The Armed Forces Institute of Pathology  
Department of Veterinary Pathology  
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Conference Moderator:  
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Washington, DC 20306 and  
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CASE I – 02-314 (AFIP 2841704)

Signalment:  9-year-old female-spayed Bichon Frise (*Canis lupus familiaris*).

History:  This Bichon Frise presented to NCSU Veterinary Teaching Hospital (VTH) with a 1-month history of vomiting, anorexia and lethargy and a 4-day history of blindness. Physical examination, radiographs, ultrasound and laparotomy detected no abnormalities except for an enlarged cecum. Treatment with dexamethasone did not relieve the vomiting and lethargy. The dog then became acutely blind and disoriented. At NCSU VTH, bilateral panuveitis and retinitis were diagnosed clinically. Systemic disease, such as protothecosis, fungal infection, ehrlichiosis or neoplasia, was suspected. The dog was euthanized due to anticipated poor prognosis.

Gross Pathology:  At necropsy, the cortices of the right and left kidneys were markedly irregular with dozens of 1-2 mm diameter, depressed, white-tan foci scattered throughout the cortical parenchyma. Three variably sized (0.5-10 cm) ulcers were present within the pyloric stomach mucosa. A moderate amount of black, granular to tarry material was present within the lumen of the distal ileum and proximal colon. The proximal colon was mildly dilated.

Laboratory Results:  A complete blood count revealed a mild thombocytosis 423,000 (181,000-350,000), a mildly elevated WBC of 26,500 (6,400-15,800), moderate neutrophilia 25,440 (3, 400- 9, 800) and a moderate lymphopenia 265 (800-3,500). Serum chemistry revealed a markedly elevated alkaline phosphatase 686 (12-150), a mildly elevated alanine transferase 139 (5-105), a mildly elevated BUN 52 (7-31), a mild hypoalbuminemia 2.3 (2.6-4.5) and mildly low bicarbonate 11 (16-26).

Contributor’s Morphologic Diagnoses:  Kidney: 1. Arteritis, lymphoplasmacytic and histiocytic (granulomatous) with necrosis and fibroplasia, marked, diffuse, chronic.
2. Interstitial nephritis, lymphoplasmacytic and histiocytic, marked, multifocal, chronic.

Contributor’s Comment: Multiple small and medium-sized arteries throughout the cortex, medulla and urinary papillary adipose tissue of the kidneys are markedly enlarged (2-3 fold). Their walls, including the tunica media, tunica adventitia and to a lesser extent the tunica intima are diffusely infiltrated and expanded by an inflammatory infiltrate comprising numerous plasma cells, lymphocytes and histiocytes. In some of the affected arteries there is hyalinization, disorganization and vacuolization of fibers within the tunica media and adventitia, as well as fibroplasia. Marked, multifocal aggregates of plasma cells, lymphocytes and histiocytes coalesce in the cortical interstitium surrounding the affected arteries. Associated with the interstitial inflammatory infiltrates are mild, patchy regions of renal tubular atrophy and glomerular sclerosis.

A similar necrotizing panarteritis was found in the heart, pancreas, thyroid gland and glandular stomach of this dog. A necrotizing panarteritis involving small and medium-sized muscular arteries of multiple visceral organs is morphologically consistent with “polyarteritis nodosa.” Chronic inflammation of multiple visceral organs often accompanied the arterial lesions. Similar inflammation involved the globes and the brain meninges, although no vascular lesions were noted.

Polyarteritis nodosa is a disease in which the small and medium-sized muscular arteries undergo severe necrotizing inflammation in a nodose (nodular) pattern. Polyarteritis nodosa occurs sporadically in all domestic animal species. It shares similarities with a human condition that is associated with hepatitis B infection (Schoen et al). The etiopathogenesis in animals is unknown; however, the occurrence is suspected to be associated with immune complex deposition in muscular arteries. In dogs, it has been reported with autoimmune diseases like rheumatoid arthritis and systemic lupus erythematosus (Maxie et al). It also occurs in "beagle pain syndrome," another idiopathic immune-mediated disease (Scott-Moncrieff et al). Recently, blue fox kits with *Encephalitozoon cuniculi* infections demonstrated multisystemic microgranulomatous inflammation and a necrotizing panarteritis, consistent with polyarteritis nodosa (Wasson et al). *Encephalitozoon cuniculi* has also been associated with nonsuppurative meningoencephalomyelitis in dogs and fox pups (Huxtable et al). No bacteria, fungi or protozoa were seen in GMS, acid-fast, PAS, Gram-stain or Giemsa special stained tissue sections of kidney.

AFIP Diagnosis: Kidney: Arteritis, granulomatous, segmental, multifocal, severe, with moderate multifocal plasmacytic and histiocytic interstitial nephritis, focal neutrophilic medullary nephritis, and multifocal interstitial fibrosis, Bichon Frise, canine.

Conference Comment: Arteritis occurs in many diseases; however, systemic transmural necrotizing inflammation of small to medium-sized muscular arteries has classically been designated "polyarteritis nodosa." As noted by the contributor, the pathogenesis is believed to involve an inflammatory response to immune complexes deposited in vessel walls. The detection of hepatitis B antigens in arteries of many affected humans, occurrence in immune-mediated diseases such as systemic lupus
erythematous, and similarity to experimental immune complex vasculitides such as the Arthus reaction support this concept. In a discussion of differential diagnosis, the microscopic lesions of several infectious diseases were considered, including those caused by *Borrelia burgdorferi, Leptospira interrogans, Ehrlichia canis, Encephalitozoon cuniculi*, and *Rickettsia rickettsii*. Renal manifestations of Lyme borreliosis include glomerulonephritis; tubular dilation, necrosis and regeneration; and interstitial lymphoplasmacytic nephritis. In leptospirosis, the usual lesions are interstitial plasmacytic, lymphocytic and histiocytic nephritis, neutrophilic tubulitis and tubular degeneration and necrosis. Renal lesions of ehrlichiosis typically include interstitial plasmacytic and lymphocytic nephritis that centers on glomeruli and plasmacytic vasculitis at the corticomedullary junction; glomerulonephritis may be observed. *E. cuniculi* causes plasmacytic to granulomatous interstitial nephritis and may cause granulomatous arteritis similar to that seen in polyarteritis nodosa. In Rocky Mountain spotted fever there is widespread necrotizing vasculitis of small veins, capillaries and arterioles with perivascular accumulations of neutrophils, lymphocytes and macrophages, and there may be a glomerulonephritis component.

In greyhounds, an idiopathic cutaneous and renal glomerular vasculopathy (Alabama rot) has been described that causes cutaneous ulceration, limb edema, and peracute renal glomerular necrosis. This condition resembles hemolytic-uremic syndrome (HUS) of humans. The kidney lesions include fibrin thrombi within glomerular capillaries, and associated necrosis and hemorrhage. The etiology is unknown, although there may be an association with ingestion of meat contaminated with *Escherichia coli* type O157:H7, similar to childhood HUS.

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**References:**

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CASE II - 02-313 (AFIP 2838702)

Signalment: 8-year-old female spayed Boston Terrier (*Canis familiaris*)

History: Presented on emergency having been rescued from a house fire where another Boston Terrier died; no superficial burns were noted. An ulcer of the left cornea was attributed to smoke injury although such ulcers are common for this breed. The patient suffered from smoke inhalation, reeked of smoke and coughed up carbonaceous sputum. Mucous membranes were initially cyanotic but became hyperemic after beginning oxygen supplementation. By pulse oximetry, measured blood $O_2$ saturation was 92% (normal >95%) prior to placement in 40% atmospheric $O_2$; intravenous (IV) fluid therapy consisted of lactated Ringer's solution, furosemide to reduce laryngeal and pulmonary edema, theophylline (a bronchodilator), and prednisone sodium succinate (short-acting steroid). Additionally, mucomyst (a mucolytic agent) in saline was given by nebulization. Gentle coupage was done every four hours to induce the cough reflex. The corneal ulcer was treated with atropine and topical antibiotics. About 20.5 hours after presentation, the dog suddenly became dyspneic and died despite CPR.

Gross Pathology: The obese 9 kg dog had no laryngeal edema at necropsy. The tracheal mucosa was diffusely red to dark brown. The lung had large areas of fairly well-defined congestion and normal pink aeration; much of the ventral lung was edematous. The cut surface exuded dark red to brown fluid.

Laboratory Results: Measured blood $O_2$ saturation was 92% (normal >95%) by pulse oximetry. Thoracic radiographs were interpreted as a mild diffuse interstitial pattern with marked expiration and under inflation. However, mild interstitial non-cardiogenic edema could not be excluded.

Contributor's Morphologic Diagnosis: Severe, bronchiectatic, necrotizing, fibrinosuppurative bronchiolitis, suppurative pneumonia and phagocytized and non-phagocytized black alveolar particles (soot)
Contributor's Comment: According to Dr. Lee-Chiong Jr., pulmonary injury following smoke inhalation is biphasic; phase I has suppuration while phase II has hyaline membrane formation and fibrosis (interstitial pneumonia). Even if chest films are normal, bronchoscopy within the first 24 hours after exposure may reveal erythema, edema, erosion, necrosis and soot. Injury to the respiratory mucosa can be due to heat and/or inhalation of gases and particulate matter acting separately or in concert. The immediate effect is loss of ciliary function and mucosal edema. Although the trachea can protect the distal airways from thermal injury, such is not always the case as with exposure to steam, explosive gases and when in close proximity to the fire and smoke (heated particles). It is not known where in the house this animal was found as regards proximity of the fire; she had no singed hair or superficial burns. She was coughing up "dark mucus". A section of trachea was not included because it was denuded of mucosa with no inflammation (artifact from over-zealous student dissection?).

Some samples of lung had normal to slightly inflamed bronchioles. Bronchiolar hemorrhage, prominent in occasional bronchioles, is not seen in the conference lung sample; many alveoli contained some erythrocytes with occasional ones in macrophages. Most of the multifocal, interstitial black pigment is presumably pre-existing anthracosis.

Hyperemic mucous membranes can be seen with CO intoxication, cyanide intoxication, increased carboxyhemoglobin or vasodilation. Despite dangerously low oxygen concentration, the arterial partial pressure of oxygen (paO₂) is often normal initially because the blood is in tension equilibrium with alveolar gas.

Respiratory and neurological complications are the most common sequels to smoke exposure in dogs. Management of smoke inhalation patients consists of maintaining a patent airway, providing adequate oxygen and addressing hemodynamic abnormalities. The use of antibiotics and steroids is controversial; the usefulness of prophylactic antibiotics has not been documented. Antibiotics are indicated if pneumonia is present.

AFIP Diagnosis: Lung: Bronchiolitis, necrotizing, acute, diffuse, severe, with moderate acute diffuse necrotizing fibrinous interstitial pneumonia and multifocal black isotropic intrahistiocytic and extracellular pigment, Boston Terrier, canine.

Conference Comment: Fire-associated lung injury may result from inhalation of toxic gases and particulate material, thermal injury and by indirect mechanisms. External burns and smoke inhalation, separately or in combination, may cause adult respiratory distress syndrome (ARDS; shock lung), as can many other disease entities. ARDS is characterized by acute diffuse damage to the alveolar capillary walls. Briefly, the pathogenesis of ARDS involves release of pro-inflammatory cytokines (TNF-alpha) and chemokines (IL-8) by monocytes and alveolar macrophages. Neutrophil aggregation and activation ensues, resulting in degranulation, secretion of lysosomal enzymes and oxygen free radicals, and production of arachidonic acid metabolites (leukotriene B₄).
This acute inflammation damages alveolar endothelium and epithelium, causing pulmonary edema, fibrin exudation, and hyaline membrane formation. Carbon monoxide (CO) does not cause direct lung injury but it is the most common cause of death in smoke inhalation. CO causes toxicity through interference with oxygen transport by having more than two hundred times the binding affinity for hemoglobin than oxygen. Binding of CO to hemoglobin forms carboxyhemoglobin (COHb), which is incapable of transporting oxygen. This decreased oxygen-carrying capacity of the blood results in anemia, and the oxyhemoglobin saturation curve is shifted to the left, resulting in tissue hypoxia. Additionally, COHb inhibits mitochondrial cytochrome c oxidase activity and interacts with myoglobin to impair oxygen transport to muscles.

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**References:**
5. Lee-Chiong Jr TL: Smoke inhalation injury - When to suspect and when to treat. Postgrad Med 105:55-64, 1999

**CASE III – 01/288 (AFIP 2841966)**

**Signalment:** Six-year-old, female English setter, canine

**History:** At consultation, the dog had a one-month history of superficial inflammation of the left eye. Ophthalmologic examination revealed mydriasis and loss of pupil reflex of the left eye, whereas the right eye was normal. The veterinarian suspected glaucoma of the left eye. Intraocular pressure was within normal range in both eyes.
The owner did not want further clinical examination or treatment, and the dog was sacrificed. The eyes were submitted for histological examination.

**Gross Pathology:** The eyes were round and of equal size, and each measured 2.5 x 2.5 x 2.3 cm (width x height x depth). In the left eye, the iris was dislocated in nasal direction. The vitreous of this eye appeared to be replaced by a large, homogenous, grayish white tumor. The right eye was normal.

**Laboratory Results:** N/A

**Contributor's Morphologic Diagnoses:**
1. Ciliary epithelial tumor, left eye, canine
2. Retinitis
3. Retinal degeneration and atrophy

**Contributor's Comment:** Due to the neoplasia, the iris is dislocated nasally, and the iridocorneal angle and the ciliary cleft on one side are narrow. Focal lymphoplasmacytic infiltrates are present in the iris. The intraocular tumor seems to arise from the unpigmented ciliary epithelium and extends into the posterior chamber and the vitreous. The tumor cells show anisocytosis and anisokaryosis, but few mitotic figures are present. In some areas the tumor adheres to and focally infiltrates the retina. A mononuclear inflammatory reaction with mainly perivascular distribution is found in the retina. Patchy retinal degeneration and atrophy are also present.

Intraocular tumors are uncommon in domestic animals. In the dog, the most common primary neoplasm of the globe is melanoma, whereas iridociliary epithelial tumor is the second most common (1, 2, 3). The latter often is often located in the posterior chamber and extends into the vitreous. Neoplasia of the ciliary body may be pigmented or nonpigmented, depending on whether it originates from the inner nonpigmented epithelium or the outer pigmented epithelium. Both adenoma and carcinoma of ciliary epithelial origin have been reported (1, 2, 3). Common sequelae to these tumors are hyphema and secondary glaucoma due to pupillary blockage or iridocorneal angle closure and obliteration of the ciliary cleft.

**AFIP Diagnosis:** Eye, left (per contributor): Iridociliary adenoma with atypia, English Setter, canine.

**Conference Comment:** Iridociliary epithelial neoplasms may exhibit a range of histologic features from papillary to solid, and pigmented or non-pigmented. The contributor's decision to diagnose "ciliary epithelial tumor" is quite reasonable. Although these neoplasms have traditionally been designated as adenomas and adenocarcinomas based on the usual general criteria, metastasis is extremely rare regardless of the presence or absence of histologic features of malignancy. Utilizing criteria described in the WHO Histological Classification of Tumors of Domestic Animals, a diagnosis of adenoma with atypia was based on lack of invasion of sclera or choroid and low mitotic rate accompanied by atypia and solid growth pattern. The
periodic acid-Schiff procedure is used to distinguish these neoplasms from metastatic carcinomas. The cells of iridociliary epithelial neoplasms are surrounded by PAS-positive basement membrane material while metastatic carcinoma cells are not. Pigmented iridociliary neoplasms must be differentiated from uveal melanocytic tumors. Conference participants also considered medulloepithelioma in the differential diagnosis. This uncommon neoplasm arises from embryonal neuroectoderm of the optic cup. In medulloepithelioma, primitive neuroepithelial cells form Homer-Wright or Flexner-Wintersteiner type rosettes that rest upon a basement membrane, although the histological appearance can be predominantly sheets of undifferentiated neoplastic cells with few rosettes. In the teratoid variant, foci of muscle, bone, cartilage or brain may be found.

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**References:**

**CASE IV - 6-4100-01 (AFIP 2860168)**

**Signalment:** 9-month-old female Viszla

**History:** Extreme weight loss, lethargy, occasional gagging

**Gross Pathology:** N/A

**Laboratory Results:**
Complete blood count and chemistry profile:
Nonregenerative normocytic normochromic anemia (PCV 22.0, 0% reticulocytes)
Hypoalbuminemia
Hypocalcemia
Hyperphosphatemia (20.1 mg/dl)
Azotemia (BUN 138 mg/dl; Creatinine 4.2 mg/dl)
TCO2 12.4 mmol/l (normal range 16-24).

Urinalysis:
- Specific gravity  1.011
- Total protein  3+

**Contributor's Morphologic Diagnosis:** Kidneys, left and right: Cysts, glomerular, disseminated, with glomerular tuft atrophy and mild multifocal chronic interstitial nephritis with fibrosis.

**Contributor’s Comment:** The histologic findings in this case are consistent with glomerular polycystic kidney disease. This is an uncommon form of polycystic kidney disease affecting glomeruli. Some pathologists refer to this condition as glomerular dysplasia. It has been described as a congenital change in two Blue Merle Collies and a similar disease is described in goldfish. This disease is congenital, and there is some evidence that the condition is heritable. Familial glomerulocystic kidney disease (GCKD) in humans has been documented as a dominantly inherited disease. Polycystic kidney disease most often involves tubules in both canine and human cases. Affected dogs are generally under a year of age, and demonstrate polyuria, polydypsia, vomiting, diarrhea and anorexia. Clinical pathologic findings include uremia and elevated creatinine and phosphorus. Urinalysis demonstrates a decreased specific gravity and proteinuria. The CBC is typically characterized by a nonregenerative anemia.

One other puppy from this litter, a neutered male, died at five months of age with similar clinical signs and identical glomerular lesions. Four other littermates were unaffected when last evaluated at over one year of age.

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**AFIP Diagnosis:** Kidney: Glomerular cysts, diffuse, with glomerular tuft atrophy and distortion, tubular dilatation, interstitial fibrosis and mild multifocal lymphoplasmacytic interstitial nephritis, Viszla, canine.

**Conference Comment:** There are four basic mechanisms that result in formation of renal cysts: obstruction, defects in the tubular basement membrane, proliferative abnormality of tubular epithelial cells, and dedifferentiation of tubular epithelial cells with loss of polarity. Both cortex and medulla, and any segment of the nephron may be affected in polycystic kidneys, although cystic dilation of the renal tubules is the most common. This case is unusual because it only involves cystic expansion of Bowman’s capsule.

As part of the discussion of differential diagnosis, renal dysplasia and familial nephropathies were considered. Renal dysplasia has been defined as disorganized development of renal parenchyma due to anomalous differentiation. The histologic criteria of renal dysplasia are the presence of structures inappropriate to the stage of development of the animal and/or the presence of clearly anomalous structures. Specific features include immature (fetal) glomeruli, immature tubules, primitive
mesenchyme, and persistent metanephric ducts. In pigs, calves and children, intrauterine ureteral obstruction is associated with renal dysplasia. Kittens infected with feline panleukopenia virus in utero, neonatal puppies infected with canine herpesvirus and calves infected with bovine virus diarrhea virus all may have renal dysplasia. Various other teratogenic agents may be involved. Progressive juvenile nephropathies (familial renal diseases) have been described in a number of canine breeds and are hereditary conditions with varied histologic features.

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**References:**

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