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CASE I – 166-04 or 1250-03 (AFIP 2941192)

Signalment: 4 year old, spayed female, Dachshund, dog (Canis familiaris).

History: The dog first presented in April 2003 for cutaneous petechiae, and was diagnosed with immune-mediated thrombocytopenia and anemia. She was treated with vincristine, cyclosporine and prednisone, and the anemia and thrombocytopenia resolved. She was then prescribed long term prednisone and cyclosporine. In May, the dog presented for an acute onset of reddening of the left eye. Ophthalmic examination revealed fibrinous anterior uveitis and increased intraocular pressure. At that time, she was also showing stranguria. Candida spp. was isolated from her urine, and treatment with itraconazole was initiated for fungal cystitis. Topical prednisone and glaucoma medications failed to control the inflammation and high intraocular pressure in the left eye, which became buphthalmic and was enucleated in June. The signs of urinary tract infection resolved, but the dog presented later in June, for evidence of uveitis in the right eye. The right eye partially responded to therapy with topical steroids, until January 2004 when the dog became blind. The right eye was then buphthalmic, and was enucleated. In the meantime, cystitis recurred several times in 2003, despite treatment with itraconazole and ketoconazole.

Gross Pathology: The right globe was 20 mm in diameter. The cornea was moderately thickened and opaque, and the anterior chamber was filled with friable tan material. The lens was irregular in shape, opaque, and partially surrounded by a thick layer of tan to brown tissue. The retina was detached, and the subretinal space was partially filled with clotted blood. The vitreous humor was cloudy. Focally at the limbus, the sclera was markedly thickened.
Contributor’s Morphologic Diagnoses:
Right eye (166-04):
1. Pyogranulomatous endophthalmitis, severe, chronic, with lens rupture and fungal yeasts and pseudohyphae.
2. Keratitis, ulcerative, neutrophilic, moderate, chronic, with vascularization.
3. Retinal detachment with severe full thickness degeneration and severe retinitis.
4. Limbus: Focal suppurative scleritis and conjunctivitis, severe, acute.

Left eye (1250-03):
1. Pyogranulomatous endophthalmitis, severe, chronic, with lens rupture and fungal yeasts and pseudohyphae
2. Keratitis, ulcerative, neutrophilic, moderate, chronic, with focal abscess and vascularization
3. Retinal detachment with moderate degeneration of inner layers

Contributor’s Comment: Both eyes had a similar endophthalmitis with lens rupture, and numerous fungal organisms consistent with Candida spp. in the anterior segment. The route of ocular infection was believed to be hematogenous, originating from a primary cystitis. Candida spp. are normal inhabitants of the gastrointestinal, upper respiratory, and genital mucosa of dogs, and alterations in local and systemic immunity can result in opportunistic infections of mucosae and mucocutaneous junctions.1 Urinary tract infection by Candida spp. in dogs and cats is often associated with concurrent diseases or drug therapy (e.g. immunosuppressive drugs, broad-spectrum antibiotics) that may interfere with host defense mechanisms and alter normal bacterial flora.2 Systemic candidiasis is an uncommon sequela of candidal cystitis.2

While Candida albicans is the most common cause of fungal endophthalmitis in humans, ocular candidiasis is rare in domestic animals.3 Fungal endophthalmitis in dogs is most commonly caused by dimorphic fungi such as Blastomyces dermatitidis.4 Endophthalmitis caused by Candida spp. has been occasionally reported in dogs and cats, resulting from hematogenous spread,3,6 or inoculation into the eye, secondary to candidal keratitis.5 In our case, both eyes showed lens rupture, and organisms were most numerous within the lens capsule and degenerate lens fibers, suggesting a tropism for lenticular tissues. However, this particular distribution of organisms has not been reported in published cases.

Candida spp. have a distinct morphology in histologic sections: they consist of round to oval yeasts that are 3 to 6 microns in size, reproduce by narrow-based budding, and form chains of elongated yeasts separated by constrictions (pseudohyphae).7 While Candida albicans is the most common isolate of this genus, at least five other species have been isolated from dogs and cats with
urinary tract infections: *C. tropicalis*, *C. rugosa*, *C. krusei*, *C. parapsilosis*, and *C. glabrata* (previously called *Torulopsis glabrata*).  

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**AFIP Diagnosis:** Eye: Endophthalmitis, pyogranulomatous, severe, diffuse, with retinal detachment, lens rupture, intracorneal abscess, and numerous yeast and pseudohyphae, Dachshund, canine.

**Conference Comment:** *Candida albicans* is a dimorphic, saprophytic, opportunistic fungus that is a normal inhabitant of the gastrointestinal, upper respiratory, and genital mucosae of dogs. Infections may develop as a result of breaks in the normal mucosal barrier, immunosuppression, or treatment with broad-spectrum antimicrobials. Antibiotic therapy reduces the number of anaerobic bacteria, allowing proliferation of *Candida* spp., and resulting in an overall change in the mucosal flora.¹,⁶

Candidiasis is mainly a disease of keratinized epithelium in young animals, especially pigs, calves, and foals. In pigs, *Candida* spp. often invade the parakeratotic material that accumulates on the gastric squamous mucosa. Thrush, candidiasis of the oral cavity, occasionally occurs in young pigs. Lesions may be confined to the tongue, hard palate, or pharynx, but often involve the esophagus, and gastric squamous mucosa as well. In calves, lesions are most often in the ventral sac of the rumen but may also involve the omasum and reticulum, and occasionally the abomasum. Gastroesophageal candidiasis in foals involves the squamous epithelium and is associated with ulceration adjacent to the margo plicatus. Grossly, the lesions are yellow-white, smooth, or wrinkled plaques that cover the mucosa. Histologically, the epithelium is spongiotic and contains yeast and abundant hyphae admixed with neutrophils and bacteria beneath the cornified layer.⁸

Localized candidal infections in dogs are reported in chronically immunosuppressed dogs and include infections of the skin and nailbed, urinary tract, ears, and gastrointestinal tract.¹ Additional factors that promote candidal urinary tract infections are thought to include an increased intestinal *Candida* spp. population (i.e. post-antibiotic treatment) and local alterations in the urinary tract environment (i.e. diabetes mellitus or aciduria).² Systemic dissemination is by embolization from primary sites of colonization and local invasion. Clinical signs of generalized infection include pyrexia and erythematous skin lesions, myositis, osteomyelitis, and ocular infections.¹

*Candida* spp. are unique fungi in that they often form yeast (blastospores, blastoconidia), pseudohyphae, and hyphae in tissue. If only blastospores are seen,
they can be confused with morphologically similar yeast forms in tissue, such as *Histoplasma capsulatum* var. *capsulatum*, *Blastomyces dermatitidis*, and poorly encapsulated *Cryptococcus neoformans*. Histoplasma capsulatum var. *capsulatum* and *Blastomyces dermatitidis* only very rarely form pseudohyphae in tissue. In some instances Candida hyphae and pseudohyphae may resemble dematiaceous fungi or other filamentous fungi. However, *Candida* spp. are not pigmented and usually there is more than one type of fungal element present. In mucocutaneous candidiasis, masses of branching, septate hyphae, pseudohyphae, and round to oval budding yeast forms measuring 3-5 µm in diameter are seen on the surface and within the epithelium. In systemic candidiasis, either all or any combination of these fungal elements may be seen. The presence of blastospores mixed with characteristic pseudohyphae or hyphae in tissue enables the pathologist to identify the fungus as a species of *Candida*.

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**References:**
CASE II – 8004-476 (AFIP 2940131)

**Signalment:** 10 month old, neutered male Golden Retriever dog (*Canis familiaris*).

**History:** A 6 month old male Golden Retriever was presented for chronic vomiting. Clinical chemistry showed a BUN of 83 (7-27) and creatinine of 3.3 (0.5-1.8) mg/dl with a hematocrit of 34 (37-55)%. The animal was maintained with periodic medical treatments and diet (Science Diet® K/D) but clinical signs and azotemia (BUN > 130 mg/dl, creatinine 13.35), hyperphosphatemia (15.43, 2.5-6.8 mg/dl) and anemia (PCV 21%) slowly progressed until the dog was euthanized at 10 months of age. The referring veterinarian noted that both kidneys were small and nodular and these were submitted in fixative for histological examination.

**Gross Pathology:** Grossly, kidneys were irregularly multinodular, firm, pale and small.

**Laboratory Results:** Final BUN > 130 (7-27) mg/dl, creatinine 13.35 (0.5-1.8) mg/dl, hyperphosphatemia 15.43 (2.5-6.8) mg/dl and PCV = 21%

**Contributor’s Morphologic Diagnoses:**
1. Renal dysplasia.
2. Chronic suppurrative pyelonephritis.
3. Multifocal mild tubular necrosis and regeneration with intratubular and intraepithelial birefringent crystals, hyaline and granular casts.

**Contributor’s Comment:** In both kidneys, the cortex is irregularly contoured and composed of radially arrayed zones of fibrosis interspersed with zones of dilated tubules. Throughout the kidney, renal corpuscles have cystically dilated Bowman’s spaces containing eosinophilic fluid; as well, a few small glomeruli with external nuclei and inapparent capillary loops (immature glomeruli) are scattered throughout, predominantly in the outer cortex. Areas of fibrosis have many large ductular structures mainly in the medulla, with degeneration of tubules, coalescence of glomeruli and moderate lymphoplasmacytic inflammation in the cortex. Medullary ducts have flattened basophilic (immature) and columnar (mesonephric) epithelium. Dilated tubules contain intraluminal eosinophilic fluid, many hyaline and fewer granular casts and scattered birefringent pale intratubular and intraepithelial crystals (calcium oxalate?). Tubules are separated by expanded proliferative pale to collagenous stroma. Areas of pale, poorly differentiated, stellate (immature) stroma are present primarily in the medulla. Cortical tubules have variable epithelium with occasional necrosis, flattening of epithelium and hyperplasia (regeneration). The pelvic and ureteral urothelium is underlain by moderate mixed lymphoplasmacytic and neutrophilic inflammation and fibrosis with varying degrees of epithelial...
degeneration, transmigration of neutrophils and intraepithelial micropustules (chronic pyelonephritis). Some sections show a focus of necrosis with exudation of fibrin and degenerating neutrophils in the renal papilla (fibrinosuppurative pyelitis, not in all sections).

Renal dysplasia is thought to arise as a consequence of perturbations in the complex chains of events involved in the embryological development of the kidneys resulting in arrest of full maturation with retention of immature structures. Histological features of renal dysplasia include fibrosis, immature glomeruli, large columnar-lined (mesonephric) ducts, immature ducts lined with flattened hyperchromatic cells and the persistence of pale poorly differentiated (immature) mesenchyme.\(^1\,2\,3\) Clinical signs of renal failure are variable and are commonly recognized at several months age.\(^1\,2\) Animals with renal dysplasia show increased susceptibility to pyelonephritis; however, cortical fibrosis is found independent of inflammatory disease. Renal dysplasia has been reported to be caused by canine herpesvirus, feline panleukopenia virus, bovine virus diarrhea virus and porcine hypovitaminosis A.\(^3\) The influence of inheritance is controversial,\(^3\) but multiple occurrences in litters\(^4\) and breeds, notably Golden retrievers\(^2\), Lhasa apsos, Shih Tzus, Boxers, Finnish harriers, Dutch kooiker, and Cocker spaniels\(^1\,4\,5\,6\) have been reported demonstrating hereditary determination or predisposition. Dogs with renal dysplasia may suffer from renal dysfunction-related conditions such as anemia and fibrous osteodystrophy\(^7\) (renal hyperparathyroidism). Nephrogenesis is largely undefined but transgenic manipulations in mice indicate cytokine and other apparently dual-purpose genes function in intercellular communication during organogenesis and that interruption or over-expression of certain genes can lead to increased incidence of renal dysplasia.\(^8\,9\) Renal dysplasia is an important cause of renal failure necessitating renal transplantation in children. Renal dysplasia has also been described in the adult horse.\(^10\)

2. Kidney, tubules: Necrosis, multifocal, with intratubular crystals.

Conference Comment: The contributor provides a thorough overview of renal dysplasia in animals. By definition, renal dysplasia is disorganized development of renal parenchyma due to abnormal differentiation. Lesions associated with dysplasia include the presence of structures inappropriate to the stage of development of the host or the development of structures that are anomalous.
Associated with and often obscuring dysplastic lesions are a number of secondary compensatory, degenerative, and inflammatory changes.¹

In humans, about 10% of all people are born with potentially significant malformations of the urinary tract. Renal dysplasias and hypoplasias account for 20% of chronic renal failure in children. Congenital renal disease can be hereditary, but is most often the result of an acquired developmental defect in utero. Dysplasia can be unilateral or bilateral and is almost always cystic. Grossly, the kidney is usually enlarged, extremely irregular, and multicystic. The cysts vary in size from microscopic to several centimeters in diameter. Microscopically, there is abnormal lobar organization and persistence of abnormal structures, including cartilage, undifferentiated mesenchyme, and immature collecting ductules. The characteristic histologic feature is the presence of islands of undifferentiated mesenchyme, often with cartilage, and immature collecting ducts.¹¹

Although microscopic features of human renal dysplasia are present in dogs, a number of differences are apparent. The consistent segmental cortical pattern of asynchronous differentiation of nephrons is not a characteristic feature of human dysplasia. In man, ducts lined by tall columnar epithelium are interpreted as persistent metanephric ducts with no analogous structure in the normally developed kidneys. The pseudostratified columnar epithelium lining medullary ducts in canine cases may similarly represent persistent metanephric ducts.¹

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References:

CASE III – Kiupel (AFIP 2942010)

Signalment: A 60 pound, 2.5 year old, female spayed, mixed breed (Border collie) dog.

History: The dog presented to the Veterinary Teaching Hospital (VTH) at Michigan State University for a previously diagnosed retinal detachment of the right eye. The dog was bright, alert and responsive, with a good appetite. Physical examination revealed a small skin lesion on the lateral surface of the hock, and bilateral retinal detachment. CBC and serum chemistry were submitted to the clinical pathology laboratory. Fine needle aspirate of the ocular fluid of the right eye and right hock were obtained for cytologic examination. Fungal cultures were obtained from the ocular fluid.

Gross Pathology: This 60 pound female spayed dog presented with mild dehydration, adequate nutrition, and minimal autolysis. The eyes had been enucleated prior to necropsy for special processing. The primary lesions were widespread foci of suspected granulomatous inflammation in multiple parenchymal organs. There were hundreds of pinpoint white foci scattered across the capsular surface of the right and left kidneys. These lesions did not extend into the inner parenchyma. There were hundreds of multifocal to coalescing, white foci scattered across the epicardial surface of the heart. These white foci extended throughout the myocardium of the left ventricular free wall and the interventricular septum. There were multifocal areas of moderate mucosal hyperemia diffusely throughout the small and large intestine. The spleen was diffusely congested and oozed blood on cut surface. There were no other gross lesions of diagnostic significance in this animal.
**Gross Morphologic Diagnoses:** 1. Kidney: Multifocal, moderate, granulomatous, interstitial nephritis (suspected).
2. Heart: Multifocal to coalescing, granulomatous cardiomyopathy (suspected).

**Histopathologic Findings:** Only heart was submitted to the conference. Sections of heart examined had multifocal areas of myocardial necrosis surrounded by moderate to severe lymphoplasmacytic and histiocytic inflammation admixed with low numbers of neutrophils and eosinophils. The lesions caused destruction of approximately 40-50% of the sections of heart examined. Within the centers of the necrotic areas were numerous Prototheca. These organisms ranged from 5-15 µm in diameter with a thin refractile wall. Some organisms had a granular basophilic cytoplasm with a small central basophilic nucleus. Others had undergone endosporulation and contained as many as 20 daughter cells. Most of the inflammation appeared centered around the spent theca cells/mother shells, which represented the remaining empty capsule wall following release of endospores. Many of the protothecal aggregates consisting of spent theca cells elicited only a moderate lymphohistiocytic inflammatory response. However, several of the larger granulomas had necrotic centers that consisted of central mineralization surrounded by cellular debris, caseous exudates, and fragmented Prototheca shells.

Other lesions: 1. Multifocal, mild, lymphoplasmacytic, and eosinophilic meningoencephalitis with necrosis and intralesional Prototheca.
3. Diffuse, moderate to severe, plasmacytic, and eosinophilic colitis with intralesional Prototheca.
4. Multifocal, mild to moderate, lymphoplasmacytic, periportal hepatitis with intralesional Prototheca and moderate, diffuse, vacuolar hepatopathy.
5. Multifocal, moderate to severe, plasmacytic, and lymphohistiocytic pancreatitis with intralesional Prototheca.
7. Bilateral, severe, pyogranulomatous panophthalmitis with complete retinal detachment, glaucoma, and intralesional Prototheca.

**Laboratory Results:** CBC and serum chemistry profiles had no significant abnormalities.

**Right ocular fluid**
Subretinal fluid from the right eye contained frequent spherical to oval-shaped basophilic organisms with a thin clear wall and central 'nucleus'. The organism measured from approximately 3-9 µm in diameter and approximately 3-10 µm in length with a clear cell wall of approximately 0.5-1 µm thick. It appeared
consistent with *Prototheca* sp. A mild inflammatory response consisting of predominately moderately to severely degenerate neutrophils was observed. Culture was recommended.

**Right hock skin lesion**
Numerous extracellular oval to reniform-shaped organism with thin clear walls were seen. The organisms varied greater than two-fold in size. Frequent mildly degenerate neutrophils were present and frequently could be seen phagocytizing the organisms.

**Urinalysis**
No significant findings.

**Cerebral spinal fluid**
Cytospin preparations of CSF were made. They were moderately to highly cellular with a large preponderance of eosinophils and lesser numbers of lymphocytes and non-degenerate neutrophils and macrophages. There were occasional macrophages with phagocytized protothecal organisms and spent organisms. Microprotein was measured to be 50 mg/dl. A 300 cell count revealed 146 eosinophils, 65 mononuclear cells, 40 small lymphocytes, and 49 neutrophils.

**Contributor’s Morphologic Diagnosis:** Heart: Multifocal, moderate to severe, granulomatous and eosinophilic, necrotizing myocarditis with intralesional *Prototheca* sp. and mineralization.

**Contributor’s Comment:** Prototheca are saprophytic achlorophyllous algae that are closely related to the green algae of the genus Chlorella.¹ They reproduce by endosporulation and may have asymmetrical cytoplasmic and nuclear cleaving leading to anywhere from 2 to greater than 20 endospores. The mother cells rupture releasing the daughter spores, which are tiny replicas of their mothers. They mature and repeat the life cycle. Empty shell casings from ruptured mother cells are usually seen amongst the intact population of organisms.¹

*Prototheca* sp. are ubiquitous organisms and may be found in sewer treatment plants (Fetter et al., 1971), potato skin (Negroni and Blaisten, 1940), tree flux (Fetter, Klintworth and Nielson, 1971),¹ and in freshly voided human and animal feces.² Prototheca rarely causes disease, but will adversely affect its host when the immune system is suppressed or challenged by a pre-existing or concurrent disease. Intact protothecal organisms normally elicit a minimal inflammatory response. Once the mother cells rupture and release the endospores, a strong lymphoplasmacytic and histiocytic inflammatory response is initiated against the spent theca shell. It has been speculated that a defect in the host’s cell mediated immune system is a more important factor in protothecal infections than a defect
or decrease in the humoral immune response.² A defect in neutrophils may allow for protothecal infections. In some hosts the neutrophils are able to phagocytose the organisms but are unable to destroy them. In these cases, there was no evidence of humoral or cell mediated immune deficiencies.

To date there are three recognized Prototheca species: P. stagnora, P. zopfii, and P. wickerhamii. Only P. zopfii and P. wickerhamii are known to cause disease in animals and humans. Both species appear morphologically similar to one another and can be differentiated based on sugar and alcohol assimilation or fluorescent antibody tests. In humans, both cutaneous and disseminated protothecosis has been reported. P. wickerhamii is most commonly associated with cutaneous lesions and P. stagnora usually results in disseminated disease in humans.

In cats and dogs, infection with Prototheca sp. is rare. There have been no reports of disseminated protothecosis in cats. Cutaneous infections in cats are caused almost exclusively by P. wickerhamii. Dogs, however, predominantly contract the disseminated form of protothecosis and invariably it is caused by P. zopfii.³ Collies appear to be more susceptible (7 out of 20 cases) than other breeds.³ Dogs with disseminated protothecosis normally present with a history of bloody diarrhea that is unresponsive to treatment. The animal continues to eat and drink well and remains bright and responsive. As the organism disseminates, clinical signs usually develop depending on the organ system affected. Besides the gastrointestinal tract, the eyes, heart, brain, liver, kidney, and skin are most commonly affected. As the disease progresses, dogs become more depressed and develop CNS signs such as ataxia, incoordination, paresis, deafness, circling and depression. Two-thirds of the reported cases include bilateral or unilateral ocular involvement and the animals normally present with retinal detachment and blindness. CBC and serum chemistry are often within reference range, but occasionally hepatic enzymes may be increased with the involvement of the liver or other organ systems. The predominant inflammatory response invoked by protothecal organisms within a dog is lymphoplasmacytic and histiocytic regardless of the organ system affected.

In this case, culture performed at MSU did not further differentiate the Prototheca organism. It was unknown if the organism is P. zopfii or P. wickerhamii. Based on the wide dissemination of the organisms, it was speculated that P. zopfii was the pathogen.

AFIP Diagnosis: Heart: Myocarditis, granulomatous and necrotizing, multifocal, moderate, with numerous extracellular and intrahistiocytic algae, etiology consistent with Prototheca sp., mixed breed, canine.
Conference Comment: As mentioned by the contributor, *Prototheca* spp. rarely cause disease but occasionally infections result in severe gastrointestinal, ocular, cutaneous, or disseminated disease. The most commonly affected domestic animals are dogs, cats, and cows. In cows, manifestation of the disease is usually in the form of mastitis caused by *P. zopfii*. Cats are most commonly affected with the cutaneous form of protothecosis (*P. wickerhamii*) and present with large, firm nodules on the limbs and feet; however, the nose, pinnae, forehead, and tailbase may also be affected. The most common clinical presentation of protothecosis in the dog is protracted hemorrhagic enterocolitis, with the colon being most severely affected. Grossly, the colon is diffusely reddened with multiple raised white nodules and multifocal ulcerations with hemorrhage. Disseminated disease involving the eyes, ears, skin, skeletal muscles, kidneys, liver, heart, spinal cord, and brain has been reported.8

*Prototheca* spp. reproduce via asexual endosporulation and have a characteristic microscopic appearance. Histologically, there are intra- and extracellular organisms that may be either small single endospores with granular cytoplasm, or large sporangia that are round to oval, 8-20 µm in diameter, have a clear 2-4 µm thick wall, and contain multiple (2-20) wedge-shaped endospores arranged radially (“Mercedes Benz emblem-like”). The cells eventually rupture leaving empty theca (mother shells) in the lesions. Organisms may be readily identified using special stains such as PAS (Periodic Acid-Schiff) or GMS (Grocott’s Methenamine Silver). Other organisms that reproduce via endosporulation include *Chlorella* sp., *Rhinosporidium seeberi*, and *Coccidioides immitis*. Ultrastructurally, a paucity of chloroplasts differentiates *Prototheca* sp. from *Chlorella* sp.10

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References:

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**CASE IV – 04/05 #1 (AFIP 2948745)**

**Signalment:** A 13-year-old male castrated Irish Setter canine.

**History:** This dog had a history of anorexia, fever, and septic peritonitis.

**Contributor’s Morphologic Diagnosis:**
2. Gallbladder: Cholecystitis, suppurative and lymphoplasmacytic, multifocal, moderate.

**Contributor’s Comment:** The submitted specimen consists of a section of gallbladder, which contains a portion of a non-encapsulated, invasive, multilobulated mass that expands, effaces, and replaces up to 90 percent of the wall. Individual lobules, which are separated by a moderate fibrovascular stroma, consist of discrete and coalescing, variably cellular sheets and packets of mildly atypical and pleomorphic cells which are separated by a delicate fibrovascular stroma. Cells are large, round to polygonal with distinct cell borders and contain a moderate amount of pale eosinophilic, faintly granular and often vacuolated cytoplasm. Nuclei are round to oval, bland, and contain coarsely granular chromatin and single, prominent nucleoli. Anisokaryosis and anisocytosis are mild and 0-1 mitotic figures are identified per 400X field. Throughout the mass, there are multiple, scattered foci of hemorrhage and necrosis and rare, entrapped biliary,
mucosal crypts. The gallbladder lumen contains a variable amount of sloughed, necrotic and degenerate tumor and epithelial cells admixed with fibrin, hemorrhage, and varying numbers of degenerate and viable neutrophils. Within the adjacent gallbladder tissue, the lamina propria-submucosa contains modest numbers of plasma cells and lymphocytes with scattered, hemosiderin-laden macrophages, with mild, multifocal cystic mucosal hyperplasia. Adherent to the serosa is a moderate cellular coagulum composed of hemorrhage, mixed leukocytes, and fibrin.

In this case, based upon the cytomorphologic and architectural characteristics, and the demonstration of neoplastic cell argyrophilia using the Grimelius method, a diagnosis of malignant neuroendocrine neoplasia (malignant carcinoid) was made. Further characterization (immunohistochemical or ultrastructural analysis) of the cells was not conducted. Additional sections, which were not included in the submitted slide series, demonstrated multiple nests of identical cells throughout a section of liver. Based upon their comparatively small size and multicentric nature, these were presumed to represent metastatic foci rather than the primary lesion.

Carcinoids are rare neuroendocrine neoplasms of both humans and domestic animals, which arise from dispersed neuroendocrine cells located in the gastrointestinal tract and other organ systems (liver, pancreas, urogenital, and tracheobronchial). Historically, the term carcinoid has been used as an umbrella term in the diagnosis of all gastroenteropancreatic neuroendocrine tumors (GEP-NET’s) regardless of biologic or clinical behavior. Recently, in an attempt to reflect their diverse histogenesis and biologic behavior, carcinoids were reclassified with the more neutral and inclusive terms: neuroendocrine tumor and neuroendocrine carcinoma. However, the term carcinoid was retained for neuroendocrine gastrointestinal tumors of both benign (carcinoid) and malignant (malignant carcinoid) forms, thus removing pancreatic neuroendocrine neoplasms from this group. Carcinoids may synthesize and secrete either a short chain polypeptide and/or biologically active amine, including serotonin (5-HT), somatostatin, gastrin, or histamine. The classic carcinoid syndrome of flushing, hypotension, diarrhea, and wheezing is due to serotonin secretion.

Definitive diagnosis is based upon histologic features, cytochemical (argyrophilia) and immunohistochemical (neuron specific enolase, chromogranin A and synaptophysin) techniques, and the ultrastructural identification of secretory granules. Hepatic and biliary carcinoids are typically negative for cytokeratin. In the dog, carcinoids are most common in aged animals and have been reported in the gallbladder, liver, lung, and throughout the gastrointestinal tract. Hepatobiliary carcinoids have been described in the dog, cat, and one cow. Additionally, there are reports of intestinal carcinoids in the horse and cow and three cases of maxillary sinus carcinoid tumors in the horse. In humans,
Carcinoids are most commonly diagnosed in the gastrointestinal tract (73.7%) and bronchopulmonary (25.3%) system.\textsuperscript{5}

Based upon their rarity, the usual biologic behavior of gastrointestinal carcinoids in dogs is uncertain, however in the previous reports, the vast majority of hepatic carcinoids demonstrated aggressive, metastatic behavior, with spread most common to the peritoneal cavity and peritoneal lymph nodes.\textsuperscript{6} In humans, the overall 5-year survival rate of all types of carcinoid tumor was 50.4%, with a localized disease (79.7%) having a predictably better prognosis than if regional (50.6%) or distant (21.8%) metastatic lesions are present. The prognosis of gallbladder carcinoids (41.3% 5-year survival rate) is poor.\textsuperscript{5}

\textbf{AFIP Diagnosis:} Gallbladder: Carcinoid, Irish Setter, canine.

\textbf{Conference Comment:} Neoplasms derived from neuroendocrine cells of the gastrointestinal mucosa are known as carcinoids because, histologically, they closely resemble some carcinomas of intestinal epithelial origin. As mentioned by the contributor, mucosal neuroendocrine cells can secrete several different hormones; however, individual cells synthesize and store a single hormone, with the active secretion being either short chain polypeptides and/or biologically active amines. It has been shown that not all neuroendocrine cells can decarboxylate an amine precursor, and the APUD (amine precursor uptake and decarboxylation) system concept has been modified and renamed the diffuse endocrine system.\textsuperscript{2} In animals, alimentary tract and hepatobiliary carcinoids are considered malignant.\textsuperscript{8}

Theoretically, tumors of the diffuse neuroendocrine system should invoke a recognizable clinical syndrome related to their secretory products, but this is not consistently observed. However, carcinoids that secrete gastrin (G cell tumors) are responsible for the Zollinger-Ellison syndrome, characterized by severe gastric hypersecretion and peptic ulceration, with watery diarrhea. The syndrome has been reported in dogs and cats, usually associated with a non-beta cell pancreatic islet cell tumor rather than a gastrointestinal tumor.\textsuperscript{2}

Grossly carcinoids are yellowish or tan on cut surface and range from annular stenosing thickenings to nodular masses and the overlying epithelium may be eroded or ulcerated.\textsuperscript{2} Tumors often have characteristic neuroendocrine features histologically, with large polygonal cells arranged in nests and packets, or more solidly cellular areas, separated by a fine fibrovascular stroma, with palisading of peripheral cells along the stroma. Cells have distinct cell borders with abundant granular cytoplasm and irregularly round, often centrally located nuclei. However, two other patterns have been recognized. One is characterized by groups of
rosettes or acinar-like structures that contain eosinophilic secretions separated by similar stroma. The other is composed of anastomosing groups and rows of cells like ribbons, consisting of mostly ovoid or spindle cells with fibrovascular stroma. Silver stains such as modified Fontana-Masson and Churukian-Schenk are useful. However, immunohistochemical stains, such as neuron-specific enolase (NSE) and chromogranin, which stain almost all neuroendocrine tumors, are now more commonly used. A varying number of neoplastic cells may stain with antibodies such as serotonin, somatostatin, gastrin, glucagon, synaptophysin, and calcitonin. Ultrastructurally, neoplastic cells contain a variable number of intracytoplasmic neurosecretory granules that are typically round, composed of an electron dense core and surrounded by an electron dense membrane.8

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