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CONFERENCE 1
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CASE I – N03-516 (AFIP 2933954)

Signalment: 12 year-old, female, Alpine Swiss, caprine, goat.

History: This 12 year-old goat presented with coughing, dyspnea and white mucous membranes. Radiographs and ultrasound revealed a 1.5-inch diameter mass on the left lung lobe. A CBC revealed evidence of anemia due to blood loss. A transtracheal wash indicated reactive respiratory epithelial hyperplasia and hemorrhage. The animal died.

Gross Pathology: The lungs were moist and poorly collapsed. Several white nodules up to 2 cm in diameter were present on the surface of all lobes. On cut section, the lung was gelatinous and bulged. Small numbers of *Haemonchus contortus* were present in the abomasum. Caseous material exuded from an abscess over the medial aspect of the right hock joint.

Laboratory Results: No parasite ova were present on fecal examination. Alpha-hemolytic streptococci were isolated from the hock joint abscess. On AGID the serum was positive for CAE virus antibody.

Contributor's Morphologic Diagnosis: Pneumonia, lymphocytic, bronchointerstitial, diffuse, severe, with alveolar proteinosis, lung.

Contributor's Comment: The histologic appearance of the lung is consistent with pneumonia caused by caprine arthritis-encephalitis (CEA) virus disease, with findings of type II pneumocyte proliferation, lymphoid infiltration and proteinaceous fluid within alveoli (alveolar proteinosis). Electronmicroscopy has shown that the proteinaceous fluid found in CAE is lung surfactant.
CEA syndrome is a viral disease of domestic goats that manifests as chronic proliferative synovitis and periarthritis and progressive pneumonia in adult goats and afebrile leukoencephalomyelitis in goat kids.[1] The causative agent, a Lentivirus, is transmitted from adult goats to kid goats via colostrum or by lateral transmission. The

CAE virus has a worldwide distribution. All breeds and ages of goats are susceptible to infection and once established the infection persists throughout the animal's life. A diagnosis is established on clinical signs, demonstration of serum antibodies on ELISA and pathological changes such as diffuse pulmonary consolidation or hypertrophic, proliferative synovitis with intra-articular rice bodies. There is a microscopic component of interstitial mastitis leading to induration and agalactia.

Viral RNA can be identified in macrophages where viral transcription occurs. Infected macrophages may be detected with immunohistochemistry techniques in tissues such a lung, udder, and lymph nodes.[2,3]

Interestingly, the mass identified radiographically in the left lung lobe turned out to be a secondary granulomatous pleuritis with intralesional *Cryptococcus neoformans* yeast organisms.[4]

AFIP Diagnosis: Lung: Pneumonia, interstitial, proliferative, lymphocytic, diffuse, moderate, with alveolar proteinosis and secondary acute bronchopneumonia, Alpine Swiss, caprine.

Conference Comment: Conference attendees discussed slide differences with some sections containing distinct lymphoid nodules, while others contained variable numbers of interstitial and perivascular lymphoid infiltrates. However, all slides were characterized by prominent type II pneumocyte hyperplasia and abundant alveolar proteinosis, which are characteristic of CAE virus.[5] Most slides also had features consistent with bronchopneumonia; bronchioles and alveoli filled with an exudate composed of degenerate neutrophils, necrotic debris, and proteinaceous fluid. This is not surprising, as secondary bacterial infections are common in animals with CAE.[5] However, no organisms were seen with H&E, B&B, B&H, or PAS.

CAE virus is a lentivirus (subfamily Lentivirinae, family Retroviridae). Lentiviruses are non-oncogenic retroviruses with clinical disease characterized by long incubation periods, persistent infection, and a progressive course. Other lentiviruses include: maedi-visna virus in sheep (ovine progressive pneumonia); equine infectious anemia virus in horses and, human, simian, bovine and feline immunodeficiency viruses.

Other causes of pneumonia in sheep and goats include:
<u>Viral:</u>
Maedi-visna virus (ovine progressive pneumonia)
Caprine Morbillivirus (Peste des petits ruminants)
<u>Bacterial:</u>
Mannheimia (*Pasteurella*) *haemolytica* (ovine pneumonic pasteurellosis)
Mycoplasma ovipneumoniae (chronic enzootic pneumonia)
Mycoplasma mycoides spp. *mycoides* large colony (contagious caprine pneumonia)
Mycobacterium bovis (tuberculosis)

Mycobacterium avium (tuberculosis)
Parasitic:
Dictyocaulus filaria
Muellerius capillaris
Protostrongylus rufescens

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CASE II – 03N0138 (AFIP 2936140)

Signalment: 2-year-old male castrated Great Dane.

History: The dog presented with a several day history of weight loss, vomiting, diarrhea, and urinary incontinence. The dog had been treated for six months with immunosuppressive doses of prednisone (1 mg/kg PO q12h for 2 weeks) for chronic lymphocytic-plasmacytic enteritis (inflammatory bowel disease).
The dog continued to have weight loss and diarrhea but also developed profound lethargy and hematuria. Despite treatment, the clinical signs worsened and two weeks later, the dog presented to the hospital recumbent, comatose, and with intermittent seizures and rotary nystagmus. Due to the poor prognosis, the owners elected to euthanize the dog.

Gross Pathology: Necropsy revealed numerous small, randomly distributed granulomas restricted to the kidneys and brain. In both kidneys, the lesions spread from the cortico-medullary junction to the cortex. The kidney lesions consisted of 0.3 to 1.0 cm in diameter soft raised tan well-demarcated raised nodules that were distributed randomly throughout the parenchyma. In the brain, lesions were found in the right

occipital lobe and right caudal cerebellar peduncle. The brain lesions were well-demarcated unencapsulated gelatinous tan foci.

Laboratory Results: Blood cultures were negative and the kidney culture revealed one colony of hemolytic *E. coli*.

Contributor's Morphologic Diagnosis: Kidney: Multifocal severe granulomatous and necrotizing nephritis with intralesional amoeba organisms.

Contributor's Comment: The histologic features observed throughout this kidney consisted of marked interstitial edema and tubular necrosis associated with marked perivascular inflammatory infiltrates mainly comprised of macrophages, lymphocytes, Langerhans type giant cells, plasma cells and small numbers of neutrophils. Admixed with these cells were large numbers of amebic organisms in two different life stages, trophozoites and cysts. The trophozoites ranged in size from 15-45 _m in diameter, and were round to oval with occasional short plump cytoplasmic processes (pseudopodia). Their cytoplasm was pale, eosinophilic, and partially vacuolated and contained a 4-6 _m in diameter round, pale-staining vesicular nucleus. In contrast, the cysts were smaller, more uniformly round, and surrounded by an undulating outer wall and an internal thick round basophilic inner wall. The cytoplasm was scarce and contained multiple, hyperchromatic basophilic granules. The nucleus was centrally located with 1-2 prominent eosinophilic karyosomes. The cystic forms were distributed throughout the renal interstitium, but were most prominent within collecting tubules. The trophozoites were more abundant near blood vessels.

In the brain, lesions associated with this case had histologic features of fibrinoid necrosis of the blood vessels and a florid perivascular infiltration of neutrophils and macrophages admixed with lakes of fibrin. There were also extensive areas of malacia associated with astrogliosis, surrounding the affected vessels. Large numbers of trophozoites were concentrated primarily in the perivascular regions of the gray matter, the meninges and the choroid plexus. The cystic forms were located further away from the blood vessels and were associated with less inflammation and necrosis.

The amoeba in this case were diagnosed as *Balamuthia mandrillaris* based on positive immunohistochemical results (performed at San Bernardino) and PCR, which used specific primers designed for this case at Dr. Sykes' laboratory (UC Davis, VMTH).

Balamuthia mandrillaris is a free-living ameba of the order Leptomyxida capable of causing fatal granulomatous amebic meningoencephalitis (GAE) in humans and animals[1]. It was first isolated from a mandrill[1,6] (*Papio sphinx*) at San Diego Zoo Wild Animal Park, then subsequently in gorillas[2] (*Gorilla gorilla gorilla*), an orangutan[3] (*Pongo pygmaeus*) and Old World primates, including a colobus monkey[4] (*Colobus guereza kikuyuensis*) and a gibbon (*Hylobates concolor leucogenys*). In recent years, *B. mandrillaris* has also been increasingly identified as a cause of GAE in humans.[1,5,6] So far, the only reports in a non-primate species have involved a horse[7] and a sheep.[8] *B. mandrillaris* has been recently isolated from environmental samples suggesting it

occupies similar habitats as other opportunistic ameba such as *Naegleria fowleri* and *Acanthamoeba* spp..[5,6] The route of invasion is still unknown, however penetration of skin or respiratory tract and subsequently hematogenous spread has been postulated.[6] Infections with *B. mandrillaris* are reported to be more common in immunosuppressed hosts such as patients with AIDS, although immunocompetent individuals also have been affected.[6] Reports of canine disease caused by free -living amebas are rare. There is a single report of kidney lesions associated with dissemination of *Acanthamoeba castellani.*[9]

There are two forms of *B. mandrillaris*, a trophozoite form and a cyst form. The trophozoite amoebic form ranges in size from 15-60 _m in diameter and has a round nucleus and a dense nucleolus. More than one nucleolus can be observed, which aids as a distinguishing feature between *B. mandrillaris* and *Acanthamoeba*.[6] The trophozoite has pale, eosinophilic, and partially vacuolated cytoplasm that can occasionally be observed branching into short plump cytoplasmic processes (pseudopodia). In contrast, the cyst form, which is the dormant form, is smaller, more spherical, uninucleated, measuring 15-60 _m, and has a prominent bilayer wall with granules positioned beneath the inner cell wall.[6]

The precise pathogenesis of *B. mandrillaris* is unknown. However, a recent review discusses the life cycle and pathogenesis of *Entamoeba histolytica.* Initial infection is through ingestion of contaminated food or water with *E. histolytica* cysts. Cysts are ingested and excysted in bowel lumen. The invasive trophozoite form invades intestinal epithelium and spreads to other sites.[10] In the case of *B. mandrillaris*, infection may occur through ulceration in skin or lower respiratory tract infection. Spread to other sites, especially brain, is thought to be hematogenous.

AFIP Diagnosis: Kidney: Nephritis, interstitial, necrotizing, pyogranulomatous, multifocal to coalescing, moderate, with amebic trophozoites and cysts, Great Dane, canine.

Conference Comment: This case was reviewed in consultation with Dr. Chris Gardiner, AFIP consultant in veterinary parasitology. The contributor provides a thorough description of the gross and histologic lesions associated with *B. mandrillaris*. Other important amebic organisms to consider include: *Acanthamoeba* spp.; *Entamoeba histolytica*; *Naegleria fowleri*; and, *Hartmannella* spp..

Acanthamoeba spp. is a free-living organism found in fresh water, soil, or sewage. Transmission is via inhalation with the lung being the primary target organ. However, the central nervous system and other organs may be affected through hematogenous spread. This organism is also known to cause granulomatous amebic encephalitis (GAE) in humans and other species. Trophozoites are 10-30 _m in diameter, contain an eccentric nucleus, a single nucleolus, and eosinophilic cytoplasm with glycogen vacuoles. Cysts are generally rare.[11]

Entamoeba histolytica is often a non-pathogenic inhabitant of the large intestine, only occasionally causes amebic dysentery in humans and nonhuman primates, and rarely affects other species. Transmission is via ingestion resulting in characteristic flask-shaped intestinal ulcers. Hematogenous and lymphatic dissemination to the brain, liver, or other organs may occur. Trophozoites are 6-50 _m in diameter, often surrounded by a clear halo, and contain an eccentric nucleus with a distinct karyosome.[12]

Naegleria fowleri is a free-living ameba that causes acute and fulminating primary amebic meningoencephalitis (PAM) primarily in young healthy humans, with rare reports in animals. *Naegleria* is commonly found in fresh water, soil, and sewage. Transmission is via inhalation with invasion of the olfactory neuroepithelium. Trophozoites are 6-12 _m in diameter with a centrally located nucleus and a large single nucleolus. Unlike *Acanthamoeba* and *Balamuthia*, cysts are generally not found in neural tissue.[13]

Hartmannella sp. is a non-pathogenic, free-living amoeba. Older isolates of *Hartmannella* suspected of being opportunistic pathogens (like *Acanthamoeba* and *Naegleria*) have now been reclassified as *Acanthamoeba*. True *Hartmannella* sp. are not known to cause CNS infections in humans or other species.[5]

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CASE III – L02-3969-1B or L04-3969-1C (AFIP 2936455)

Signalment: Adult, unknown sex, *Boa constrictor*.

History: History of lethargy, regurgitation, head tremors and death.

Gross Pathology: Uric acid deposits in multiple visceral organs (visceral gout).

Laboratory Results: None

Contributor's Morphologic Diagnoses:
Liver: There are multifocal, large, circular areas of acute hepatocellular necrosis surrounded by minimal inflammation. Within the center of most foci are shards of clear spaces surrounded by cellular debris, histiocytes and acidophilic fibrillar material (dissolved uric acid tophi). Approximately 80% of hepatocytes contain single to multiple, prominent, eosinophilic, circular 5-10 micron diameter, intracytoplasmic inclusion bodies. Randomly scattered individual to small clusters of hepatocytes are shrunken, hypereosinophilic and have fragmented nuclei (necrosis).

Kidney: There is severe architectural distortion by scattered large aggregates of necrotic cellular debris, mineralized basophilic material and dilated tubules containing shards of clear material and mineralized debris. Dilated tubules are lined by fragmented, shrunken, hypereosinophilic epithelial cells, many containing large eosinophilic prominent intracytoplasmic inclusion bodies (as previously described). Tubule lumens are filled with mineralized basophilic granular debris and shards of clear material surrounded by histiocytes and lymphocytes. The interstitium is widened by bands of edema fluid mixed with scattered lymphocytes and histiocytes.

Stomach: Lining epithelial cells contain large numbers of 5-15 micron diameter, deeply eosinophilic intracytoplasmic inclusion bodies.

Lung: Epithelial cells lining bronchi and alveoli contain single to multiple, brightly eosinophilic 5-7 micron diameter, intracytoplasmic inclusion bodies.

1. Hepatitis, granulomatous with uric acid deposition and multifocal hepatocellular necrosis.
2. Urate nephrosis, severe, chronic with tubular dilatation and mineralization.
3. Inclusion bodies, multifocal/multiorgan, epithelial cells and hepatocytes, diffuse.

Contributor's Comment: Histologic lesions indicate the cause of death is visceral gout secondary to Boid inclusion body disease (IBD). Gout is a common sequela to chronic infection or debilitating conditions in reptiles with dehydration often being a primary compounding issue. Underlying viral infections (IBD) also lead to secondary bacterial infections due to immunosuppression and debilitation.

Boid inclusion body disease (IBD) is a fatal disorder of boid snakes caused by a retrovirus that was described in 1994.[1] Clinical signs of IBD include chronic regurgitation and central nervous system disorders manifested in head tremors, disorientation and paresis and/or paralysis. Histologic examination reveals numerous eosinophilic intracytoplasmic inclusion bodies in epithelial cells of all major organs, in hepatocytes and within neurons of the CNS. Inclusion bodies contain an antigenically distinct 68 kDa protein.[2] In all snakes with CNS disease, nonsuppurative meningoencephalitis with neuronal degeneration and perivascular cuffing was present and viral particles resembling type C retrovirus were detected in the brain, pancreas, and kidney as well as in cultured kidney cells. The disease was shown to be transmissible by cell free primary kidney culture supernatants from infected *Boa constrictor* snakes to young Burmese pythons (*Python molurus bivittatus*) or by liver homogenates from *Boa constrictor.*[2] These data imply that a C type retrovirus may indeed be the causative agent of IBD.

AFIP Diagnoses: 1. Liver: Mineral deposition (gouty tophi), multifocal, with minimal granulomatous inflammation, boa constrictor (*boa constrictor*), reptile.
2. Liver, hepatocytes: Inclusion bodies, eosinophilic, intracytoplasmic, multifocal.
3. Liver, hepatocytes: Degeneration, multifocal, moderate, with random single cell necrosis.

Conference Comment: The contributor provides a thorough overview of boid inclusion body disease (IBD), a fatal disorder of boid snakes, thought to be caused by a retrovirus. It is well established that snakes with IBD have increased susceptibility to secondary infections and a variety of neurological signs. It is not surprising this snake likely developed gout secondary to IBD.

Gout is a common clinical finding in reptiles and may also affect birds, humans, non-human primates, and the Dalmatian dog. There are two forms of gout in birds and reptiles: articular and visceral. Articular gout is less common and presents as white deposits on tendon sheaths. Visceral gout is more common and presents as chalky

white patches on visceral surfaces. Gout results from hyperuricemia (elevated plasma uric acid concentration), which may be caused by impaired renal function and clearance of urates, nephrotoxic drugs, dietary excesses (protein and calcium) and deficiencies (vitamin A), and dehydration.[3] Nucleic acids ingested in foods undergo enzymatic hydrolysis to yield free purine (adenine, guanine) and pyrimidine bases. In humans, the formation of uric acid from purine degradation has been extensively studied and requires xanthine oxidase:

Adenine>hypoxanthine>xanthine>uric acid>allantoin>allantoic acid>urea

Guanine>xanthine>uric acid>allantoin>allantoic acid>urea

In order to conserve water, birds and reptiles excrete uric acid rather than urea.[4,5] The majority of uric acid excretion is via renal tubular secretion and is largely independent of urine flow rate. When hyperuricemia occurs, uric acid crystals may be deposited in joints, viscera, or extra-visceral sites.[6] The crystals that are deposited in tissues (urate tophi) are often dissolved during processing. Histologically, all that remains are large aggregations of clear acicular clefts, frequently surrounded by granulomatous inflammation.

In humans, gout may be the result of a deficiency in hypoxanthine guanine phosphoribosyl transferase (HGPRT), leading to increased production of uric acid due to synthesis of purine nucleotides from non-purine precursors. A complete lack of HGPRT occurs in the uncommon X-linked Lesch-Nyhan syndrome seen in males that is characterized by hyperuricemia, severe neurologic deficits, and occasionally gouty arthritis.[7]

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CASE IV – 0404975 (AFIP 2937765)

Signalment: Approximately 16 month-old female B6C3F1 mouse (*Mus musculus*)

History: The mouse was a sentinel animal and did not receive any treatment. It was found dead at approximately 16 months of age.

Gross Pathology: Macroscopic examination revealed about 5 cc of a red fluid in the abdominal cavity. The spleen was enlarged (32x6x3 mm) and the mediastinal lymph node was enlarged (3x) and dark. A red mass was found on the right ovary (47x31x19 mm).

Laboratory Results: None

Contributor's Morphologic Diagnosis: Yolk Sac (Carcinoma) Tumor

Contributor's Comment: The tumor is composed of nests, clusters or ribbons of discrete cells embedded within an abundant eosinophilic matrix. The cells vary in size from small to large and have distinct borders and hyperchromatic nuclei.[1,2,3]

AFIP Diagnosis: Ovary: Yolk Sac Carcinoma, B6C3F1 mouse, rodent.

Conference Comment: Conference attendees had difficulty with tissue identification. Some sections contain rare follicles at various stages of development. Tumors arising from ovarian tissue are divided into three broad categories based on embryological origin: tumors of surface epithelium, tumors of gonadal stroma, and tumors of germ cells. Tumors may also arise from more than one of the three embryological lineages (mixed tumors) or from nongonadal support tissues, including smooth muscle, vascular, or fibroblastic tissue.[4]

Epithelial tumors may arise from ovarian surface epithelium, subsurface epithelial structures (SES) in canines, and the rete ovarii. These tumors commonly appear as unilateral or bilateral multinodular, cystic outgrowths extending from the ovarian surface. Examples of epithelial tumors include papillary or cystic adenoma, or less frequently papillary or cystic adenocarcinoma. These tumors are common only in the dog as SES are unique to this species.[5]

Gonadal stromal tumors, also known as sex cord-stromal tumors, arise from granulosa, theca, or interstitial cells. Granulosa cell tumors (granulosa-theca cell tumor) are the most common ovarian tumor in the cow and mare. Granulosa cell tumors in the mare frequently produce inhibin, which is thought to cause atrophy of the contralateral ovary. Theca cells may be present in these tumors and either cell population may be luteinized. Thecomas (theca cell tumor) are rare tumors composed of lipid-containing cells of stromal origin, resembling theca interna cells. Interstitial cell tumors (luteoma, lipid cell tumor, steroid cell tumor) are composed of large rounded cells with round central nuclei, resembling Leydig, luteal, or interstitial gland cells. However, the origin of these cells has not been clearly identified.[6]

Germ cell tumors may fail to differentiate (dysgerminoma), differentiate into somatic tissue (teratoma), or differentiate into extraembryonic structures (yolk sac carcinoma, choriocarcinoma). The dysgerminoma is an uncommon tumor, which is comparable to the more common seminoma of the testicle. This malignant tumor is composed of cells that resemble primordial germ cells. Teratomas are rare tumors thought to arise from totipotential germ cells that have differentiated into two or more embryonic layers (endoderm, mesoderm, ectoderm). Most of these tumors are composed of a variety of tissues and are generally benign.[6] Yolk sac carcinomas can be distinguished histologically by nests and cords of neoplastic polygonal to cuboidal cells embedded in abundant amounts of a characteristic eosinophilic PAS-positive matrix.[2]

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