> Multiple, persistent and recurring histiocytomas have also been described. Such tumors may progress to a malignancy characterized by dissemination to various organs. This condition has been designated Langerhans cell histiocytosis. Cutaneous histiocytosis is a non-neoplastic, reactive condition characterized by nodules of histiocytic cells that express CD45, CD18, CD1, CD11c, MHC II and E-cadherin. Mature lymphocytes and neutrophils are often scattered amongst the histiocytic cells. The mitotic rate is variable. Systemic histiocytosis is generally similar to cutaneous histiocytosis but has a more extensive distribution. The immunohistochemical profile is the same. Sites most commonly affected include lymph nodes, eyelids, sclera, nasal cavities, lungs, spleen and bone marrow.

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