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CASE I – 02-1123 (AFIP 2933943)

Signalment: 1-year-old, male castrated, Singapura, cat (Felis domesticus).

History: Presented with lethargy, persistent fever, enlarged mesenteric lymph nodes, enlarged kidneys, abdominal and thoracic effusions. No history of diarrhea except when fed pumpkin/goat milk diet recommended by breeder.

Gross Pathology: Very thin, icteric cat with 20 ml of gelatinous serosanguinous thoracic fluid and 80 ml of similar abdominal fluid; enlarged lymph nodes (sternal, cranial mediastinal, mesenteric, colonic); multifocal to coalescing yellow-white nodules in liver, spleen, lung, lymph nodes, and kidneys; multiple tan-green 3 to 6 mm irregularly shaped raised ulcerated foci on mucosa of cecum.

Laboratory Results: Anemia, thrombocytopenia, hyperbilirubinemia, elevated alkaline phosphatase, negative feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV) titers; Feline coronavirus titer 1:1600

Contributor’s Morphologic Diagnoses: 1. Severe multifocal ulcerative typhlitis with innumerable intralesional trichomonads (Tritrichomonas foetus).  
2. Cecum: Severe multifocal necrotizing and lymphoplasmacytic vasculitis (FIP).

Contributor’s Comment: This is a section of cecum with areas of mucosal necrosis and ulceration. The ulcers are filled with innumerable, irregularly pyriform to elliptical, 5 x 10 µm, pale-staining basophilic protozoal organisms (trichomonads). These organisms extend into the underlying submucosa and muscularis in some sections. There is granulation tissue and neutrophilic inflammation associated with
the ulcers, but not always with the organisms. Many of the adjacent mucosal crypts contain trichomonads as well. Several blood vessels in the submucosa, muscularis, and serosa are surrounded or obscured by neutrophilic and lymphoplasmacytic inflammation. There are also areas of fibrinoid necrosis characterized by karyorrhectic debris (nuclear dust) and fibrin replacing and expanding the walls of blood vessels. There are mixed populations of bacteria (predominantly filamentous) on the ulcerated surface and extending into the areas of mucosal necrosis.

*Tritrichomonas foetus* is a recently recognized primary enteric pathogen of cats.¹ Natural infections have been associated with large bowel diarrhea and ulceration of the colonic mucosa.² Although the organism was previously identified as *Pentatrichomonas hominis*, rRNA gene sequence analysis, restriction enzyme digest mapping, and light, transmission, and scanning electron microscopy have identified the agent as *Tritrichomonas foetus*, the same organism that causes reproductive disease in cattle.¹ Experimental infection of domestic shorthair cats resulted in diarrhea which resolved after 7 weeks followed by persistent infection.⁴ In previously reported natural and experimental cases, invasion through the mucosa has not occurred. In this case, the combination of feline infectious peritonitis and trichomonosis may have synergistically resulted in more severe enteric lesions.

**AFIP Diagnosis:** Cecum (per contributor): Typhlitis, necrotizing, histiocytic, neutrophilic and lymphoplasmacytic, transmural, multifocal, severe, with ulceration, granulation tissue and myriad protozoa, Singapura, feline.

**Conference Comment:** There is considerable variation among slides. In some sections, there is a perivascular inflammatory infiltrate suggestive of feline infectious peritonitis while in others the inflammation is more diffuse. Precise identification of protozoa in histologic sections is often impossible without utilization of special techniques. Methods of identification of intestinal flagellates include direct cytologic examination of feces suspended in saline solution, protozoal cultures, immunohistochemistry, electron microscopy and PCR. Characteristic cytologic features of *Tritrichomonas foetus* include three anterior flagella, one posterior free flagellum, an undulating membrane, a single nucleus, a stout axostyle, and a stout costa.¹ In this case, the identity of the organism was confirmed by PCR (personal communication, Dr. Jody L. Gookin, North Carolina State University).

Genital trichomoniasis is a contagious venereal disease of cattle. Bulls can be carriers with early infections resulting in balanoposthitis with a purulent discharge. As the infection becomes chronic, there is no discharge, organisms are present in
low numbers and often concentrated in the glans penis. Cows are infected during coitus, and a vaginitis with mucoid floccular discharge develops within a few days. Following the vaginitis, the organism localizes to the uterus and cervix, causing endometritis and cervicitis, and results in repeat breedings, abortion, or pyometra. There are no specific lesions in the aborted fetus. However, large numbers of organisms can be isolated from the fetal fluids and stomach. The placental lesions are not characteristic, and include a white to yellow flocculent exudate, placental thickening, and hemorrhagic cotyledons.\textsuperscript{5}

\textit{T. foetus} has been recently demonstrated to be a feline pathogen that causes large bowel diarrhea in young cats. The factors that result in the rare instances of invasive infections such as this one have yet to be determined.

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\textbf{References:}

\textbf{CASE II – HB3973 (AFIP 2943308)}

\textbf{Signalment:} 5-year-old, female (spayed), Shiba-dog, canine.

\textbf{History:} The dog was presented for hematuria. By ultrasonography, a polypoid round mass, approximately 2 cm in diameter, protruding into the lumen of bladder was noted on the mucosal surface at the cranio-ventral wall of the bladder. Partial cystectomy was performed to remove the affected bladder wall.
Gross Pathology: The firm, 2 x 2 x 1.5 cm mass protruded on the mucosal surface. The polypoid mass had a smooth surface but was extensively ulcerated. The cut surface was solid, white and mildly edematous. The border on the cystic wall was well defined.

Laboratory Results: No atypical cells were detected by fine needle aspiration.

Contributor’s Morphologic Diagnosis: Urinary bladder: Cystitis, eosinophilic, chronic, Shiba-dog, canine.

Contributor’s Comment: Sections were obtained from either of two paraffin-embedded blocks.

The mass was located in the submucosa and was composed of a diffuse proliferation of fibrous tissue that contained fibrocytes, fibroblasts, lymphocytes, plasma cells, abundant blood vessels, and numerous eosinophils. Most of the mucosal epithelium on the mass was ulcerated and numerous neutrophils infiltrated the superficial layer of the mass. There was mild epidermal hyperplasia with Brunn’s nests, mild proliferation of blood vessels, mild focal edema and hemorrhage with hemosiderin-laden macrophages in the mucosa adjacent to the mass. These histological findings are consistent with those of eosinophilic cystitis previously described in dogs.²

The lesion is considered a variant of polypoid cystitis, one in which eosinophils are the predominant component.¹ The alternative name of inflammatory fibrous polyps has been suggested.³ A differential diagnosis includes fibroma, which lacks eosinophilic infiltration. There appears to be some overlap between the diagnosis of fibrous polyps and fibroma and the interpretations of such lesions are not unanimous.³

The etiology and pathogenesis of eosinophilic cystitis are still unknown.² The lesions occur in a variety of breeds of dogs ranging in age from 8 months to 15 years, with an average of 8 years.³ Hematuria is the most common clinical sign in dogs. The lesions usually have a benign clinical course and surgical excision is curative.

AFIP Diagnosis: Urinary bladder: Polypoid eosinophilic cystitis, Shiba, canine.

Conference Comment: As the contributor noted, a variety of names have been utilized for similar lesions including fibroma, fibrous polyp, eosinophilic cystitis, polypoid eosinophilic cystitis, cystitis with fibroplasia, and mesenchymal tumor
with inflammation. Although pathologists may not agree on nomenclature, the histological features include: hyperplastic, often ulcerated transitional epithelium; a nodule of fibrous connective tissue confined to the propria/submucosa; abundant vascular supply; inflammatory cells with a predominance of eosinophils; and occasionally foci of granulopoiesis, eosinophilopoiesis, cystitis glandularis and Brunn’s nests. The mesenchymal cells are surrounded by a material that stains as collagen with Masson’s trichrome. Immunohistochemically, the mesenchymal cells are not immunoreactive for desmin and muscle specific actin.3,4 Definitive differentiation of inflamed fibrous neoplasms from proliferative fibrous inflammatory lesions is often problematic.

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CASE III – 2004903384 (AFIP 2937492)

Signalment: Five-year-old, female, ferret (Mustelae putorius furo).

History: An intact female domestic ferret was evaluated for bloody stool. Clinical signs included emaciation, loss of body weight and abdominal swelling due to ascites. Generalized alopecia and anemia were also observed. Blood biochemical examinations revealed increased enzyme activities of aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactose dehydrogenase (LDH) and alkaline phosphatase (ALP), and increased level of total bilirubin. Mild hypoglycemia was also detected. Despite various supportive treatments, the ferret died three months after first presentation to the animal hospital.
**Gross Pathology:** The liver was yellow to light tan and slightly enlarged, with a coarse multi-nodular appearance (Fig.1).

**Laboratory Results:**
At first presentation:
- WBC 10400/µl
- ALT over 1000 IU/l
- T-Cho 252.2 mg/dl
- Ht 26.3%
- AST 540 IU/l
- TG 87.6 mg/dl
- Hb 7.8g/dl
- ALP 200 IU/l
- BUN 33 mg/dl
- T-Bil 0.1 mg/dl
- Glu 118.5 mg/dl

About 1 week prior to death:
- WBC 8800/µl
- ALT 267 IU/l
- T-Bil 4.3 mg/dl
- Ht 29.7%
- AST 154 IU/l
- BUN 51.1 mg/dl
- Hb 10.1g/dl
- ALP 125 IU/l
- Glu 136.3 mg/dl

**Contributor’s Morphologic Diagnosis:** Massive hepatocellular necrosis and various degenerative changes in hepatocytes (ie; eosinophilic granules, lipid and bile pigment accumulations, severe vacuolation). Regenerative nodules of hepatocytes and cholangiocellular (bile ducts) proliferation (so-called toxic hepatopathy or chronic progressive hepatitis, consistent with Copper toxicosis).

**Contributor’s Comment:** Copper storage hepatopathies in Bedlington terriers and West Highland White terriers are well documented in the literature. The disorder in Bedlington terriers is an inherited autosomal recessive defect. In West Highland White terriers, although the disorder is also thought to be an inheritable liver disease, not all of the affected dogs show signs of liver disease. In domestic ferrets, an identical disease condition with similar clinical features and histopathological changes is reported,¹ and thought to have an inheritable component.

The main histopathological changes in this specimen are massive to focal necrosis of hepatocytes, with mild fatty change and severe vacuolation. In addition to these changes, there are eosinophilic granules in the cytoplasm of degenerative hepatocytes. These granules stain positive for rhodanine, a copper-specific stain. Accumulation of an intracytoplasmic eosinophilic material is also present in Kupffer cells and macrophages.

Other lesions include mild fibrosis with mononuclear cell infiltration, reactive proliferation of cholangiolar epithelial cells, bile duct obstruction (bile thrombus or cholestasis), and regenerative hepatocellular nodules. This ferret also had bilateral adrenocortical adenomas and an islet cell tumor that are thought to be the cause of the generalized alopecia and hypoglycemia.
The genetic defect in the Bedlington terriers causes expression of an abnormal hepatic metallothionein. Defective metallothionein results in reduced biliary excretion of copper and excessive copper becomes sequestered in hepatocellular lysosomes. The association between an increased hepatic copper concentration and its relationship to tissue injury is controversial in dog breeds other than the Bedlington terrier.

Occlusion of the major bile duct has been shown to cause elevation of hepatic copper concentration in cats, but not in dogs. Chronic hepatitis, chronic cholestasis and cirrhosis have been shown to lead to increased tissue copper concentrations in dogs, but these findings are not known in ferrets. The cause of copper toxicosis in this ferret is unknown, and a genetic predisposition is also unknown.

AFIP Diagnosis: Liver: Cirrhosis, characterized by multifocal necrosis, regenerative nodular hepatocellular hyperplasia, fibrosis, biliary hyperplasia, canalicular cholestasis, hepatocellular lipidosis, extramedullary hematopoiesis and eosinophilic refractile hepatocellular cytoplasmic granules, ferret, mustelid.

Conference Comment: Copper-associated liver diseases are well recognized in animals and humans. Copper toxicosis results from disruption of normal copper homeostasis or accumulation of copper in excess of metabolic requirements and may be either primary or secondary. Primary copper toxicosis results from an inherited metabolic defect. Secondary copper toxicosis results from an underlying pathologic process that leads to abnormally high intake, increased absorption, or reduced excretion of copper. To better understand copper-associated diseases, one must first understand copper homeostasis in mammals.²

Dietary copper is absorbed primarily in the proximal small intestine where transport from the lumen into the intestinal mucosa is a carrier-mediated process, with a saturable transport component, which may be influenced by other dietary factors. Most of the copper within the intestinal epithelium is found within the cytosol bound to metallothioneins. From here, copper enters the portal circulation bound to albumin or other carrier proteins, and is primarily transported to the liver, with small amounts entering the kidney. Once in the liver, copper undergoes three processes: hepatocellular uptake, intracellular distribution and utilization, and copper export, with each of these steps tightly regulated by transporters, chaperones, and other proteins. ATP7B protein is required for copper incorporation into ceruloplasmin in the liver, for biliary excretion, and possibly for transport of copper into a vesicular compartment, where it may be delivered to lysosomes and interacts with metallothionein. The main route of excretion of copper is in the bile. While some
copper is excreted into plasma as a complex with ceruloplasmin, very little copper crosses the glomerular capillaries.²

Familial copper storage disorders occur in Wilson’s disease in humans, Long Evans Cinnamon (LEC) rats, toxic milk mice, Bedlington terriers, and West Highland White terriers. Wilson’s disease is an autosomal recessive inherited disorder of copper metabolism and results in copper accumulation in the liver, cornea, and brain. The gene defect has been localized on human chromosome 13 and codes for ATP7B, a copper transporting P-type ATPase. The mutations occur throughout the entire gene, leading to variable clinical presentations. The resulting liver disease may mimic a wide variety of common liver conditions, including fulminant hepatic failure, chronic hepatitis, and cirrhosis. The LEC rats and toxic milk mice are the only known valid animal models of Wilson’s disease. The canine copper toxicosis locus in Bedlington terriers has been mapped to canine chromosome region CFA 10q26, and recently a mutated MURR1 gene was discovered in animals with the disease.²

Secondary copper toxicosis, characterized by copper retention secondary to an underlying disease has been documented in primary biliary cirrhosis in humans, chronic active hepatitis in Doberman pinschers, and Skye Terrier hepatitis. Primary biliary cirrhosis is a chronic, progressive, often fatal liver disease that results in cirrhosis and liver failure. Although the pathogenesis is unknown, an immune-mediated mechanism is suspected, and copper accumulation is a secondary event. Similarly, the cause of chronic active hepatitis in Doberman pinschers is unknown, but is also thought to be immune-mediated, with copper accumulation within the centroacinar (portal) areas occurring secondarily. Skye Terrier hepatitis is characterized by intracanalicular cholestasis, with copper accumulation, hepatocellular degeneration, and ultimately cirrhosis. In this disease, copper accumulates primarily in the periacinar (centrolobular) areas.²

Regardless of the cause, cirrhosis and hepatic failure are often the end result. Initially, as hepatocytes degenerate, become necrotic, and are lost, the liver will become hyperplastic, leading to both micro- and macro-nodular regeneration. These nodules form at varying times and therefore, as in this case, have varying histological appearances. Some regenerative nodules are composed of hepatocytes with intracytoplasmic lipid vacuoles while others are not. As this process continues, normal hepatic architecture is lost and, as is seen in this case, it may be difficult to identify a “normal” hepatic lobule.

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CASE IV – D04-23121 (AFIP 2938283)

Signalment: 12-year-old, spayed female, Labrador Retriever mixed breed dog (*Canis familiaris*).

History: The dog presented to a local practitioner for a soft tissue swelling, of unknown duration, that extended from the left metacarpal pad distally over the left forepaw. Systemic antibiotics in combination with epsom salt soaks failed to resolve the swelling. Incisional biopsies from the left metacarpal pad and adjacent interdigital skin were submitted for histopathological examination.

Gross Pathology: In a single biopsy, nests, islands, acinar and tubular arrangements of tumor cells extend from the dermal-epidermal junction to all surgical borders. Tumor cells have indistinct cell borders, are cuboidal to columnar to polygonal with a high nuclear to cytoplasmic ratio. One to two layers of cells line the tubular structures. The nucleus is centric, oblong to oval to round with finely stippled chromatin and a single nucleolus. The cytoplasm is scant and pale pink. Anisokaryosis and anisocytosis are moderate. Mitoses are present (0 to 1 per 40X objective field). Binucleate and trinucleate cells and karyomegaly are rare. Occasional angular nucleolar forms are noted. The arrangements of tumor cells are surrounded by an abundant fibrous connective tissue stroma (scirrhous reaction). A moderate infiltrate of plasma cells, small lymphocytes and eosinophils is present in the supporting stroma. Several normal eccrine glands are surrounded by the arrangements of tumor cells.

Contributor’s Morphologic Diagnosis: Eccrine carcinoma

Contributor’s Comment: Eccrine carcinoma is a malignant tumor showing differentiation to eccrine secretory epithelium.\(^1\) The tumor is rare but has been reported in the footpads of the dog and cat where these glands are normally located.\(^1,2,3\) Lesions may affect multiple toes in cats.\(^2\) Affected areas are swollen and often the overlying epidermis is ulcerated.\(^1,2\) There may be invasion of adjacent bones of the digit. Eccrine carcinomas are highly aggressive tumors that exhibit rapid metastasis to lymph nodes and subcutaneous tissues of the affected limb.\(^2,3\) Visceral metastasis has not been reported for eccrine carcinomas.\(^1,3\) Most cases

References:
are treated by excision of the tumor with wide margins.\textsuperscript{1} If the spread of the tumor is confined to the leg then amputation of the leg is a reasonable option.\textsuperscript{3}

**AFIP Diagnosis:** Foot pad: Adenocarcinoma, Labrador Retriever cross, canine.

**Conference Comment:** Exocrine glands are composed of highly specialized epithelial cells and discharge their secretory product via a duct onto an epithelial surface. Exocrine glands can be classified according to two major characteristics: the morphology of the gland, and the means of discharge of the secretory product. Exocrine glands are either simple, with a single, unbranched duct, or compound, with a branched duct system. These glands secrete their product in one of three ways: merocrine (eccrine) secretion involves the process of exocytosis; apocrine secretion involves the release of membrane-bound vesicles; and holocrine secretion involves the discharge of the whole secretory cell.\textsuperscript{4}

The eccrine glands develop independently of the hair follicle, with the duct opening directly onto the surface of the epithelium.\textsuperscript{5} They are found only on the glabrous skin, such as the footpad of dogs and cats, the frog region of ungulates, the carpus of pigs, and the nasolabial region of ruminants and pigs.\textsuperscript{5,6} These glands have been designated eccrine based on their mode of secretion. However, it is now known that these glands excrete their substances by a variety of secretory modes, including microapocrine blebbing. Some authors now prefer the term atrichial glands.\textsuperscript{5}

The apocrine glands develop embryologically as part of the hair follicle complex and are found in all haired skin areas, although only associated with the primary hair follicles. The ducts of the apocrine glands open in the superficial portion of the hair follicle.\textsuperscript{5} Apocrine gland activity is rarely visible in domestic animals, except in the horse. Other apocrine glands include the interdigital glands of small ruminants, glands of the external ear canal and eyelids of domestic animals, anal sac glands of dogs and cats, and the mental organ of pigs.\textsuperscript{6} Previously, the mode of secretion was thought to involve the pinching off of apical blebs of cytoplasm. However, more recent studies have shown this to be largely artifact with sweat production resulting from a combination of processes including holocrine secretion, vesicle exocytosis, active ion and water transport, and a minor contribution from microapocrine blebbing. Due to this fact, some authors now prefer the term epitrichial or paratrichial glands.\textsuperscript{5}

Differentiation of eccrine carcinoma from apocrine carcinoma is exceedingly difficult and requires knowledge of the site of origin of the tumor (footpad in the dog or cat). In dogs, the normal eccrine gland is composed of a secretory coil, a
ductular segment that courses through the dermis and an intraepidermal segment. The secretory coil consists of a single layer of cuboidal to columnar epithelial cells and a single layer of fusiform myoepithelial cells. The ductular segment is composed of two layers of non-secretory cuboidal epithelial cells. The duct opens on the footpad surface.\textsuperscript{7} Carcinoembryonic antigen (CEA) is present in both the ductular and secretory portions of the gland\textsuperscript{8} and has been reported to be useful in identification of eccrine carcinomas in animals.\textsuperscript{2,7} In this case, neoplastic cells are immunohistochemically negative for CEA and no unique features of eccrine differentiation were found. This neoplasm may be an eccrine carcinoma but the possibility of metastasis from another site should be excluded. Particularly in cats, occult pulmonary adenocarcinomas sometimes metastasize to one or more footpads and may be misdiagnosed as eccrine carcinomas.

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