Joint Pathology Center
Veterinary Pathology Services

WEDNESDAY SLIDE CONFERENCE 2011-2012

Conference 25

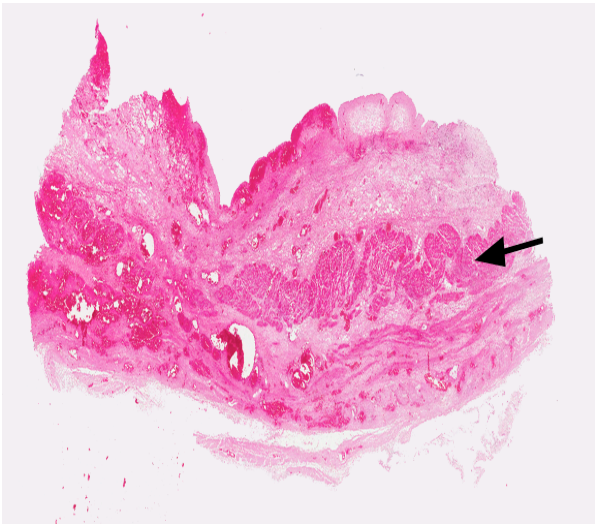
16 May 2012

CASE I: N315/07 (JPC 3126927).

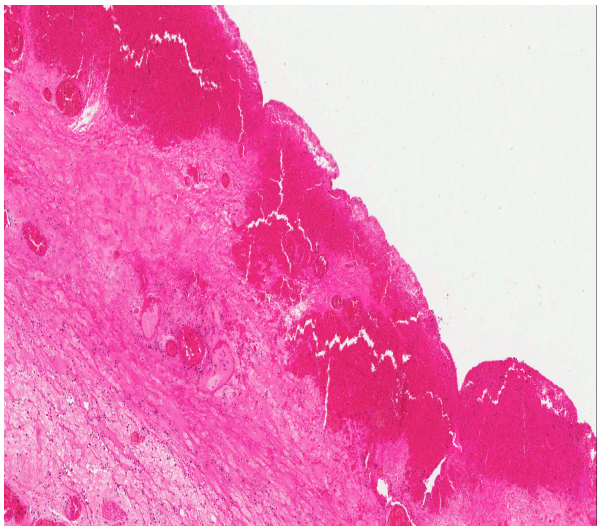
Signalment: Four-year-old female Belgian blue cross-breed, bovine *(Bos taurus)*.

History: Access to 'rough' grazing. Presented with stranguria and hematuria.

Gross Pathology: Ammoniacal smell on opening the peritoneal cavity in which a diffuse fibrin-rich exudate and approximately 60 liters of urine-containing fluid is present. There is perforation of the bladder wall approximately 4cm proximal to the urethral exit within an approximately 16cm diameter, soft red mass raised above the mucosal surface. A similar lesion extends along the ventral bladder wall towards the ureteral openings. The distal 30cm long segment of the esophagus is diffusely mottled red and pale with longitudinal sloughing of the mucosa (consistent with



1-1 . Ox, urinary bladder: Marked transmural thickening of the wall of the urinary bladder by edema. The arrow marks the location of the muscular tunic. (HE 4X)



1-2. Ox, urinary bladder: There is total loss of the mucosal epithelium with suffusive hemorrhages within the submucosa, and marked edema beneath. Vessels throughout the section contain emigrating neutrophils, and occasional vasculitis is seen. (HE 160X)

persistent reflux resulting in extensive erosion/ ulceration).

Contributor's Histopathologic Description: Sloughing of urothelium with an irregularly elevated exposed stromal surface containing abundant engorged, ectatic blood vessels of varying diameter lined by well-differentiated endothelial cells with adjacent stromal hemorrhage, fibrinous exudate and scattered leukocytes. These changes extend transmurally with evidence of vasculitis & thrombosis. Fibrinocellular exudate was noted on the serosal surface of the intestine (peritonitis).

Contributor's Morphologic Diagnosis: Bladder: Vascular congestion, ectasia, and hemorrhage, with attendant vasculitis, thrombosis and fibrinous exudation; diffuse; severe.

Contributor's Comment: The gross and histopathological changes in the bladder are consistent with bladder perforation and peritonitis secondary to hemangiomatous lesions in the bladder wall. Such lesions are associated with the long-term ingestion of bracken fern in cattle (Enzootic hematuria). This animal had been on rough grazing with access to such fern.

Enzootic hematuria occurs in mature cattle, is characterized by hematuria and anemia, and is associated with hemorrhages or neoplasms particularly of the bladder. The syndrome is attributed to the long-term ingestion of bracken fern (*Pteridium aquilinum* subsp. *Aquilinum*) and can be reproduced experimentally.[3,5] Bracken fern contains several toxins including a thiaminase, carcinogens (quercetin, shikimic acid, prunasin, ptaquiloside, ptaquiloside Z, aquilide A), and a "bleeding factor".[1] Administration of ptaquiloside to guinea pigs results in hemorrhagic cystitis suggesting that this is a significant toxin in the induction of hematuria.[5]

Cattle fed low levels of bracken fern develop microscopic, followed by macroscopic, hematuria. Microhematuria is usually associated with petechial or ecchymotic hemorrhages of the bladder mucosa with microscopic evidence of vascular ectasia and engorgement and these vessels are prone to hemorrhage. Nodular hemangiomatous lesions also develop.[3] Occasionally, macroscopic hematuria is associated with these non-neoplastic changes, but usually results from the development of tumors which ulcerate and hemorrhage into the bladder lumen.[3] Several types of epithelial and mesenchymal neoplasms may develop, and in over 50% of affected cattle, mixed epithelial–mesenchymal neoplasms develop. Papillomas, fibromas, and hemangiomas with carcinomas are most commonly found.[1,3,5]

JPC Diagnosis: Urinary bladder: Necrosis, transmural, diffuse, with marked hemorrhage, vascular ectasia, and necrotizing vasculitis.

Conference Comment: Conference participants discussed obstruction as a likely and more commonly encountered candidate condition for the lesion in this case, and possibly the cause of the histologic lesion. The expected neoplasia with hemorrhagic cystitis was not visible in the slide, and the grossly described masses may have caused an obstruction and the subsequent transmural hemorrhage and necrosis of the bladder wall, leading to the rupture.

This cow likely then had post-renal azotemia, and although serum was not available for analysis, conference participants considered the option of measuring the aqueous humor of the eye at necropsy to determine if the animal was azotemic, since creatinine is not protein-bound and diffuses freely in both the eye and the abdominal fluid. The urea nitrogen and creatinine of the abdominal fluid could be compared to that of the aqueous humor, and in the case of a ruptured urinary bladder, the concentrations in the abdominal fluid should approach double that of the serum or humor.[2,4]

Additional clinical pathology abnormalities expected in a cow with post-renal azotemia would be hyperphosphatemia, since azotemia is the primary cause of elevated phosphorous in veterinary medicine due to decreased excretion from decreased glomerular filtration rate, and hyponatremia and hypochloremia due to loss in the urine and diffusion along the concentration gradient. Although small animals often have metabolic acidosis associated with renal failure, cattle present with metabolic alkalosis due to rumen atony and subsequent acid sequestration. This is due to stasis of ruminal content, similar to that seen in cattle with displaced abomasum or ileus. Conference participants expected a high plasma total CO_2 and total bicarbonate (HCO_3^-) and respiratory compensation indicated by a high $_pCO_2$. Although hyperkalemia is expected with post-renal azotemia, the accompanying metabolic alkalosis in cattle drives potassium into cells in exchange for hydrogen following its concentration gradient to the extracellular space. An expected gross finding in this case would be bilateral hydronephrosis or hydroureter secondary to the obstruction.[2,3,4]

Contributor: UCD Veterinary Sciences Centre
UCD School of Agriculture, Food Science and Veterinary Medicine
University College Dublin
Belfield
Dublin 4, Ireland
www.ucd.ie

References:

1. Hopkins NCG. Aetiology of enzootic haematuria. *Vet Rec*. 1986;118:715–717.
2. Langston C. Acute uremia. In: Ettinger SJ, Feldman EC, eds. *Textbook of Veterinary Internal Medicine*. 7th ed. Vol 2. St. Louis, MO: Saunders Elsevier; 2010:1969-83.
3. Maxie MG, Newman SJ. The urinary system. In: Maxie MG, ed. *Jubb, Kennedy and Palmer's Pathology of Domestic Animals*. 5th ed. Vol. 2. Philadelphia, PA: Elsevier Saunders, 2007:518-520.
4. Tripathi NK, Gregory CR, Latimer KS. Urinary system. In: Latimer KS, ed. *Duncan and Prasse's Veterinary Laboratory Medicine: Clinical Pathology*. 5th ed. Ames, IA: Wiley-Blackwell; 2011:270-80.
5. Xu LR: Bracken poisoning and enzootic haematuria in cattle in China. *Res Vet Sci*. 1992;53:116–121.

CASE II: 11-4158 (JPC 4002911).

Signalment: 6-month-old male intact Shih Tsu mix dog *(Canis familiaris)*.

History: The puppy was presented to the veterinary teaching hospital 15-18 hours after ingesting up to 8 Midol tablets (500mg acetaminophen, 60mg caffeine, 15mg pyrilamine maleate per tablet). No decontamination had been attempted. The patient was treated with N-acetylcysteine and Denamarin, plus Norm-R fluids at ½ maintenance dose. The puppy exhibited signs of hepatic encephalopathy and was euthanized due to poor prognosis.

Gross Pathology: There was generalized mild icterus of subcutis and mucous membranes. The liver was diffusely pale tan to yellow with a distinct reticular pattern. At the time of necropsy, the urine was transparent yellow.

Laboratory Results: Presentation:
ALT = 261
AP = 239.
One day later:
ALT = 17, 090
AP = 578
Total bilirubin = 4.5
Urine was coffee colored.

Contributor's Histopathologic Description: Liver: Approximately 50% of the liver parenchyma was involved in acute degenerative to necrotizing changes. There was extensive coagulative necrosis of hepatocytes adjacent to all central veins and extending to the midzonal regions. Necrotic hepatocytes were rounded up and contained hypereosinophilic, fragmented cytoplasm. Scattered cells lacked nuclei, while others contained pyknotic to karyorrhectic nuclei. Sinusoids adjacent to central veins were filled with red blood cells (congestion).

Kidney: Widely scattered tubules within the cortex and medulla contained dark orange-brown globules (presumptive hemoglobin). There were similar pigment globules within the cytoplasm of widely scattered epithelial cells lining these tubules. Proximal convoluted tubular epithelium had scattered degenerate cells with hypereosinophilic cytoplasm and pyknotic nuclei. Regenerative epithelial cells were rare. The urinary spaces of several glomeruli were moderately dilated and filled with weakly eosinophilic protein fluid residue. There was similar protein fluid within numerous tubules within the cortex.

Within the stomach (not shown) were numerous lymphocytic nodules in the lamina propria, associated with large, silver positive, spiral bacteria (presumptive *Helicobacter* sp.) in the superficial mucus and glands.

Contributor's Morphologic Diagnosis: 1. Diffuse, acute, severe centrilobular hepatocellular necrosis.
2. Diffuse, mild to moderate hemoglobinuric nephrosis (presumptive).
3. Diffuse, moderate, chronic gastritis (tissue not submitted).

Contributor's Comment: The lesions in this puppy were compatible with acute acetaminophen intoxication. The toxic dose of acetaminophen in dogs ranges from 200-600mg/kg[6]; this 4kg puppy ingested up to 4grams in 8 Midol tablets. The recommended therapeutic dose in dogs is 15mg/kg every 8 hours. By contrast, cats are much more susceptible to toxicity and toxicosis has been seen with doses as low as 10mg/kg.

Acetaminophen (N-acetyl-p-aminophenol) is a widely used over-the-counter analgesic and antipyretic drug considered very safe in humans at therapeutic doses and having fewer gastrointestinal side effects than aspirin or ibuprofen.[4] Yet poisoning by acetaminophen accounts for approximately half of all cases of acute liver failure in people in the US and Britain. Poisoning in dogs and cats is usually associated with administration by well-intentioned by uninformed owners, or by accidental ingestion as in this case.[6]

The liver is a common target of toxicosis, especially from ingested toxins, due to several factors.[7] The liver is exposed to high concentrations of ingested compound via the portal circulation; exogenous and endogenous compounds concentrate in the liver by binding to transport proteins and enzymatic sites; and as the primary site of biotransformation of ingested compounds it is exposed to high concentrations of metabolites. Hepatic biotransformation of xenobiotics occurs in 2 phases: phase I involves metabolism generally by mixed function oxidases, and phase II involves detoxification of metabolites by conjugation with water, sulfate, glucuronate, glutathione and others. Toxicity occurs when metabolism into toxic metabolites overwhelms conjugation systems. As such the centrilobular hepatocytes (zone 3), with high concentrations of mixed function oxidases, are most susceptible to toxicity from compounds that are metabolized to toxic intermediates requiring conjugation. Acetaminophen is a classic example of such a compound.

Mechanisms of acetaminophen induced liver injury have been recently reviewed.[4] Although still under intense investigation, hepatotoxicity occurs in 5 primary steps: 1) metabolism into reactive metabolite by cytochrome P450 (CYP); 2) consumption of glutathione leading to excess reactive oxygen and

nitrogen species; 3) increase oxidative stress resulting in alterations in calcium homeostasis and mitochondrial permeability; 4) loss of mitochondrial ability to synthesize ATP and 5) loss of ATP leading to necrosis.

At non-toxic doses, acetaminophen is metabolized by direct conjugation to glutathione and the non-toxic conjugates are excreted in urine and bile.[6] At toxic doses, glutathione is overwhelmed and metabolism is shunted to the CYP system, resulting in the toxic metabolite N-acetyl-p-benzoquinone imine (NAPQI). NAPQI requires glutathione for detoxification; with glutathione already severely depleted, NAPQI binds covalently to cellular proteins and enzymes, disrupting membranes and leading to oxidative stress. Depletion of glutathione also leads to increased reactive oxygen and nitrogen species. N-acetylcysteine, developed for treatment of acetaminophen toxicity, increases detoxification of NAPQI by direct conjugation and through increased glutathione synthesis. This compound, and S-adenosylmethionine (an intermediary in production of cell membranes and glutathione), have been used effectively in dogs and cats with acetaminophen toxicity.[6] Although uncoupling of mitochondrial permeability transition with subsequent loss of ATP is considered the primary mechanism of acetaminophen induced hepatotoxicity, other mechanisms that have been explored are altered hepatic blood flow due to necrosis of sinusoidal endothelium, and the role of inflammation, chemokines and cytokines both in development of toxicity and in hepatic repair.[4]

Methemoglobin formation is the primary mechanism of toxicity in cats; hepatotoxicity occurs only at high doses. Cats are more susceptible to acetaminophen toxicity than dogs because of much lower levels of glucuronyltransferase.[6] In addition, feline red blood cells have more sulfhydryl groups than other species, making them highly susceptible to oxidative injury. In contrast, dogs develop methemoglobinemia only at higher toxic doses. Histologic lesions of hemoglobinuric nephrosis in this case, although mild, support the likelihood that this puppy ingested high enough doses of acetaminophen to produce metahemoglobinemia.

The other toxic principle in Midol tablets is caffeine, a methylxanthine in the same class of compounds with theobromine and theophylline.[2] Toxic doses for dogs range from 110-200mg/kg; the 4kg puppy ingested up to 480mg, making direct toxicity from caffeine a possible complication. Caffeine is also metabolized by the liver; hepatic damage from acetaminophen could have compromised caffeine metabolism and enhanced its toxicity in this case. Signs of caffeine toxicity are vomiting, tremors and seizures. There are no gross or histologic lesions related to toxicity, although it is possible that the terminal CNS signs in this dog may have been due to a combination of liver failure and caffeine toxicity.

JPC Diagnosis: 1. Liver: Necrosis, centrilobular, diffuse. 2. Kidney, proximal tubules: Degeneration and necrosis, multifocal, mild, with hemoglobin casts.

Conference Comment: Heinz bodies, which are foci of denatured globin apparent as a membranous inclusion in the erythrocyte, are expected to be present in a peripheral blood smear in this case due to the oxidative damage to erythrocytes from acetaminophen toxicity, and are an indicator of intravascular hemolysis. Heinz body formation results from oxidative damage that causes disulfide links between glutathione and globin chains, resulting in aggregation and precipitation of globin in the cell. Also, the predicted mean cell hemoglobin concentration (MCHC) would be increased due to artifact from measured Heinz bodies which would artificially increase the MCHC. Luna hemoglobin stain can be used to confirm the hemoglobin casts within the renal tubules.[3]

The serum hepatic chemistry changes in this case are typical of acetaminophen toxicosis, with normal hepatic enzymes on the first day and massive increases by the third day, which demonstrates the clinical importance of not ruling out hepatic necrosis even when hepatic enzymes are normal when first measured. The reason the alanine transaminase (ALT) is markedly increased and the alkaline phosphatase (AP) is relatively normal the day after presentation is ALT, in addition to aspartate aminotransferase (AST), is a leakage enzyme and increases with hepatic degeneration and necrosis, while AP is an inducible enzyme mainly useful in detecting cholestasis and originates from the biliary tree.[1]

Conference participants discussed how hemoglobinuric nephrosis is a misnomer, as hemoglobin is not directly nephrotoxic. Hemoglobin passes into the glomerular filtrate after haptoglobin saturation, resulting in formation of granular casts. The combination of ischemia and hypoxia due to anemia and hypotension, as well as tubular obstruction, and interstitial edema contribute to the tubular necrosis. Conference participants discussed the common causes of coffee colored urine in dogs, and cystitis with concurrent hematuria is the most likely source, with hemoglobinuria being next, and myoglobinuria being very rare.[5] Conference participants interpreted the eosinophilic fluid within Bowman's space as either autolysis or reflux from tubular necrosis.

Contributor: Washington State University

Department of Veterinary Microbiology and Pathology
Pullman, WA 99164-7040
www.vetmed.wsu.edu

References:

1. Bain PJ. Liver. In: Latimer KS, ed. *Duncan and Prasse's Veterinary Laboratory Medicine: Clinical Pathology*. 5th ed. Ames, IA: Wiley-Blackwell; 2011:213-23.
2. Carson TL. Methylxanthines. In: Peterson ME, Talcott PA, eds. Small Animal Toxicology, 2nd ed. St Louis, MO: Elsiever; 2006: 845-852.
3. Fry MM, McGavin MD. Bone marrow, blood cells, and the lymphatic system. In: McGavin MD, Zachary JF, eds. *Pathologic Basis of Veterinary Disease*. 5th ed. St. Louis, MO: Mosby; 2011:705-11.
4. Hinson JA, Roberts DW, James LP. Mechanisms of acetaminophen-induced liver necrosis. In: Utrecht J, ed. *Adverse Drug Reactions: Handbook of Experimental Pharmacology*. Berlin, Germany: Springer-Verlag; 2010:368-405.
5. Maxie MG, Newman SJ. Urinary system. In: Maxie MG, ed. *Jubb, Kennedy, and Palmer's Pathology of Domestic Animals*. 5th ed. Vol. 2. Philadelphia, PA: Saunders Elsevier; 2007:432-6.
6. Sellon RK. Acetaminophen. In: Peterson ME, Talcott PA, eds. *Small Animal Toxicology*. 2nd ed.St. Louis, MO: Elsiever; 2006: 550-557.
7. Stalker MJ, Hayes MA. Liver and biliary system. In: Maxie MG, ed. Jubb, Kennedy and Palmer's Pathology of Domestic Animals. 5th ed. Edinburgh, Scotland: Elsevier; 2007:364-367.

CASE III: 10-2049 (JPC 4004362).

Signalment: 10-month-old male castrated Scottish terrier dog (*Canis familiaris*).

History: The dog was diagnosed with a urinary tract infection 4 months prior to presentation, and was treated with antibiotics. The infection resolved but there was ongoing, waxing and waning hematuria. At the time of presentation, there had been a recent onset of polyuria and increased urgency to urinate. Contrast radiographs at the time of presentation revealed a filling defect in the urinary bladder. Ultrasound imaging showed a broad-based, heteroechoic mass arising near the trigone region of the bladder. A portion of the urinary bladder was surgically resected and submitted for histologic evaluation.

Gross Pathology: A segment of bladder wall approximately 2 x 3 cm was submitted for biopsy with an attached 2 x 4 x 3 cm, polypoid, soft, red-brown mass that protruded into the lumen of the bladder. Approximately 2 cm of ureter were also submitted.

Laboratory Results: CBC:
WBC 18,100/ul
Neutrophils 14,118/ul
Lymphocytes 543/ul
Monocytes 1,629/ul

Serum Chemistry:
Albumin 2.6 g/dl (N: 3.0-3.9)

Urinalysis:
Albumin 500 ug/dl (3+)
Blood 250/ul

Contributor's Histopathologic Description: Multiple histologic sections were examined with similar findings. Arising from the mucosal epithelium is a multilobular mass supported by a fibrovascular core. Lobules of the mass are composed of a background of neoplastic spindle cells with a myxomatous stroma admixed with frequent multi-nucleated, large, elongate or rounded cells with abundant, fibrillar, eosinophilic cytoplasm. The elongate cells occasionally have prominent cross-striations and are consistent with myogenic "strap cells." The multiple nuclei of the elongate and large round cells have peripheralized chromatin with 1-2 prominent nucleoli. The spindle cells in the background have indistinct cell borders with scant to moderate pale eosinophilic cytoplasm around a central oval nucleus. The nuclei have coarsely clumped to vesicular chromatin and often have 1-2 prominent nucleoli. There is marked anisocytosis and anisokaryosis. Mitotic figures are observed with 14 per 10 high power fields. Each lobule of the mass is supported by a fibrovascular core and is lined by transitional epithelium. The ureter has hyperplastic epithelium, and there appears to be a portion of a neoplastic lobule that is within the ureteral lumen, but not attached to the wall of the ureter.

Contributor's Morphologic Diagnosis: Urinary bladder: Botryoid rhabdomyosarcoma.

Contributor's Comment: Botryoid rhabdomyosarcomas are rare tumors in dogs that most frequently occur in the urinary bladder of young, large breed dogs. There are four categories of rhabdomyosarcomas that are recognized in people, including embryonal, botryoid, alveolar, and pleomorphic. Embryonal rhabdomyosarcomas are characterized by the presence of primitive myogenic cells that occur in two forms, either with large, well-differentiated rhabdomyoblasts on a background of smaller round cells, or a myotubular arrangement with spindle cells forming a myxoid arrangement and often with multinucleate cells and strap-like cells that may or may not have cross striations. Botryoid rhabdomyosarcomas are generally regarded as a variant of embryonal rhabdomyosarcoma with a histologic appearance consistent with the myotubular form, and a gross appearance of a polypoid, grape-like pattern, that often projects into the lumen. The presence of myogenic cells is diagnostic, and myogenic origin can be confirmed with a number of immunohistochemical markers including desmin, muscle-specific actin, and myoglobin. In addition, myogenin and MyoD can be used to identify specific stages of myogenesis.[7] PTAH stains can also be used to try to recognize cross-striations if they are present. In this case, the prominent multinucleated and strap-like cells are diagnostic. In addition, there is strong immunohistochemical staining for muscle specific actin.

Saint Bernards are often listed as being overrepresented in the occurrence of botryoid rhabdomyosarcomas based on a 1973 paper with a case series in which 4 of 7 dogs were Saint Bernards.[5] However, in a review of published cases of canine botryoid rhabdomyosarcomas, no additional cases in Saint Bernards have been described, and there have been at least three cases reported in golden retrievers.[1,7] Other breeds affected include Labrador retriever, Maltese, Newfoundland, Rottweiler, Basset hound, miniature poodle, and a great Dane.[1,5,6,8,9,10] In addition to occurring in the urinary bladder, a few case reports have described botryoid rhabdomyosarcomas in the genital tract as well,[1,9] and there is also a case report of an embryonal rhabdomyosarcoma in the oropharynx and temporal muscles of a young Bassett hound.[6]

Botryoid rhabdomyosarcomas typically have a poor prognosis. The metastatic rate is not well-reported as several cases are euthanized close to the time of initial diagnosis or there is a lack of follow-up in many cases. Out of 14 cases of genital or urinary tract botryoid rhabdomyosarcomas described in case reports, at least five of them had widespread metastases to multiple organs including liver, lungs, lymph nodes, heart, subcutaneous tissue, muscle, gingiva, adrenal gland, spleen, and kidney.[1,5,6,10]

JPC Diagnosis: Urinary bladder: Botryoid rhabdomyosarcoma.

Conference Comment: The contributor provided an excellent discussion of botryoid rhabdomyosarcoma and the associated pathology. Conference participants discussed the following common clinical sequella to this neoplasm. Urinary outflow obstruction is a common finding with these neoplasms, resulting in post-renal azotemia, hematuria, dysuria, and stranguria. The proteinuria and large amount of albumin in the urine can be attributed to the hematuria. Hypertrophic osteopathy is reported to occur concurrently with botryoid rhabdomyosarcoma, thought to be due to vascular or neurogenic stimuli which affect changes in the peripheral vascular supply, as seen with pulmonary masses. Poorly oxygenated blood passes through arteriovenous shunts, producing local passive congestion and poor tissue oxygenation and stimulating proliferation connective tissue, including the periosteum and the synovial membrane. The affected animals are usually young and present bilaterally symmetrical, nonedematous soft tissue swellings affecting primarily the distal portions of all four limbs. The initial soft tissue swellings are soon accompanied by a diffuse periosteal new-bone formation, which may ultimately affect all the bones of the limbs, and the bone lesions resolve after tumor removal.[2,3,4]

Contributor: N.C. State University
College of Veterinary Medicine
Population Health and Pathobiology – Histology Lab
1060 William Moore Dr.
Raleigh, NC 27607
http://www.cvm.ncsu.edu/dphp/path/anatomicpath.html

References:

1. Bae IH, Kim Y, Pakhrin B, et al. Genitourinary rhabdomyosarcoma with systemic metastasis in a young dog. *Vet Pathol*. 2007;44:518-520..
2. Brodey R. Hypertrophic osteoarthropathy in the dog: A clinicopathologic study of 60 cases. *J Am Vet Med Assoc*. 1971;159:1242.
3. Cooper BJ, Valentine BA. Tumors of muscle. In: Meuten DJ, ed. *Tumors of Domestic Animals*. 4th ed. Ames, IA: Iowa State Press; 2002:354.
4. Halliwell WH, Ackeman N. Botryoid rhabdomyosarcoma of the urinary bladder and hyperosteoarthropathy in a young dog. *J Am Vet Med Assoc*. 1974;165:911.
5. Kelly DF. Rhabdomyosarcoma of the urinary bladder in dogs. *Vet Pathol.* 1973;10:375-384..
6. Kim DY, Hodgin EC, Cho DY, et al. Juvenile rhabdomyosarcomas in two dogs. *Vet Pathol*. 1996;33:447-450.
7. Kobayashi M, Sakai H, Hirata A, et al. Expression of myogenic regulating factors, Myogenin and MyoD, in two canine botryoid rhabdomyosarcomas. *Vet Pathol*. 2004;41:275-277.
8. Kuwamura M, Yoshida H, Yamate J, et al. Urinary bladder rhabdomyosarcoma (sarcoma botryoides) in a young Newfoundland dog. *J Vet Med Sci*. 1998;60:619-621.
9. Suzuki K, Nakatani K, Shibuya H, et al. Vaginal rhabdomyosarcoma in a dog. *Vet Pathol*. 2006;43:186-188.
10. Takiguchi M, Watanabe T, Okada H, et al. Rhabdomyosarcoma (botryoid sarcoma) of the urinary bladder in a Maltese. *J Small Anim Pract*. 2002;43:269-271.

CASE IV: N08-659 (JPC 3134301).

Signalment: 6-year-old castrated male bloodhound (*Canis familiaris*), canine.

History: Acute onset of renal failure. The dog died naturally.

Gross Pathology: Both kidneys had a slightly granular (irregular) surface and were light brown. The parietal pleura and intercostal muscles were diffusely mineralized. The endocardial surface of the left atrium was diffusely mineralized; smaller areas of mineralization were present in the pulmonary artery. The lungs were mottled pink to purple, were irregularly firm. Approximately 50% of randomly sampled lung sections sank in formalin.

Laboratory Results: Plasma Chemistry: (only relevant findings listed)

BUN	155 mg/dL	(9-24)
Creat	7.0 mg/dL	(0.6-1.6)
Tot Prot	6.3 mg/dL	(5.6-7.6)
Albumin	2.0 g/dL	(3.1-4.2)
Globulin	4.3 g/dL	(2.1-3.7)
A/G ratio	0.5	(0.9-1.9)
Calcium	8.9 mg/dL	(9.9-11.5)
Phos	25.4 mg/dL	(2.2-4.6)
Sodium	164 mEq/L	(146-153)
Chloride	128 mEq/L	(110-117)
Bicarb	12 mmol/L	(16-23)
Anion Gap	28.6	(16-24)

Urinalysis: (only relevant findings listed)

Specific gravity	1.013
pH	7.0
Protein	2+
WBC	2-6
RBC	25-30

Rare transitional and squamous epithelial cells; Rare cellular casts

Urine Leptospirosis PCR – negative

Blood Gases		
pH	7.051	(7.31-7.42)
Bicarb	13.6	(17-24)
Base excess	-17.3	(02)
PO2	64.9	(85-95)
PCO2	48.6	(29-42)

Contributor's Histopathologic Description: Lung: There is widespread marked mineralization of bronchial walls and alveolar septa. The bronchial epithelium is occasionally ulcerated. The bronchial lumens and alveoli contain varying combinations and concentrations of fibrin, neutrophils, macrophages and erythrocytes. In some areas large, plump fibroblasts are present. Several blood vessels contain haphazardly arranged fibrin and neutrophils. Mutifocally there is fibrin, intermixed with neutrophils and macrophages, on the pleural surface.

In the left atrium (not submitted) there is marked mineralization surrounded by degenerate neutrophils, macrophages and karyorrhectic nuclear debris. The overlying endocardium is thickened. Similarly, the mesothelium lining the intercostal muscles (not submitted) is ulcerated and replaced by a sheet of fibrin. The underlying collagen is mineralized and surrounded by neutrophils, macrophages and karyorrhectic nuclear debris.

Contributor's Morphologic Diagnosis: Lung: Marked acute diffuse mineralization and fibrinosuppurative pneumonitis.

Contributor's Comment: The clinical presentation of uremic pneumonitis is consistent with adult respiratory distress syndrome (ARDS). Possible causes of ARDS include, but are not limited to: thermal or caustic injury, viral infections, ingested toxins, septicemia, disseminated intravascular coagulation, chronic left heart failure, pancreatitis, surfactant dysfunction, ventilator-induced injuries, adverse drug reactions, and uremia.[2]

Uremic pneumonitis results from diffuse alterations in alveolo-capillary permeability combined with complicating factors.[1] These additional factors include, but are not limited to: alterations in coagulability[1], fluid overload, pulmonary hypertension, decreased oncotic pressure, and metabolic acidosis-induced pulmonary vasoconstriction.[5] The intensity of the azotemia does not correlate with the presence of uremic pneumonitis.[1] One study examining the prevalence of uremic pneumonitis in humans that had died of glomerulonephritis found that uremic pneumonitis occurred exclusively in those patients that had rapidly progressive (and very inflammatory) mesangioproliferative glomerulonephritis.[1]

The uremia-associated damage to the alveolus and capillaries results in leakage of plasma into the alveoli and interstitium.[1] The resultant histologic lesions are characterized by diffuse alveolar capillary damage, protein-rich interstitial and intra-alveolar edema, atelectasis, alveolar hemorrhages and hyaline membranes.[5] Mineral is frequently deposited on the walls of the alveolar ducts and pulmonary arterioles.[9] This tissue damage ultimately results in recruitment of neutrophils and macrophages. In rats, proteolytic enzymes and oxidants derived from the increased numbers of macrophages in the interstitial spaces are believed to be responsible for the destruction of elastic fibers, collagen and proteoglycans in the alveoli.

Similarly, increased numbers of neutrophils mediate destruction through elastase, cathepsins, collagenase, myeloperoxidase and other oxidants.[5] The resulting enzymatic and oxidative injuries exacerbate the uremia-associated damage to the alveolus and capillaries.

Cardiovascular lesions are also associated with uremia. Acute renal failure may result in fibrinoid vascular necrosis (arterial hyaline degeneration), while chronic renal failure produces hyperplastic arteriosclerosis. Mural endocarditis associated with uremia is typically confined to the left atrium and large elastic arteries, as was seen in this case. This lesion begins with deposition of glycosaminoglycans in the subendocardium/intima. This may progress to necrosis of the lining endothelium as well as the collagen, elastin and reticulin fibers with secondary inflammation. As in this case, concurrent mineralization can be marked.[8]

Nonrenal lesions of uremia are more likely to occur in cases of chronic renal failure than in cases of acute renal failure. Mineralization of the intercostal spaces, beneath the parietal pleura, as was seen in this case, is common. It is preceded by necrosis of the subpleural connective tissue with extension to the intercostal muscles and overlying parietal pleura. The pathogenesis of diffuse tissue mineralization in uremia is not completely clear. Uremic mineralization is likely a combination of dystrophic and metastatic mineralization. In dogs, renal failure is usually associated with hyperphosphatemia and hypocalcemia, as was seen in this dog. This may be complicated by concurrent renal secondary hyperparathyroidism.[9]

The increased anion gap in combination with decreased bicarbonate is consistent with a metabolic titration acidosis. The increased anion gap is likely due to the uremic acids. Additionally, the PCO2 is high (respiratory acidosis) and the PO2 is low (hypoxemia). The combination of these blood gas findings suggests decreased alveolar ventilation secondary to the marked uremic pneumonitis. This dog had both a metabolic and a respiratory acidosis.

Despite the acute onset of clinical signs of renal failure reported in this case, the renal lesions were chronic and consisted primarily of a lymphoplasmacytic interstitial nephritis with marked glomerulocystic change. The inciting cause of the renal failure in this dog is not known.

JPC Diagnosis: Lung: Alveolitis, chronic and necrotizing, focally extensive, severe, with marked mineratlization, hyaline membranes, emphysema, and fibrinous pleuritis.

Conference Comment: Even though there is hypocalcemia due to renal failure, there is still widespread soft tissue mineralization due to the drastic hyperphosphatemia. Mass law is the product of serum phosphorus and calcium, and soft tissue mineralization occurs when this exceeds 70.[3] In the moderator's experience, the most common location for uremic pneumonitis is in the first third or fourth portion of the dorsal diaphragmatic lobes, and not in cranioventral lobes.

Conference participants discussed the fact that this dog likely had glomerular disease as the inciting cause of chronic renal failure because of the proteinuria and serum hypoalbuminemia. Renal and hepatic disease are the two primary sources of hypoalbuminemia, and only renal disease will preserve globulins as in this case. The two primary glomerular lesions in dogs in chronic renal failure are glomerulonephritis and amyloidosis. Cystitis is the most common cause of proteinuria in dogs, but concurrent hypoalbuminemia does not occur as in this case. The proteinuria must be evaluated in light of the erythrocytes present, which in this case are minimal, because hematuria contributes protein through albumin, globulin, and hemoglobin. Additionally, the urine dilution must be taken into consideration; the urine is dilute in this case, and therefore the proteinuria is significant.[4,10,11,12]

Conference participants differentiated this as a case of chronic renal failure from acute renal failure for the following reasons: the presence of serum hypoalbuminemia, since albumin has a half-life of around 20 days; the presence of glomerular disease, as acute renal failure of glomerular origin is extremely rare; the presence of soft tissue mineralization[4,10,11,12], and the presence of non-regenerative anemia due to decreased erythropoietin production by the kidneys and uremia-induced erythrocyte fragility, since anemia is usually not present with acute renal failure.[6]

Conference participants discussed the azotemia as a mixture of pre-renal and renal origin, since the hypernatremia and hyperchloridemia point to dehydration and renal failure usually results in hyponatremia and hypochloridemia. Mixed metabolic and respiratory acidosis is present in this case, as mentioned by the contributor. In addition to the respiratory component being due to mineralization of pulmonary septa and decreased alveolar ventilation, pulmonary thrombosis is another likely cause, although this was not present in the slides.[4,10,11,12] This is due to the loss of antithrombin III from glomeruli, placing the dog in a hypercoagulable state. The most common locations for thrombosis are the lungs and the aortic quadrification.[7] Renal failure also usually produces vasculitis, especially in the midzonal region of vessels, and this is generally prominent in the lungs and

gastrointestinal tract, although this was not present in this case.[4,11]

Contributor: University of Tennessee
College of Veterinary Medicine
Department of Pathobiology
2407 River Drive, Room A201
Knoxville, TN 37996-4542

References:

1. Bleyl U, Sander E, Schindler T. The pathology and biology of uremic pneumonitis. *Intensive Care Med*. 1981;7:193-202.
2. Caswell JL, Williams KJ. Respiratory system. In*: Jubb, Kennedy, and Palmer's Pathology of Domestic Animals*. 5th ed. Vol. 2. Edinburgh, Scotland: Saunders Elsevier; 2007:564-567.
3. Cortadellas O, Fernandez del Palacio MJ, Talavera J, et al. Calcium and phosphorus homeostasis in dogs with spontaneous chronic kidney disease at different stages of severity. *J Vet Intern Med.* 2010;24:73-79.
4. Dibartola SP. Clinical approach and laboratory evaluation of renal disease. In: Ettinger SJ, Feldman EC, eds. *Textbook of Veterinary Internal Medicine*. 7th ed. Vol 2. St. Louis, MO: Saunders Elsevier; 2010:1955-69.
5. Heidland A, Heine H, Heidbreder E, et al. Uremic pneumonitis: evidence for participation of proteolytic enzymes. *Contr Nephrol*. 1984;41:352-366.
6. King LB, Giger U, Diserens D, et al. Anemia in chronic kidney failure. *J Vet Intern Med*. 1992;6(5): 264-270.
7. Kuzi S, Segev G, Haruvi E, et al. Plasma antithrombin activity as a diagnostic and prognostic indicator in dogs: a retrospective study of 149 dogs. *J Vet Intern Med*. 2010;24(3):587-96.
8. Maxie MG, Robinson WF. Cardiovascular system. In: *Jubb, Kennedy, and Palmer's Pathology of Domestic Animals*. 5th ed. Vol. 3. Edinburgh, Scotland: Saunders Elsevier; 2007:30.
9. Maxie MG, Newman SJ. Urinary system. In: *Jubb, Kennedy, and Palmer's Pathology of Domestic Animals*. 5th ed. Vol. 2. Edinburgh, Scotland: Saunders Elsevier; 2007:432-436.
10. Polzin DJ. Chronic kidney disease. In: Bartges J, Polzin DJ, eds. *Nephrology and urology of small animals*. West Sussex, England: Wiley-Blackwell; 2011:433-471.
11. Polzin DJ. Chronic kidney disease. In: Ettinger SJ, Feldman EC, eds. *Textbook of Veterinary Internal Medicine*. 7th ed. Vol 2, St. Louis, MO: Saunders Elsevier; 2010:1990-2021.
12. Tripathi NK, Gregory CR, Latimer KS. Urinary system. In: Latimer KS, ed. *Duncan and Prasse's Veterinary Laboratory Medicine: Clinical Pathology*. 5th ed. Ames, IA: Wiley-Blackwell; 2011:270-80.