



## WEDNESDAY SLIDE CONFERENCE 2016-2017

# Conference 10

9 November 2016

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### CASE I: AzVDL 02-3362 (JPC 4019839).

**Signalment:** Nine-year-old, female, Siamese cross, (*Felis catus*).

**History:** The cat presented for chronic cystitis unresponsive to antibiotic therapy and dietary changes. Pneumocystogram revealed a thickened uneven bladder wall with a small lumen. The cat was referred to an internal medicine service with the primary differential diagnosis of neoplasia. Ultrasound showed an irregular mass in the bladder wall at the trigone. A “traumatic catheterization” of the bladder was performed and cytologic preparations were submitted for evaluation.

**Gross Pathology:** None.

**Laboratory results:** The CBC at presentation to the specialty service was within reference interval. The only abnormality in the chemistry profile was hyperglycemia. The abnormalities in the urinalysis included glucosuria, mild pyuria and large numbers of variably sized transitional epithelial cells.

**Cytologic Description:** The preparation has large areas of dense cellularity. There are numerous linear structures (nematode uterus) containing oval bioperculated ova are present within the dense areas. Well-preserved and degenerate parasite ova are also scattered throughout the background. The ova are approximately 60 microns in length with a granular interior and a thick refractile shell. In the thinner areas of large cellular densities, the nucleated cells are present in organized sheets with well-defined cytoplasmic borders. The cells have round nuclei with mild anisokaryosis and a scant to small amount of basophilic cytoplasm. The background has a large number of lysed and degenerate cells with fewer small clusters of intact epithelial cells showing the same morphology as those within the dense clusters. There are areas of monolayer adjacent to the dense clusters with a moderate number of neutrophils and eosinophils. Eosinophils, neutrophils, and small lymphocytes are found throughout the background. Occasional small lymphocytes contain a few eosinophilic to azurophilic granules.

Table 1: Capillarid Species

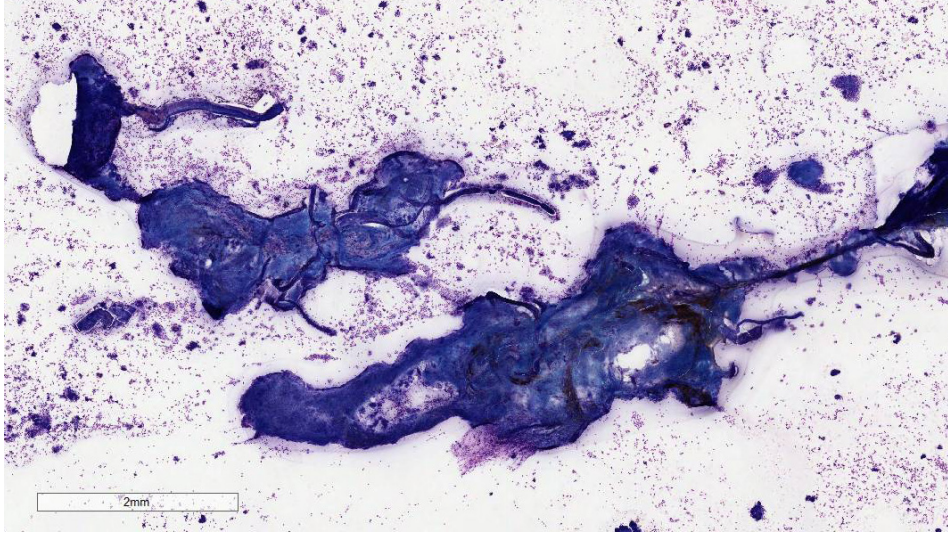
Name	Location	Host
<i>Eucoleus bouhmi</i>	frontal sinus	fox, dog
<i>Eucoleus aerophilus</i>	bronchi	dog, cat, fox
<i>Aonchotheca putorii</i>	stomach, intestine	bear, hedgehog, raccoon, swine, bobcats, mustelids, cat
<i>Aonchotheca</i> spp	intestine	ruminants
<i>Calodium hepaticum</i>	liver	rodents, many occasional hosts including humans.
<i>Pearsonema plica</i>	urinary bladder	dog, fox, wolf
<i>Pearsonema feliscati</i>	urinary bladder	cat

**Contributor’s Cytologic Diagnosis:**

Transitional cell hyperplasia with mild suppurative and eosinophilic inflammation and fragmented *Pearsonema* (*Capillaria*) *feliscati* nematode and numerous bio-perculated eggs.

**Contributor’s Comment:** Urinary nematodiasis is caused by several genera and affects numerous species of domestic and wild animals (Table 1).<sup>2, 5,10</sup> The nematode species found in the kidney, ureters or renal vasculature are associated with clinical disease. The most spectacular of which is the giant kidney worm of dogs, *Dioctophyme renale*, that eventually destroys and replaces the renal parenchyma. Nematodes of the genera *Pearsonema* (*Capillaria*), on the other hand, are found within the urinary bladder and are often an incidental finding with minimal clinical disease evident.<sup>2,10</sup> The capillarid

nematodes have been placed in several new genera based on location within the host, the most accepted of which are *Eucoleus* (nasal sinus and bronchi), *Aonchotheca* (intestine) and *Pearsonema* (urinary bladder) (Table 2).<sup>2</sup> *Pearsonema plica* and *P. feliscati*, infect the domestic dog, fox, wolf, and cat. In most cases, the nematode is loosely attached to the urinary bladder mucosa and, less often, ureteral mucosa with mild inflammation and edema evident on histologic examination of the affected tissue.<sup>7,8</sup> Clinical disease is uncommon but has been reported in the dog and fox and rarely in the cat.<sup>7,8</sup> The prevalence of these parasites in the dog and cat is not known. However, a prevalence of 76% and 59% has been reported in two dog breeding kennels in the United States.<sup>7</sup> In this heavily parasitized population, hematuria, dysuria and pollakiuria were common findings in the dogs with confirmed infection.



Urinary bladder, cat. Several large aggregates of protein encase tangential sections of adult nematodes. (green arrows.) (Wrights, 16X)

In the cat, the disease is rarely reported in the United States;<sup>6</sup> however, in Australia, an incidence of greater than 30% was found in one survey study.<sup>8</sup> No evidence of clinical cystitis was seen in the infected cats. On histological examination of the urinary bladder in the infected cats, the nematodes were superficially embedded in the mucosa with no breaching of the basal layer or basement membrane. A moderate inflammatory infiltrate that included eosinophils was seen in association with the embedded parasite. The lifecycle for *P. feliscati* is not determined.<sup>2,6</sup> It is assumed to be similar to *P. plica* which is thought to be through the earthworm as an intermediate host or a transport host such as a bird. Adult worms are 2.5 to 5 cm in length. The ova

are elongate and approximately 60 microns in length and 27 microns in width. They have bipolar plugs (bioperculate), a thick shell with “globular” ridges enclosing a single cell.<sup>10</sup> The literature does not provide morphologic or biological

characteristics other than the host to distinguish *P. plica*

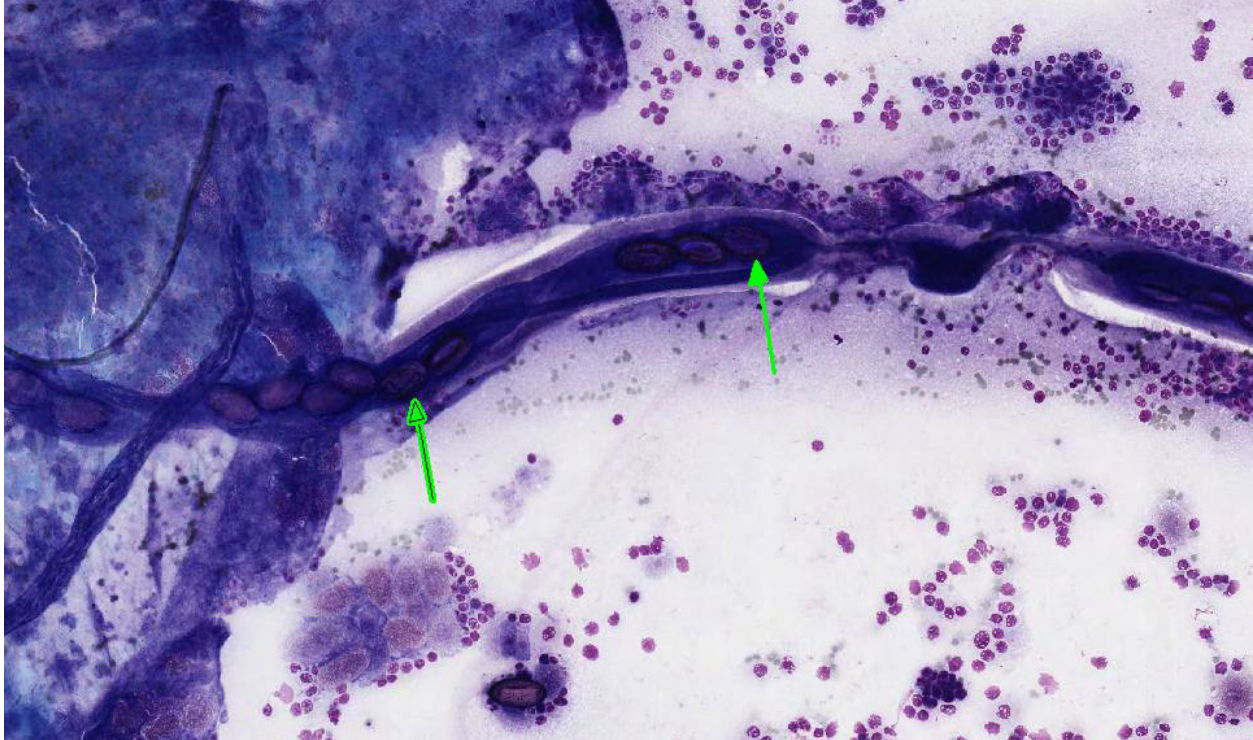
and *P. feliscati*. The cat is included in host species for both *P. feliscati* and *P. plica* in *Georgis’ Parasitology for Veterinarians* with no mention of differential characteristics.<sup>2</sup> The capillarid in this case is given as *P. feliscati* based on host.

**JPC Cytologic Interpretation:** Presence of *Peasonema* spp nematode fragments and ova, mild transitional cell dysplasia, and low grade eosinophilic and neutrophilic inflammation, Siamese cross, *Felis catus*.

**Conference Comment:** The contributor provides a compelling cytologic specimen and outstanding review of capillarid

Table 2: Urinary Nematodes

Name	Host
<i>Dioctophyme renale</i>	dog, mink
<i>Pearsonema plica</i> , <i>P. feliscati</i>	dog, fox, wolf, cat
<i>Stephanurus dentatus</i>	swine
<i>Trichosomoides crassicauda</i>	rats
<i>Crassicauda boopis</i>	whales



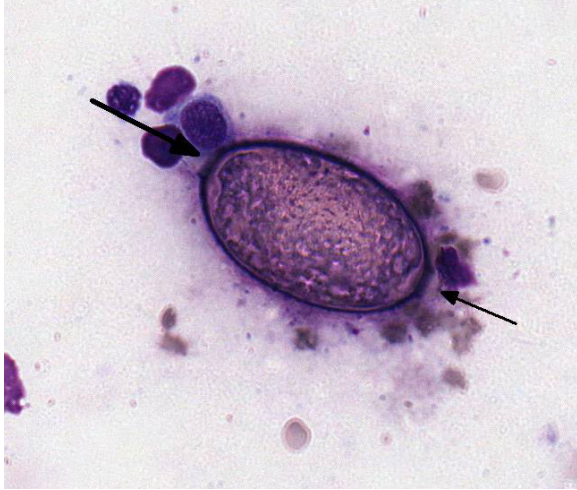
*Urinary bladder, cat. Tangential sections of the adult female parasites contain numerous 25x50um eggs within the uterus. (Wrights, 124X).*

nematodes affecting a wide variety of veterinary species. As mentioned by the contributor, the *Capillaria* genera have been reclassified based on the location of the adult parasite in the host; however, the genus name *Capillaria* is still widely used in the veterinary literature.

Typically, infection with *Pearsonema feliscati* is of little pathologic significance to the cat and is usually considered an incidental finding. Most studies show no relationship between the presence of adult capillarids in the bladder and significant cystitis.<sup>8,9</sup> Histologically, *Pearsonema feliscati* resides in the superficial epithelium of the urinary bladder and does not penetrate the basement membrane.<sup>5</sup> However, if the ureters become occluded with adult nematodes, cats may display the clinical signs of post-renal obstruction. The highest reported number of adult worms present from a single urinary bladder was 25 and

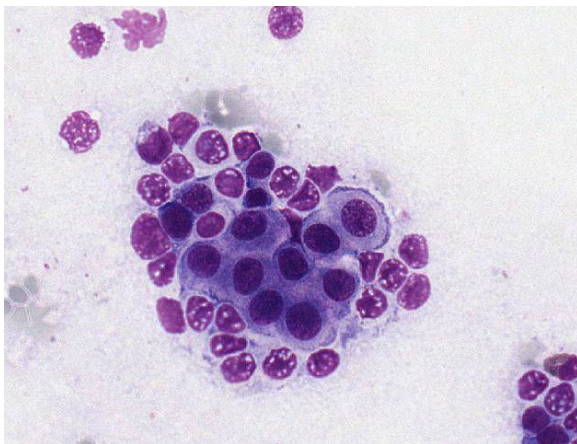
large numbers of eggs were found in all bladders containing five or more adults.<sup>9</sup> In this case, the mild to moderate eosinophilic and neutrophilic inflammation may be secondary to a high parasite burden.

In both dogs and cats, *Pearsonema plica* has been reported in the urinary bladder and ureter submucosa and is typically associated with mild subclinical inflammation and edema.<sup>1,7</sup> There is a higher prevalence of the parasite in wild red foxes (*Vulpes vulpes*) in many European countries and it is associated with an increased pathogenicity. This can result in severe cystitis, pollakiuria, dysuria and hematuria in this species.<sup>1,3</sup> In this case, both *Pearsonema plica* and *Pearsonema feliscati* have been implicated in urinary bladder infection in cats, conference participants could not distinguish between two cytologically.



Urinary bladder, cat. Eggs are 25x50um, brown, with a bioperculated (arrows) brown refractile shell and granular contents. (Wrights, 830X)

Conference participants readily identified numerous bioperculate eggs free within the sample and inside the reproductive tract of adult nematode fragments. *Pearsonema* spp are a subclassification of aphasmid nematodes of the family *Trichuridae*. Histologically, aphasmid nematodes are characterized by thin eosinophilic cuticle, reduced polymyarian-coelomyarian musculature, two hypodermal bacillary bands, a stichosome esophagus, a spiny sheath and oval bioperculate eggs.<sup>4</sup> Cytologically, specific features of the adult



Urinary bladder, cat. There are numerous clusters of transitional epithelial cells with in the specimen. (Wrights, 523X)

nematode can be more difficult to appreciate than on histologic tissue section. However, the presence of the highly characteristic ova confirms the presence of a urinary capillarid nematode.

Participants also noted vacuolation, binucleation, anisokaryosis, and prominent nucleoli within the reactive sloughed urothelium. Transitional epithelial cells are among the most pleomorphic cells in the body and can demonstrate marked reactive change in response to a variety of insults. For this reason, the conference moderator reminded participants that care must be taken prior to over-interpreting reactive urothelium as malignancy.

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#### References:

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## **CASE II: 15N0368 (JPC 4084209).**

**Signalment:** Ten-year-old, mare, quarterhorse, (*Equus ferus caballus*).

**History:** This animal presented to the teaching hospital in November of 2014 for weight loss. At that time, blood work revealed hyperproteinemia and elevated blood ammonia (see laboratory results below). Ultrasound of the liver revealed rounded margins. A liver biopsy was performed and revealed nodular regeneration, bridging fibrosis, and arteriolar and bile duct proliferation. The clinical suspicion at that time was chronic pyrrolizidine alkaloid toxicity despite an

absence of hepatocellular cytomegaly or karyomegaly.

The patient re-presented in January of 2015 for increasing lethargy, dull mentation and waxing and waning appetite. The horse was treated with minocycline, metronidazole, pentoxifylline, lactulose, vitamin E, and prednisolone.

The patient presented again in February of 2015 due to progression of clinical signs and failure to respond to treatment. Euthanasia was elected.

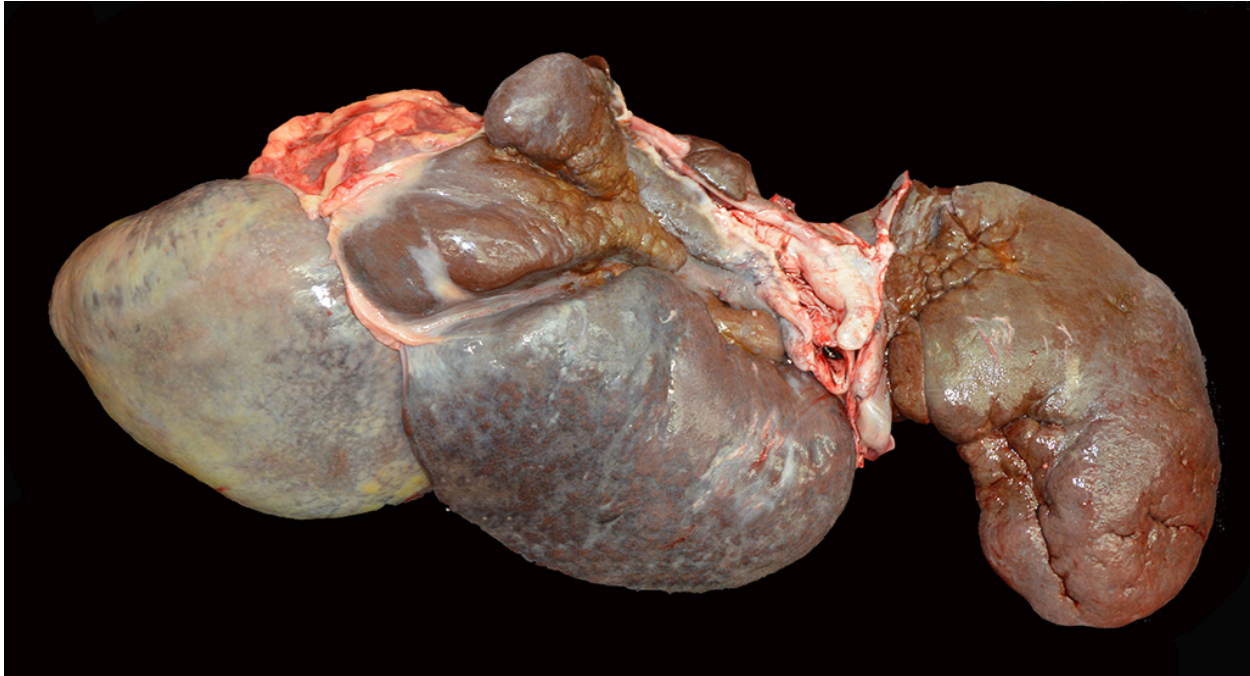
**Gross Pathology:** At necropsy, the liver was markedly reduced in size weighing 3.1 kg (0.7% of body weight) and had thick rounded margins. Some of the lobes appeared multinodular and there were multifocal areas of capsular fibrosis

### **Laboratory results:**

February 2015: (reference ranges)  
GGT 294 IU/L (8-22)  
SDH 16 IU/L (0-8)  
Resting bile acids 36 uMOL/L (4-11.5)  
Plasma ammonia 242 UG/DL (5-59)

Postmortem liver heavy metal screen  
Iron 5100 ppm (100-300)

**Histopathologic Description:** Liver: Within all sections, the hepatic capsule is variably thickened, and the lobular architecture is pronounced due to marked portal to portal bridging fibrosis. Dissecting bands of fibrosis variably infiltrate the surrounding parenchyma causing isolation of hepatic lobules and smaller clusters of hepatocytes. Rare isolated hepatocytes appear hyper-eosinophilic with pyknotic to karyolytic nuclei (individual cell apoptosis). Diffusely, hepatocytes contain variable amounts of coarse, dark brown, granular pigment (hemosiderin). Kupffer cells and



*The liver was markedly reduced in size weighing 3.1 kg (0.7% of body weight) and had thick rounded margins. Some of the lobes appeared multinodular and there were multifocal areas of capsular fibrosis (Photo courtesy of: VMTH Anatomic Pathology, 1 Garrod Drive, University of California, Davis, CA 95616 [http://www.vetmed.ucdavis.edu/vmth/lab\\_services/anatomic\\_pathology/index.cfm](http://www.vetmed.ucdavis.edu/vmth/lab_services/anatomic_pathology/index.cfm))*

macrophages, which course throughout areas of fibrosis, contain similar, but more variably sized, dark brown cytoplasmic granules (hemosiderophages). Areas of fibrosis also contain small to moderate numbers of lymphocytes and plasma cells, with rare neutrophils, and abundant variably sized bile ducts and small-caliber blood vessels. Occasional small aggregates of lymphocytes and plasma cells are observed throughout the parenchyma. In some areas, the hepatic parenchyma has been completely replaced by mature fibrous tissue and proliferating bile ducts. In addition, mature fibrous tissue occasionally appears to occlude central and portal veins with rare evidence of recanalization (venoocclusive disease). Within one section there are large, multifocal areas of acute hemorrhage and edema that cause separation and disorganization of the hepatic cords. Occasional individual collagen bundles are segmentally darkly amphophilic (siderocalcinosis). Within the most severely

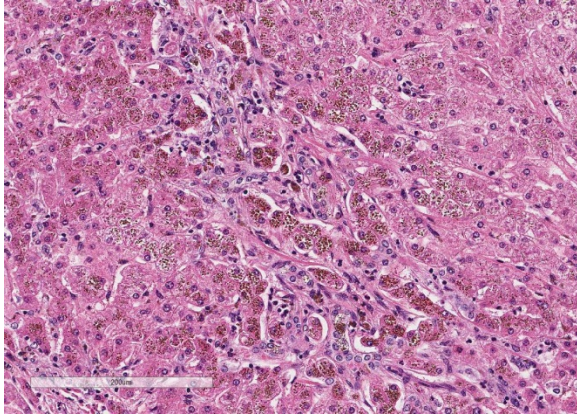
affected sections, there are frequent, irregular, refractile crystals associated with small numbers of multinucleated giant cells and epithelioid macrophages (foreign body response).

**Contributor's Morphologic Diagnosis:**

Liver: Severe, chronic, bridging portal and capsular fibrosis with lobular collapse, veno-occlusion, biliary hyperplasia and marked hepatocellular hemosiderosis.

**Contributor's Comment:**

The abundant hepatocellular and Kupffer cell pigment was confirmed as iron using Perls' iron stain. Heavy metal analysis of the liver revealed an iron concentration of 5100 ppm, far exceeding the normal upper limit of 300 ppm. Perl's staining also revealed iron deposits within smooth muscle trabeculae of the spleen, and within renal tubular epithelium at the corticomedullary junction. Iron within splenic trabeculae and within fibrous tissue in the liver is occasionally



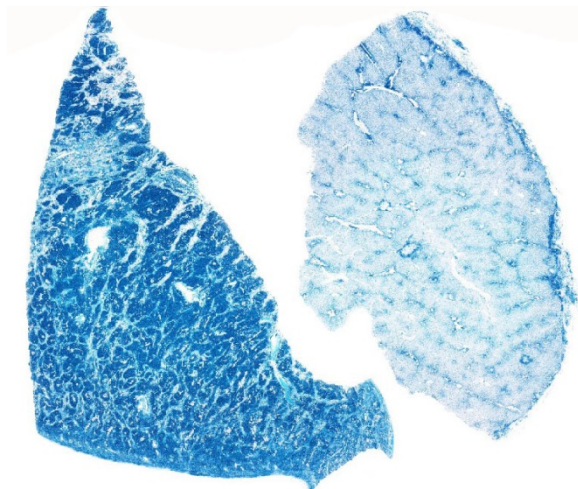
*Liver, horse. There is moderate bridging portal fibrosis which breaches the limiting plate and entraps hepatocytes (center). Hepatocytes, especially in portal areas, contain abundant intracytoplasmic iron. (HE, 168X)*

deposited in conjunction with calcium salts (siderocalcinosis). In addition, the most severely affected sections shows deposition of refractile clear crystals that are associated with a granulomatous foreign body response. These crystals are not birefringent under polarized light.

With the exception of certain avian species, including mynahs and toucans, hemochromatosis is a rare condition in domestic species. A hereditary form of hemochromatosis has been reported in Salers and Salers-cross cattle,<sup>8</sup> and there have been individual case reports in horses.<sup>6</sup> Cases of dietary iron overload have also been reported in sheep and cattle. Iron storage disease is classically divided into two entities: hemosiderosis (iron overload in the absence of clinical signs) and hemochromatosis (iron overload leading to hepatic damage including fibrosis, inflammation, and liver failure). In human medicine, iron storage disease is additionally subdivided into primary and secondary categories. Primary iron storage disease involves an inherent abnormality in iron metabolism. In humans, this is most commonly the result of one of two missense mutations in the HFE gene which encodes a protein involved in the interaction between

transferrin and the transferrin receptor.<sup>9</sup> Secondary hemochromatosis occurs from excessive intestinal absorption of iron either due to iron excess within the diet, or as a response to increased demand for erythropoiesis. Secondary hemochromatosis can occur with any condition leading to chronic hemolysis. Although a very small amount of iron is eliminated through the bile, the body has no natural way of responding to excess iron and therefore iron accumulates over time, primarily in the liver. Iron accumulation results in hepatocellular toxicity through production of free radicals and organelle dysfunction, including lysosomal injury.<sup>8</sup> This can lead to hepatocellular necrosis that progresses to bridging fibrosis, bile duct hyperplasia, and venoocclusive disease, as observed in this case. In humans, hemochromatosis can also increase the risk of hepatocellular neoplasia<sup>9</sup> and in birds, has been shown to predispose to certain bacterial infections such as *Yersinia pseudotuberculosis*.<sup>4</sup>

Distinguishing between primary and secondary iron storage disease can be especially difficult in chronic cases. In



*Liver, horse. The liver stains deep blue with a Perl's iron stain. (Perl's iron, 5X) (Photo courtesy of: VMTH Anatomic Pathology, 1 Garrod Drive, University of California, Davis, CA 95616 [http://www.vetmed.ucdavis.edu/vmth/lab\\_services/anatomic\\_pathology/index.cfm](http://www.vetmed.ucdavis.edu/vmth/lab_services/anatomic_pathology/index.cfm))*



humans, the pattern of hemosiderin deposition can be helpful.<sup>6</sup> In primary iron storage disease, hemosiderin accumulates first in hepatocytes while in secondary hemosiderosis, iron accumulates first within Kupffer cells and macrophages (reticulo-endothelial system). However, this requires that the liver is examined early in disease progression. In this case, a primary abnormality in iron metabolism is suspected based on the lack of clinical or histologic evidence of a second underlying disease process leading to chronic hemolysis, and feeding of a standard equine diet.

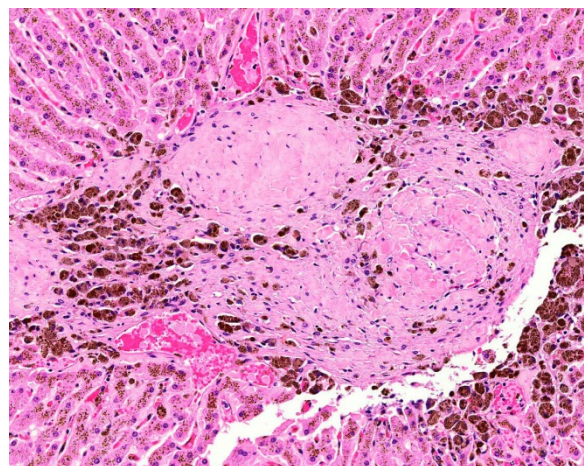
**JPC Morphologic Diagnosis:** Liver: Fibrosis, portal and bridging, diffuse, marked with hepatocellular degeneration and loss and intra-hepatocellular hemosiderosis, Quarterhorse, *Equus ferus caballus*.

**Conference Comment:** The contributor provides an outstanding example and thorough review of hemochromatosis in humans and veterinary species. Free iron is highly toxic to tissues due to its ability to participate in the generation of hydroxyl radical formation via the Fenton or Haber-Weiss reaction with hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) leading to lipid peroxidation and DNA damage.<sup>5</sup> As a result, iron is typically bound to transferrin while in circulation and either ferritin or hemosiderin when stored and sequestered in tissue. When iron is bound to these proteins, it cannot participate in these injurious reactions. Ferritin concentration is highest in the liver, spleen, and bone marrow and is stored in hepatocytes and/or macrophages.<sup>1,3,5,7</sup>

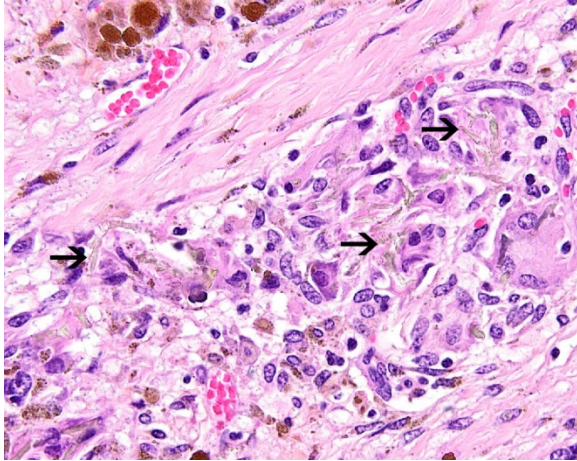
In hepatocytes, iron is derived from plasma transferrin, while iron stored within macrophages is a result of erythrocyte breakdown. Normally, to offset the attritional loss of daily iron, duodenal

enterocytes absorb approximately 1 to 2 mg of iron per day from the diet via divalent metal transporter-1 (DMT-1) and a heme carrier protein-1 (HCP-1) on the luminal surface of the enterocytes.<sup>5,9</sup> Iron is transported from the cytoplasm of the enterocyte to the circulation by ferroportin.<sup>1,7</sup> Absorbed iron circulates bound to transferrin and is used primarily by erythroid precursors in the synthesis of heme. Macrophages in the spleen clear dead and dying erythrocytes and release the iron from heme to export it to the circulation or store it in ferritin. In iron-overload, transferrin is quickly saturated and iron is stored in the liver and various other tissues due to the lack of a regulated pathway for effective iron excretion.<sup>3</sup>

As mentioned above, hepatocytes are a major site of iron storage as ferritin and are also responsible for the production of type II acute phase protein, hepcidin, in response to inflammatory cytokine, interleukin-6.<sup>1,3,5,7</sup> Hepcidin is transported in by blood by alpha-2-macroglobulin and blocks the release of iron from enterocytes and



*Liver, horse. Occasionally, fibrosis of portal areas obliterates portal veins (veno-occlusive disease). (HE, 100X) (Photo courtesy of: VMTH Anatomic Pathology, 1 Garrod Drive, University of California, Davis, CA 95616 [http://www.vetmed.ucdavis.edu/vmth/lab\\_services/anatomic\\_pathology/index.cfm](http://www.vetmed.ucdavis.edu/vmth/lab_services/anatomic_pathology/index.cfm))*



*Liver, horse: Multifocally, non-refractile crystals are present within aggregates of epithelioid macrophages and multinucleated giant cells. (HE, 400X) (Photo courtesy of: VMTH Anatomic Pathology, 1 Garrod Drive, University of California, Davis, CA 95616 [http://www.vetmed.ucdavis.edu/vmth/lab\\_services/anatomic\\_pathology/index.cfm](http://www.vetmed.ucdavis.edu/vmth/lab_services/anatomic_pathology/index.cfm))*

macrophages by degrading the iron exporter, ferroportin. In humans, decreased hepcidin synthesis caused by mutations in the hepcidin gene, *HAMP*, causes severe hemochromatosis in juveniles.<sup>1,5</sup>

Within the cytoplasm, iron is stored as ferritin, which is reconverted into iron as needed by the body. If tissue ferritin levels are high, ferritin aggregates into hemosiderin globules, which is much more difficult to revert back to free iron. In hepatocytes overwhelmed with iron, most iron is stored as hemosiderin. Ferritin and hemosiderin readily stain with Pearls Prussian blue, demonstrated nicely in this case.<sup>1,5</sup>

Iron is a direct hepatotoxin and iron overload often results in the formation periportal bridging fibrosis with little inflammation.<sup>1,5</sup> In addition to the markedly elevated postmortem liver heavy metal screen (Iron: 5100 ppm [100-300]), clinical pathology data from the provided serum biochemistry supports the histologic

findings in this case. Elevated sorbitol dehydrogenase (SHD: 16 IU/L [0-8]) and elevated plasma ammonia (242 UG/dL [5-59]) indicate hepatocellular injury and decreased hepatic function respectively. In addition, elevated gamma-glutamyl transpeptidase (GGT: 294 IU/L [8-22]) and elevated resting bile acids (36 uMOL/L [0-20]) indicate cholestasis and biliary hyperplasia with decreased hepatobiliary function.<sup>1,2,5,8</sup>

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#### **Clin Path Data:**

See charts appended at end of document.

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**CASE III: B110209 (JPC 4086860).**

**Signalment:** Eight-year-old, female, Labrador retriever, (*Canis familiaris*).

**History:** The dog had a history of polyuria and polydipsia with several urinary

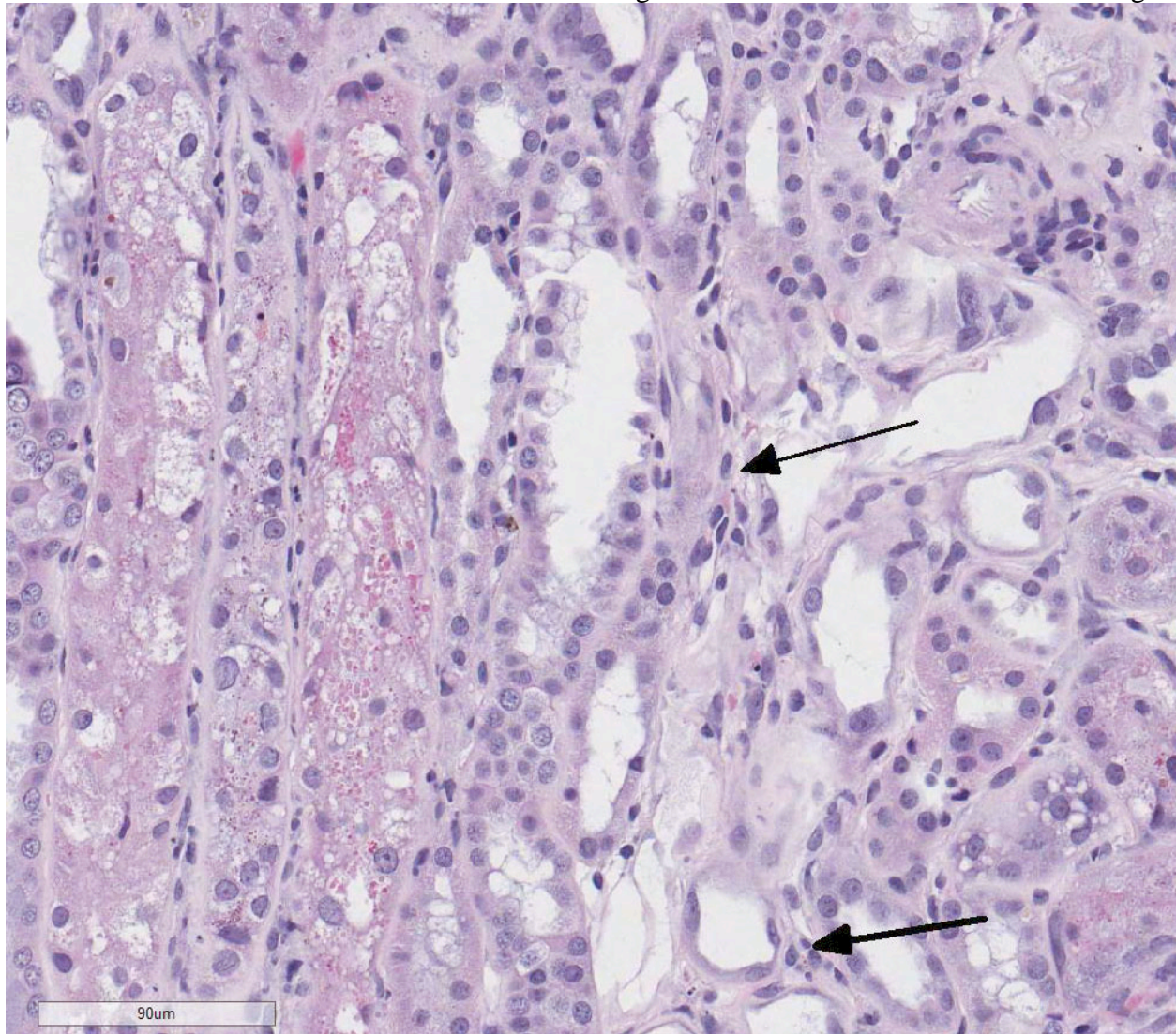
accidents. Otherwise, she was clinically healthy. Initial blood work showed azotemia (BUN: 26 mg/dL [reference range: 5-20]; serum creatinine: 2.0 mg/dL [reference range: 0.6-1.6]) and glucosuria (4+) with normal blood glucose. There was also increased ALT (458 IU/L [reference range: 10-55]). Her urine was isosthenuric and contained fine granular casts. Her blood pressure was normal (systemic blood pressure: 140 mmHg). There was no history of exposure to toxins. Subsequent blood work one month later showed increased azotemia (BUN: 23 mg/dL; serum creatinine: 3.0 mg/dL), ALT (707 IU/L), and mild proteinuria (UPC: 1.3 [normal <0.5]).

**Gross Pathology:** A wedge biopsy of the renal cortex was submitted for evaluation. Wedge biopsies of liver were also harvested and submitted to a different diagnostic laboratory. No gross abnormalities were observed at surgery.

**Laboratory results:**

The unfixed renal tissue that had been submitted for IF evaluation, and a portion of the liver sample were submitted to Colorado State Diagnostic Laboratory to measure copper. There was evidence of copper hepatopathy (copper 2,690 ppm [>1,500 ppm in the liver is considered toxic]) and copper in the kidney 243.00 ppm (relevant reference range >100 ppm in non-hepatic tissue being indicative of toxicity). Urine was also submitted approximately 10 days after the biopsy. SDS-PAGE analysis of urine demonstrated proteinuria due to the presence of low molecular weight proteins, consistent with tubular damage and absence of glomerular injury. An aliquot of this urine sample was submitted to PennGen which documented generalized aminoaciduria and glucosuria without ketonuria or cystinuria warranting a diagnosis of acquired Fanconi syndrome.

glomeruli have minimal to mild mesangial



*Kidney, dog. At left, tubular epithelium is swollen by clear vacuoles (hydropic degeneration) and numerous brown to pink intracytoplasmic granules. There are few necrotic and sloughed cells within the obliterated lumen. At right, atrophic and ectatic tubules are surrounded by collagen (arrows) which is infiltrated by low numbers of lymphocytes and neutrophils. (HE, 224X)*

**Histopathologic Description:** (H&E): There is loss of the apical brush border of the proximal tubules. Scattered tubules are necrotic with cellular casts within lumens and attenuated or absent epithelial lining. Tubules are dilated and undergoing degeneration with single cell necrosis and apoptosis. The tubular epithelial cells contain variably sized cytoplasmic vacuoles with abundant granular pigment. There is marked epithelial cell karyomegaly. A few

expansion and the interstitium is mildly expanded by fibroplasia with scattered aggregates of lymphocytes and macrophages.

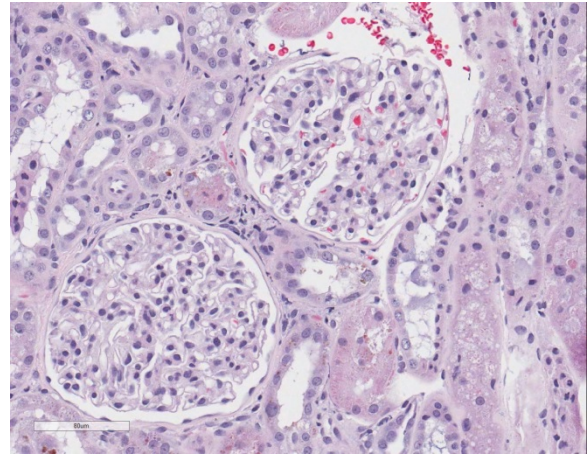
Special stains: Rhodanine stain: Scattered tubular epithelial cells contain small and large red-brown granules, consistent with copper. PAS demonstrates multifocal marked loss of the apical brush borders. The trichrome stain demonstrates a few

large regions of mild to moderate interstitial fibrosis.

**Contributor's Morphologic Diagnosis:**

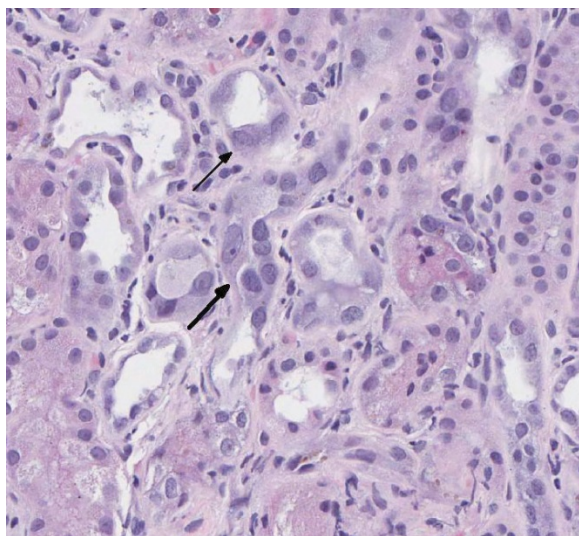
Moderate to severe tubular degeneration with necrosis, regeneration, atrophy, epithelial cell karyomegaly and scattered intracytoplasmic copper within tubular epithelial cells. Mild multifocal interstitial fibrosis.

**Contributor's Comment:** The lesions presented in this case are indicative of renal proximal tubular injury, which was clinically supported by the urinalysis results. These acquired lesions have been associated with copper storage hepatopathy as a part of Wilson's disease in humans and dogs. Acquired Fanconi syndrome is characterized by impaired reabsorptive function of the proximal renal tubules. Clinical features include excessive loss of water, glucose, amino acids, uric acid in the urine, and electrolyte abnormalities. The inherited form of Fanconi-like syndrome is well described in Basenji dog and is thought to be due to increased amounts of cholesterol in the



*Kidney, dog. Glomeruli are mildly enlarged, hypercellular and have increased basement membrane material. Bowman's capsule is also expanded. (HE, 256X)*

normal dogs. In contrast, acquired proximal renal tubulopathies have been loosely characterized in the literature and is attributed to many causes including copper hepatopathy, leptospirosis, hypoparathyroidism, ethylene glycol toxicity, antibiotic, and chicken jerky treats.



*Kidney, dog: Tubules are occasionally lined by regenerating epithelium with large nuclei and basophilic cytoplasm. (HE, 256X)*

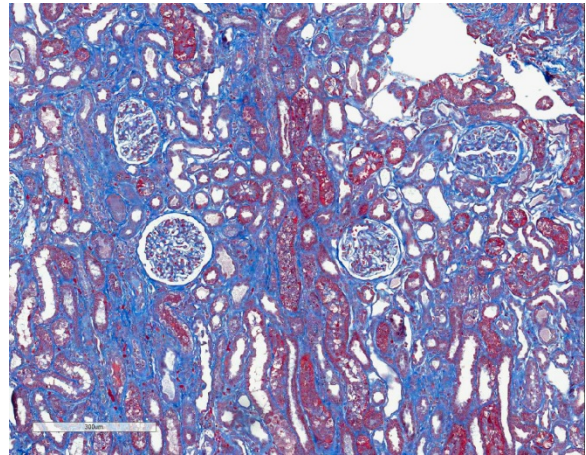
tubular epithelial brush border compared to

In humans, Wilson's disease is an autosomal recessive disorder of copper metabolism caused by mutations in the *ATP7B* gene. Decreased expression of this gene leads to decreased biliary excretion of copper resulting in hepatic copper accumulation. Patients with Wilson's disease also accumulate copper in various tissues including the brain, eye, and kidney. Copper storage diseases have been reported in several canine breeds including Bedlington terrier, Labrador retriever, Doberman pinscher, Dalmatian, Skye terrier and West Highland white terrier. The inherited form of copper storage disease has been well documented in Bedlington terrier in which the copper metabolism domain containing 1 (*COMMD1*) gene is affected. The *COMMD1* protein is important for copper excretion into bile during states of elevated intracellular copper. Hepatic histopathology of copper associated hepatopathies generally

present with mixed inflammation (neutrophilic, lymphoplasmacytic, histiocytic) and is usually localized to the centrilobular regions. Centrilobular necrosis, bridging fibrosis, and cirrhosis have also been described in copper-associated hepatitis. Of note, chronic liver injury will lead to increased amounts of copper in the hepatocytes, sometimes making it difficult to discern whether intracellular copper is the cause or the effect of the liver injury.

A few case series/reports have documented acquired proximal renal tubulopathies associated with copper storage hepatopathy in dogs. Breeds included are: Clumber spaniel, West Highland white terrier, Cardigan Welsh corgi, and Labrador retriever. The renal histologic findings in previous reported cases were consistent with the case presented here. Histologic evaluation of the renal tissues showed proximal tubular epithelial degeneration, necrosis, and regeneration. The tubular epithelial cells were plump with variably sized vacuoles. Using rhodanine stain, one case reported copper deposition was mainly localized to the corticomedullary junction and medullary areas; however copper staining can be variable. Therefore, mild tubular epithelial cell degeneration and loss of the apical brush border in the setting of clinical symptoms of Fanconi syndrome should alert the pathologist to possible copper-mediated damage to the renal proximal tubules. Assay of copper levels in the liver or kidney samples supports this pathogenesis.

In previous case reports of copper hepatopathy induced proximal renal tubular disease, there was improvement and resolution of clinical signs with copper chelation therapy, specifically using d-penicillamine. Additional therapies including supportive care, antioxidants, and

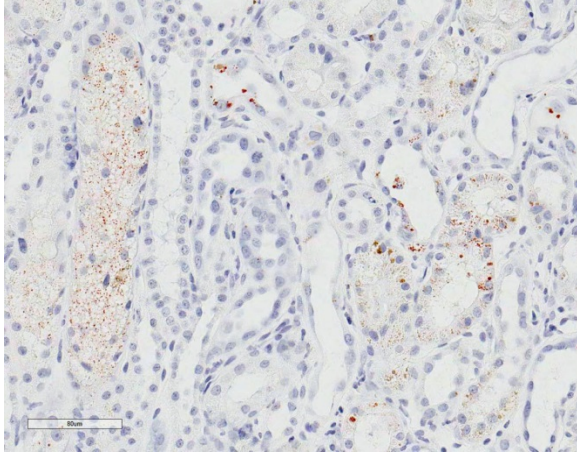


*Kidney, dog. A Masson's trichrome demonstrates the large amount of fibrous connective within the interstitium, which is difficult to visualize on the HE-stained section. (Masson's trichrome, 88X)*

low copper diet can also contribute to improvement of clinical signs.

**JPC Morphologic Diagnosis:** Kidney, tubules: Epithelial degeneration, regeneration, and necrosis, diffuse, marked, with karyomegaly, few tubular casts, intracytoplasmic pigment and interstitial fibrosis, Labrador retriever, *Canis familiaris*.

**Conference Comment:** The contributor provides an excellent example and thorough review of copper-associated acquired Fanconi-like syndrome. This syndrome is characterized by polyuria, polydipsia, hyposthenuria, glucosuria with normoglycemia, hyperphosphaturia, proteinuria, and amino aciduria due to impaired renal tubular absorption of glucose, phosphates, sodium, potassium, uric acid, and amino acids.<sup>1,2,4,7</sup> In this case, this animal had glucosuria with normoglycemia and aminoaciduria indicating poor proximal convoluted tubular functioning. Glucose is normally resorbed in the renal proximal tubules via the sodium-glucose co-transport system.<sup>1,7,9</sup> The concentration gradient established by this system also promotes sodium resorption from the tubular fluid. In



*Kidney, dog: A rhodanine stain demonstrates abundant copper within degenerate/necrotic tubules. (Rhodanine, 252X)*

congenital or acquired tubular defects of Fanconi-like syndrome, glucose is not resorbed and will cause an osmotic diuresis. This diuresis causes a marked decrease in kidney's ability to concentrate urine and will increase urine volume; indicated by polyuria and isosthenuria reported in this case.<sup>1,7,9</sup> The polydipsia is likely secondary to compensation from increased fluid loss in the urine.

Conference participants discussed the significance of the reported presence of low molecular weight proteins in the urine using sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE). In general, there are four main types of proteinuria: pre-renal, glomerular, tubular, and hemorrhagic/inflammatory. In pre-renal proteinuria, small proteins such as hemoglobin dimers, myoglobin, and light chains are present in the plasma at increased concentrations and pass through the glomerulus and are incompletely resorbed by fully functioning tubules.<sup>8</sup> Glomerular proteinuria is characterized by damage to the glomerulus, thus enabling high molecular weight and negatively charged proteins to leak into the filtrate and pass into the urine due to loss of selective permeability.<sup>8</sup> In tubular proteinuria, proximal renal tubules

are damaged or defective so low molecular weight proteins, like smaller globulins and some albumen, do not get resorbed from the ultra-filtrate and are excreted in the urine. Hemorrhagic/inflammatory proteinuria occurs due to hemorrhage or inflammation within the renal tubules, renal pelvis, or lower urinary tract. In this case, SDS-PAGE detected low molecular weight proteins within the urine and suggests that the primary lesion is in the proximal tubules rather than the glomeruli.<sup>8</sup> This finding is confirmed by the histopathology of the kidney in this case. The characterization of proteinuria by SDS-PAGE is a useful antemortem clinical tool to identify the main pathophysiologic mechanism involved.

Although not reported in this case, this animal was likely in a secretory metabolic acidosis due to renal tubular acidosis and loss of bicarbonate through the urine. In cases of Fanconi-like syndrome, the renal proximal tubules fail to resorb filtered bicarbonate.<sup>3</sup> Other causes of secretory metabolic acidosis include vomiting of intestinal contents rich in bicarbonate, diarrhea, and an inability to swallow saliva rich in bicarbonate in ruminants during dysphagia.<sup>3</sup> The hallmark of this type of acidosis is concurrent hyperchloremia as the body attempts to maintain electroneutrality. In addition, the anion gap will typically be normal because unmeasured anions are not increased.<sup>3</sup>

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**Clin Path Data:**

See chart appended at end of document.

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### CASE IV: 16-2046 (JPC 4084201).

**Signalment:** Three-year-old, male, English setter mix, (*Canis familiaris*).

**History:** The three-year-old intact male English setter mix was picked up by county animal control when it was found roaming freely in a small rural community in Southern Arizona. Aspirate cytology from the preputial mass and several cutaneous masses were submitted.

**Gross Pathology:** The dog had a large ulcerated circumferential mass effacing the preputial mucosa and numerous variably sized cutaneous masses throughout the caudal dorsum, right and left flank, and inguinal regions. The superficial cervical lymph nodes were enlarged.

### **Laboratory results:**

The dog was positive for *Ehrlichia canis* using in-house ELISA testing.





*Preputial mass, dog. The prepuce is markedly expanded by a large ulcerated neoplasm, in addition to other masses on the caudal dorsum, flank, and inguinal regions. (Photo courtesy of: Arizona Veterinary Diagnostic Laboratory, University of Arizona, <http://azvdl.arizona.edu/>)*

**Cytologic Description:** The aspirate preparations from the dermal masses all revealed the same process. The preparations have high cellularity with large numbers of intact cells for evaluation. There is minimal hemodilution. The nucleated cell population consists of round cells with moderate anisokaryosis and anisocytosis. The nuclei are round with coarse “ropey” chromatin and often have a single large pale lightly basophilic nucleolus. The cytoplasm is lightly basophilic and contains small to moderate numbers of discrete round vacuoles. Mitotic figures are common and atypical mitoses are seen. There are occasional neutrophils and small lymphocyte seen intermixed with the neoplastic round cells.

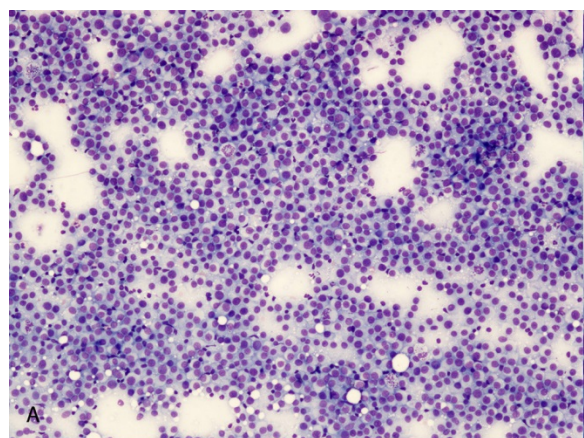
The cytology preparations from the prepuce showed the same cytological findings.

**Contributor’s Cytologic Diagnosis:** Transmissible venereal tumor (TVT) metastatic to skin.

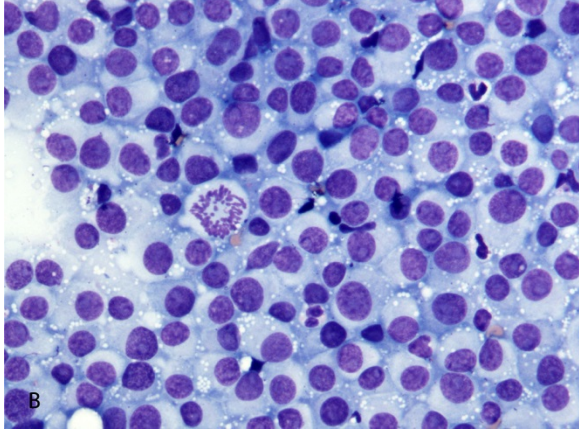
**Contributor’s Comment:** Transmissible venereal tumor is a transplantable neoplasm that affects members of the canid family

(domestic dogs, coyotes, foxes, and wolves).<sup>3</sup> The tumor has a global distribution and highest prevalence in regions with limited canine population control. The tumor spreads by sexual contact and is usually localized to the mucosal surface of the external genitalia of both male and female dogs. However, masses have been reported in the mucosal surfaces of the nasal passage, oral mucosa, anus, and conjunctival surfaces of the eye.<sup>3,7</sup> Metastatic disease is not common but has been documented. In most cases, metastasis is to the regional lymph nodes, but extension of the neoplasm to skin, kidney, brain, bone, peritoneum, and other tissues has been reported.<sup>1,3</sup> The tumor cells are aneuploid and have a unique long interspersed nuclear element (LINE-1) that may be useful to confirm TVT origin in cases involving tumors in unusual sites.<sup>10,12</sup>

While TVT is a relatively uncommon tumor in most of the United States, rural areas that have higher numbers of intact dogs, such as many parts of Southern Arizona, cases are seen on a regular basis. The histological and cytological characteristics of the neoplastic cells along with the location of the mass in



*Preputial mass, dog. The cytologic preparation is densely cellular on a background of light blue protein. (Wright-Giemsa, 100X)*



*Preputial mass, dog. Neoplastic cells are monomorphic with mild anisokaryosis and a few lymphocytes and neutrophils in the background. (Wright-Giemsa, 200X)*

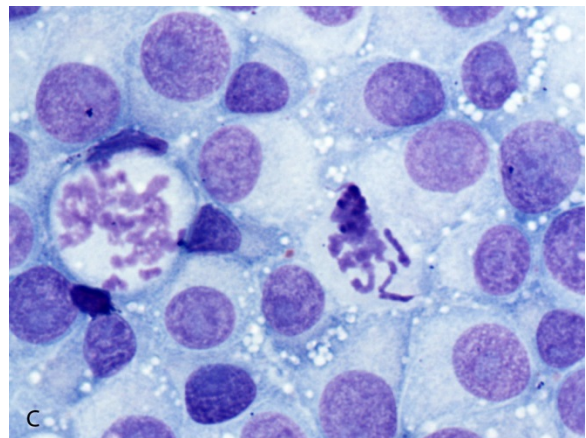
association with the external genitalia make the diagnosis of this tumor relatively straight forward. In this case, the cytological and histological findings from the skin lesions and the preputial lesion were identical supporting metastatic disease. There is one report of a prepubertal female dog without any genital involvement.<sup>4</sup> It is proposed that the tumor cells were transplanted from the dam by cohabitation and grooming/social behaviors. While multicentric disease cannot be ruled out, it is unlikely that multiple sites of transplantation through intact haired skin would explain the presence of the skin lesions in this adult male dog with a concurrent preputial mass.

**JPC Cytologic Diagnosis:** Fine needle aspirate, cutaneous mass: Transmissible venereal tumor, English setter mix, *Canis familiaris*.

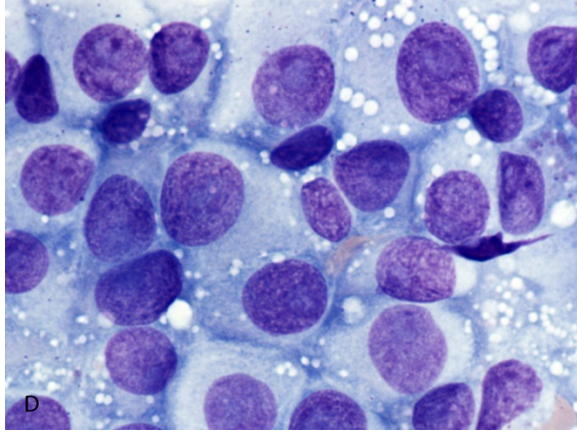
**Conference Comment:** Canine transmissible venereal tumor (TVT), also known as Sticker tumor or venereal granuloma, is an extremely old and remarkably stable transmissible cancer that first arose in canids approximately 11,000 years ago.<sup>2,5</sup> Based on genetic studies, the founder breed is thought to be closely related to wolves or ancient Eastern Asian dog breeds.<sup>1</sup> TVT dispersed

across several continents about 500 years ago and is currently found on every continent in the world other than Antarctica.<sup>5,12</sup> It is the oldest known continuously passaged somatic cell lineage.<sup>5</sup> As mentioned by the contributor, TVT is mainly transmitted during coitus, but can also be transmitted by licking, biting, or rubbing behaviors.<sup>2,8</sup> The infecting cells are physically transplanted and grow as a xenograft in host tissue. Neoplastic cells are thought to be of histiocytic origin and are immune-positive for vimentin, lysozyme, alpha-1-antitrypsin, glial fibrillary acidic protein, and are immune-negative for cytokeratin, S100, and muscle markers.<sup>1,2,9</sup>

Typical gross findings of TVT include solitary or multiple papillary, nodular, ulcerated, and inflamed masses on the mucous membranes of the penis, prepuce, vulva, and vagina, and/or skin and subcutis of the head, neck, limbs, trunk, scrotum, and perineum. There is occasional extension to the uterus and cervix.<sup>2,9</sup> A recent study demonstrated ocular lesions as the single manifestation of TVT with extension to the adjacent conjunctiva and nictitating membrane, presumably by extra-genital



*Preputial mass, dog. Neoplastic mast cells have moderate amounts of light blue cytoplasm and discrete vacuoles. There are two mitotic figures in this field. (Wright-Giemsa, 600X)*



*Preputial mass, dog. Nuclei are mildly anisokaryotic with prominent nucleoli. Few lymphocytes are present in between neoplastic cells. (Wright-Giemsa, 600X)*

inoculation.<sup>3</sup> As mentioned by the contributor, metastasis uncommonly occurs in the draining lymph node.<sup>9</sup>

After transmission, tumorous lesions typically appear within two months. Conference participants discussed the pathogenesis of the tumor growth, stabilization, and regression phases. The initial growth stage is called the progressive phase (P). During the P phase, almost all TVT cells lack expression of major histocompatibility complex (MHC) I and II due to production of inhibitory cytokine transforming growth factor-beta (TGF-beta). This allows the TVT cells to grow and evade immune destruction by cytotoxic T-lymphocytes. After three to nine months, the tumor stabilizes and begins to spontaneously regress. During the regression (R) phase, interleukin-6 (IL-6) from infiltrating lymphocytes is thought to work in conjunction with interferon-gamma (IFN-gamma) to antagonize TGF-beta and increase MHC I and II expression on TVT cells.<sup>1,8-10</sup>

In addition to TVT, conference participants also discussed the devil facial tumor disease (DFTD), which is an emerging rapidly fatal transmissible tumor that is decimating the wild Tasmanian devil population.<sup>8,11</sup> This tumor is of Schwann cell origin and is

spread through biting. Tumors occur primarily in the mouth, head, and neck. DFTD cells evade immune destruction via production of TGF-beta and down regulation of MHC-I and II expression, similar to TVT. However, unlike TVT, spontaneous regression has not been reported in DFTD, and mortality occurs in all affected animals via starvation and frequent metastasis.<sup>8</sup> Other transmissible tumors include clam leukemia of soft shell clams and the contagious reticulum cell sarcoma of Syrian hamsters first described in the 1960's.<sup>6,8,11</sup>

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#### **References:**

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# Case 2 - Clinicopathologic Data

## Chemistry 15C02406 Final Report

<b>Patient#:</b> <b>Name:</b> <b>Breed:</b> EQ-QH <b>Sex:</b> F <b>Color:</b> Red Dun <b>Birth:</b> 2005
---

Provisional Diagnosis/History: Chronic Liver Failure

Equine Foal Reference Intervals

LisAccn	Procs	SpecimenType	Vessel	Method	Collected	DrawnBy	Comment
15C02406	7794	Whole Blood	RTT	VEN	03Feb15 at 3:00pm.	azr	

Procedures Requested: 7794 Liver Panel-Large Animal

Liver Panel-Large Animal	Result	Horse Ref	Units	Comments
TOTAL PROTEIN	7.1	5.8-7.7	G/DL	
ALBUMIN	3.2	2.7-4.2	G/DL	
GLOBULIN	3.9	1.6-5.0	G/DL	
AST	315	168-494	IU/L	
ALKALINE PHOSPHATASE	212	86-285	IU/L	
GGT	294	8-22	IU/L	
SDH-37	16	0-8	IU/L	
BILIRUBIN TOTAL	1.5	0.5-2.3	MG/DL	
BILIRUBIN DIRECT	0.2	0.2-0.6	MG/DL	
BILIRUBIN INDIRECT	1.3	0.3-1.7	MG/DL	
HEMOLYSIS INDEX	11	0-14		
ICTERIC INDEX	3	0-4		
LIPEMIC INDEX	5	0-<1		

HEMOLYSIS INDEX: A hemolysis index value between 0 and 14 will not affect test results. ICTERICUS INDEX: An icterus index value between 0 and 4 will not affect test results. LIPEMIA INDEX: A lipemic index value between 1 and 149 will effect the following test:TRIG.

Ammonia	Result	Horse Ref	Units	Comments
AMMONIA, PLASMA	242	5-59	UG/DL	

Bile Acid	Result	Horse Ref	Units	Comments
BILE ACIDS PRE/RESTING	36		uMOL/L	

Reference 0-20 umol/L

## Case 3 - Clinicopathologic Data

### Initial blood work:

BUN: 26 mg/dL [reference range: 5-20]

Creatinine: 2.0 mg/dL [reference range: 0.6-1.6]

Blood glucose: WNL

ALT (458 IU/L [reference range: 10-55]).

### Urinalysis:

Glucosuria (4+)

Her urine was isosthenuric and contained fine granular casts.

### Subsequent blood work one month later:

BUN: 23 mg/dL;

Serum creatinine: 3.0 mg/dL

ALT (707 IU/L)

### Urinalysis:

Mild proteinuria (UPC: 1.3 [normal <0.5])

SDS-PAGE analysis demonstrated proteinuria due to the presence of low molecular weight protein.

An aliquot from the urine sample documented generalized amino aciduria and glucosuria without ketonuria.