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Conference Moderator: LTC Thomas Larsen, DVM, Diplomate, ACVP
Chief, Experimental Pathology Branch
USAMRIID, Frederick, MD 21702

CASE I - 02-H1222A (AFIP 2839773)

Signalment: 21-year-old female, Quarterhorse, Equine, *Equus caballus*

History: 21-year-old quarter horse mare, full term pregnancy. History of weight loss and anorexia for three weeks. Intermittent fever. Auscultation demonstrated wheezes and crackles. No response to Gentamycin, Oxytetracycline, and Butazolidin. Abdominal ultrasound revealed multiple hypoechoic areas in the spleen. Thoracic ultrasound revealed surface defects in the caudodorsal lung. Tentative diagnosis was disseminated neoplastic disease. Horse was euthanatized at the ISU VTH.

Gross Pathology: At necropsy, the mare is very thin. Multiple firm white raised nodules were present on the capsular surfaces of the spleen, liver, kidneys, lung, mediastinal lymph nodes and left adrenal gland. On cut surface, these nodules were solid and uniformly white. Disseminated nodules were present throughout the spleen, which ranged in sized from 0.5 cm to 3.0 cm in diameter, and extended deeply into the cut surface. Multiple splenic vessels were filled with dull white friable and adherent masses (thrombi). Multifocal 1 cm to 3 cm nodules were present throughout the hepatic parenchyma which extended into cut surfaces, and formed a 3 cm x 3 cm coalesced mass in the hilus region. Multiple thrombi were present in the hepatic vessels. Few 1.5 cm nodules were noticed in the cortex and medulla of both kidneys. Numerous nodules ranging from 2 mm to 3 cm in diameter were present on the pleural and cut surface of the lungs. The larger of these nodules had ulcerated surfaces. Multiple thrombi were present in the pulmonary vessels. The mediastinal lymph nodes were roughly 5 times their normal size with multiple to coalescing nodules replacing most of the normal gross node architecture. A 0.5 cm nodule was present within the left adrenal gland cortex. Additionally there were multifocal mucosal ulcerations in the cecum.

Laboratory Results:
CBC: Hemogram: Normal
Leukogram: Low normal leukocytes with left shift and toxic neutrophils, lymphopenia, and hyperfibrinogenemia

Serum chemistries: Normal with exception of a mild hypoalbuminemia

Contributor's Morphologic Diagnosis: Lung: Pneumonia, granulomatous, multifocal to coalescing, severe, with myriad intracellular yeast consistent with *Histoplasma capsulatum*.

Contributor's Comment: Grossly, the white nodules on numerous organs were consistent with widely metastatic neoplasia, which was the leading antemortem differential diagnosis. Microscopically however, these nodules are composed of an inflammatory cell infiltrate. This population consists of large numbers of macrophages intermixed with fewer neutrophils, plasma cells, and lymphocytes. Multinucleate giant cells are common. Most macrophages have abundant cytoplasm, which are filled with yeast. These are round, approximately 3-5 microns in diameter with a dense basophilic core surrounded by a thin clear rim. Yeast were positive by Grocott-Gomori methanol silver nitrate staining. The morphology of the intracellular yeast is consistent with *Histoplasma capsulatum*.

Differential diagnoses considered in this case included *Leishmania* sp. and other species of *Histoplasma*. Visceral leishmaniasis, to the best of the authors knowledge, has not been reported in the United States in horses, and no kinetoplast (seen with *Leishmania*) was identified in these organisms. *H. farciminosum* is the cause of enzootic lymphangitis and has similar morphologic appearance as *H. capsulatum*; however, it typically has a different tissue distribution and has been eradicated from the Western Hemisphere. *H. capsulatum* var. *duboisii*, the cause of African histoplasmosis, has a different appearance histologically, and geographically is limited to Africa.

H. capsulatum is a dimorphic fungus common to North, Central, and South America, which grows both in soil and in animal tissues. *H. capsulatum* grows as a mold in soils, especially those that are rich in nitrogen. Environments that are highly contaminated with bird or bat feces are especially suited to promote growth of the mold form. Once in animal tissues, *H. capsulatum* transforms into the yeast form and may remain localized (i.e. lung), or may distribute widely throughout the body. Histoplasmosis is common in the central United States especially along the Mississippi, Missouri, and Ohio rivers. A large number of animal species can be infected with *H. capsulatum* and common hosts include dogs, cats, bats, guinea pigs, and humans.

H. capsulatum is an intracellular pathogen which can survive within the host's monocytes and macrophages. Following inhalation microconidia transform into the yeast form which are taken up by macrophages. Mechanisms used by the yeast to survive within the macrophage include inhibition of phagosomal acidification, and inhibition of phagolysosome development (1). Typical of most intracellular pathogens, the ability of the host to mount a strong cell mediated immune response is critical to overcoming infection (2).

Systemic infection by this fungus is uncommon in horses, but pulmonary and disseminated histoplasmosis has been reported (3,4). As this is not a contagious disease, exposure of animals (including humans) is usually through contaminated soil (aerosols and ingested), and typically leads to mild self-limiting disease which is cleared by an immunocompetent host. Immunosuppression likely facilitated disseminated disease in this case. This may be explained, in part, by the age of the horse and the

stress of advanced pregnancy. No gross lesions were identified in the placenta. Unfortunately, the fetus was not necropsied in this case. Cases of abortion and neonatal death have been associated with histoplasmosis of the mare. Granulomatous placentitis was typically noted in these cases (5). While no direct animal to human transmission of histoplasmosis has been documented, there is potential for humans and other animals to share a common source of infection, such as heavily contaminated soil.

AFIP Diagnosis: Lung: Pneumonia, pyogranulomatous, diffuse, severe, with myriad intrahistiocytic yeast, Quarterhorse, equine, etiology consistent with *Histoplasma capsulatum*.

Conference Comment: The contributor has provided a concise summary of equine histoplasmosis. Other dimorphic fungi include *Blastomyces dermatitidis* and *Coccidioides immitis*.

Contributor: Department of Veterinary Pathology, College of Veterinary Medicine, Iowa State University, Ames, IA, 50011

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CASE II - HN1727 (AFIP 2839343)

Signalment: 9-month-old, female, Japanese Black calf, bovine

History: This calf showed growth retardation and elongated hooves. A genetic analysis revealed the calf is under claudin-16/paracellin-1 deficiency.

Gross Pathology: The calf's hooves were slightly elongated. Clear subtle peritoneal and pericardial fluids were slightly increased. Both kidneys were rather small and were slightly increased in firmness. On the cut surface, the cortex was diffusely muddled and whitish. The borderline between the cortex and medulla was indistinct. The mesenteric lymph nodes were mildly enlarged. Oval foramen was patent in the heart.

Laboratory Results:
Hematology: WBC $100x10^2$ /ul, Hb 10.8 g/dl, Ht 31.6 %, PLT $63.0x10^4$ /ul, TP 7.0 g/dl, AST 75 IU, ALT 25 IU, BUN 62.6 g/dl, Cre 2.83 g/dl,
iP 8.35 g/dl, Ca: 8.5 g/dl
Urinalysis: Cre 2.8 g/l, NAG: 3.8 u/l, NAG index 1.38 u/g, urinary specific gravity 1.019, occult blood (-), protein 10, glucose (-), pH 5,
urobilinogen (-), ketone (-), urinary sediment (leukocyte, bacteria, epithelial cells, casts, crystals) (-)

Contributor's Morphologic Diagnoses: Renal dysplasia; Mesangial proliferative glomerulonephritis, moderate; Interstitial nephritis, moderate; Bovine claudin-16/paracellin-1 deficiency; Japanese Black cattle

Contributor's Comment: Histologically, linear to irregularly shaped, sometimes coalescing, fibrotic areas are scattered in the cortex and medulla. The areas contain hypoplastic urinary tubules and glomeruli with thickened peritubular basement membrane and Bowman's capsule. In the cortex, glomeruli are decreased in number and enlarged due to mesangial cell proliferation. Interstitial mononuclear cell infiltrations are prominent particularly in the fibrotic areas. Urinary tubules are sometimes covered with regenerative or enlarged epithelial cells and contain hyaline and a few calcium casts.

Bovine claudin-16/paracellin-1 (CL-16/PCLN-1) deficiency is an autosomal recessive chronic renal disorder in Japanese Black cattle. This disorder was diagnosed preliminarily by increased blood urea nitrogen, creatinine, and urinary protein levels. This is associated with failures in glomerular filtration and tubular resorption. Such failures invariably result from defects in selective filtration and absorption in renal epithelium. Hypoplastic renal tubules and extensive interstitial fibrosis with inflammatory cell infiltration are observed in the affected kidney.

The first four exons of CL-16/PCLN-1, which encodes a member of the claudin family of tight junction proteins, were deleted in the affected cattle. Genetic analysis for detecting the defect of CL-16/PCLN-1 gene is established and this disease can be prevented by disclosing the carrier cattle of CL-16/PCLN-1 deficiency.

Claudin is a major component of tight junctions (TJs) that has an important role in sealing the intercellular space, in maintaining the structure between apical and basolateral membranes, and cell polarity. At least 20 members of the claudin family have been identified, all of which have four transmembrane domains. They show specific tissue distribution patterns depending on the claudin species. Claudin proteins are thought to form pores in TJs and to mediate paracellular conductance. Mutations in CL-16/PCLN-1 in humans cause renal Mg^{2+} and Ca^{2+} wasting, suggesting that CL-16/PCLN-1 is required for paracellular Mg^{2+} and Ca^{2+} transport in renal epithelium.

AFIP Diagnosis: Kidney: Renal dysplasia, characterized by decreased glomeruli, mesangioproliferative glomerulonephritis, tubular epithelial hypertrophy, hyperplasia and disorganization, and chronic interstitial nephritis, Japanese Black, bovine.

Conference Comment: Mutations permanently alter DNA. Those mutations that affect the germ cells are inherited by the progeny. Since codons are composed of three nucleotides, insertions or deletions of nucleotides that are not multiples of three, result in frameshift mutations and alterations in the reading frame of DNA. A point mutation is the substitution of a single nucleotide base, and there are two types: missense mutations and nonsense mutations. Missense mutations are point mutations within the coding sequence that lead to substitution of one amino acid by another. A nonsense mutation is a point mutation that results in a stop codon that prematurely terminates translation.

Classically, there are three patterns of inheritance that involve single genes, autosomal dominant, autosomal recessive, and X-linked. As the contributor noted, this case of renal dysplasia is an example of autosomal recessive inheritance, which occurs when both alleles of a gene locus are mutants. Typically in autosomal recessive disorders, there is a young age of onset, complete penetrance, and a more uniform expression of the defect than in autosomal dominant disorders.

Contributor: Laboratory of Comparative Pathology, Graduate School of Veterinary Medicine, Hokkaido University, Sapporo 060-0818, Japan

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CASE III - 12-45080 (AFIP 2841062)

Signalment: 1-year-old, female spayed, Labrador Retriever cross, (*Canis familiaris*)

History: History of sneezing and unilateral (right sided) epistaxis for three months. Fever at presentation.

Gross Pathology: The gross lesion was described by the RDVM as a large, pink to tan, proliferative, fleshy mass (visible on examination of the nares) present in the rostral aspect of the right nasal cavity. The mass was vascular and bled readily with sneezing or irritation.

Laboratory Results: CBC: No significant abnormalities

Contributor's Morphologic Diagnosis: Nasal mucosa / submucosa: Rhinitis, lymphohistiocytic, chronic, severe, diffuse with epithelial hyperplasia and squamous metaplasia, and numerous intralesional sporangia and trophocytes, canine, etiology consistent with *Rhinosporidium seeberi*

Contributor's Comment: Microscopic Findings: Diffusely, the submucosal stroma and lamina propria are expanded and the mucosa is verrucously elevated by a marked infiltrate of macrophages, lesser numbers of lymphocytes, plasma cells, aggregates of neutrophils, and numerous, spherical, variably staged protistan parasites (trophocytes, intermediate sporangia, mature sporangia) consistent with *Rhinosporidium seeberi*. The trophocytes range in size from 10-100 um diameter, have a thick (2-3 um), hyaline, double contoured wall, basophilic granular cytoplasm, and a variably identifiable, central, eosinophilic, 10-12 um nucleus (karyosome) with a prominent nucleolus. Intermediate sporangia contain similar basophilic granular cytoplasm however lack a nucleus. The mature sporangia range in size from 100 – 350 um, have a thinner (~1 um) unilamellar wall and contain a myriad of variably sized (2-10 um diameter) endospores (sporangiospores) which are smaller and flattened (young spores) at the periphery and larger and rounder (mature spores) centrally within the sporangia. In most sections, there are ruptured sporangia with released endospores that are frequently surrounded by aggregates of neutrophils both in the tissue and at the

mucosal surface. Folded, crescent shaped sporangia are also present. The mucosa is diffusely hyperplastic, up to 4 times normal, with regional transition of non-ciliated, columnar, pseudostratifed epithelial cells to squamous epithelium (squamous metaplasia) and rare focal areas of ulceration.

Classification: The phylogeny of *Rhinosporidium seeberi* still seems to be somewhat controversial in the literature. Formerly, *R. seeberi* was classified as a fungus. Recently, based on polymerase chain reaction analysis of it's 18S rRNA gene, it has been suggested to be a member of the DRIP's clade, a novel clade of aquatic protistan parasites. The "DRIPs" clade obtains its name from the other organisms classified in this group: *Dermocystidium* spp., Rosette Agent, *Ichthyophonus* spp., and *Psorospemium* spp., however the term Ichthyosporea has been proposed for future taxonomy of this group of microbes. Based on recent PCR analysis the *Dermocystidium* genus appears to be the nearest phylogenetic relative to *R. seeberi*. *Dermocystidium salmonis* is recognized in salmonids causing gill inflammation and epithelial hyperplasia with intralesional spherical endospore containing organisms.

Epidemiology: Rhinosporidiosis is a disease of humans and animals which is endemic in India, Sri Lanka, and Southeast Asia yet rare and sporadic in North and South America. In the Americas, Rhinosporidiosis has been reported in the horse, cattle, mules, goats, swans, a wood duck, dogs, and most recently one cat (JVDI 13(4), 2001). We have only identified eleven documented cases of canine Rhinosporidiosis in North America spanning from 1976 to 1986. No cases of canine rhinosporidiosis have been reported for the last 15 years (since 1986). This specific case was diagnosed in Fort Colllins, Colorado at the CSU Diagnostic Lab, however the tissue was sent from a veterinary hospital in Marietta, Georgia, a region more likely to manifest this disease.

General: Rhinosporidiosis is a chronic, non-infectious, granulomatous disease which affects mucus membranes, particularly of the nasal cavity however infection of the vagina, penis, subconjunctival sac, and ears have been reported in man. A unilateral, polypoid mass of the rostral aspect of the nasal cavity/nares is the classical lesion with clinical signs of sneezing, unilateral epistaxis, and/or stertorous breathing. Although there are three reports worldwide of disseminated disease in humans, Rhinosporidiosis does not typically disseminate or cause systemic illness. No reports of disseminated disease have been identified in animals. The source of infection and the route of transmission have not been definitively elucidated but there is a widely accepted association of the organism with stagnant water.

Three developmental stages of Rhinosporidium exist in tissue: 1) The trophocyte or juvenile sporangia which is 10-100 um in diameter, has a 2-3 um unilamellar hyalinized wall, granular to flocculent cytoplasm, and a central nucleus (karyosome) with a prominent nucleolus, 2) The intermediate sporangia which are larger than trophocytes, have a thicker, bilamellar wall, and lack a nucleus, and 3) The mature sporangia (the hallmark of *R. seeberi*) which range from 100-400 um in diameter, have a unilamellar wall, lack a nucleus, and contain numerous mature and immature endospores (2-10 um) which are present centrally and peripherally within the sporangia respectively. These endospores are released through a pore in the sporangium into the surrounding tissues, develop into trophocytes, and the cycle continues.

Differential diagnoses: Three other agents, which, like *R. seeberi*, reproduce by endosporulation include *Coccidioides* sp., *Prototheca* sp., and *Chlorella* sp. Of these,

Coccidioides sp. may be the most difficult to differentiate. Multiple distinguishing histologic features between these two organisms do exist. These include: 1) Mature sporangia of *R. seeberi* are much larger than the mature spherules of *C. immitis*, 2) the endospores of *R. seeberi* are both flat and round (varying stages) and are larger than endospores of *C. immitis* which are only round, 3) sporangia and endospores of *R. seeberi* stain uniformly with Gomori methamine silver (GMS), PAS, and Gridley whereas only the walls of *C. immitis* stain with PAS, and 4) the endospores of *R. seeberi* contain inner granules while those of *C. immitis* do not.

This was the first case of canine rhinosporidiosis diagnosed at the CSU Veterinary Diagnostic Lab, although again, the specimen was sent from a veterinary hospital in Marietta, GA (The Greater Atlanta Veterinary Medicine Group). The nasal mass in this animal was surgically removed without any complications and submitted for biopsy on February 14, 2002. Following surgery, both the sneezing and epistaxis subsided and there has been no evidence of recurrence or other signs of related illness in this patient thus far.

AFIP Diagnosis: Nasal mucosa: Rhinitis, proliferative, chronic-active, diffuse, moderate, with erosion, ulceration, squamous metaplasia, and numerous sporangia and trophocytes, etiology consistent with *Rhinosporidium seeberi*, Labrador Retriever cross, canine.

Conference Comment: The contributor has provided an excellent review of canine rhinosporidiosis.

Contributor: Colorado State University, Department of Microbiology, Immunology, and Pathology, 1682B Campus Delivery, Fort Collins, CO, 80523-1682

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CASE IV - 00-4047-5 (AFIP 2838994)

Signalment: 2.5-year-old Holstein cow

History: Animal found dead.

Gross Pathology: Severe fibrinonecrotic bronchopneumonia affecting 50% of the lungs.

Laboratory Results: *Haemophilus somnus* was isolated in large amounts from the pneumonic lesions. They were negative for *Mannheimia haemolytica* and *Pasteurella multocida.* Search for bovine herpesvirus-1, respiratory syncytial virus, BVD virus, PI3 virus and *Mycoplasma bovis* with the FA technique was negative.

Contributor's Morphologic Diagnosis: Fibrinonecrotic bronchopneumonia

Contributor's Comment: In this lung, there is a severe necrotizing bronchiolitis and a fibrinous alveolitis with neutrophils, macrophages and many degenerate inflammatory cells appearing as round cells with pyknotic nuclei. Focal areas of parenchymal necrosis infiltrated by degenerate inflammatory cells are present. These lesions are compatible with those commonly observed in the acute fibrinous pneumonia caused by *H. somnus.* The fibrinous pneumonia caused by *H. somnus* is very similar grossly to that caused by *Mannheimia haemolytica*. Histologically, the bronchiolar necrosis is more extensive and there are no clusters of degenerate inflammatory cells with elongated or streaming nuclei (oat cells) as those seen in pneumonias caused by *M. haemolytica* and its leukotoxin. The round cells with pyknotic nuclei are probably degenerate alveolar macrophages by the effect of *H. somnus* toxins, possibly endotoxins. The most common pneumonic lesion caused by *H. somnus* is an acute to subacute suppurative bronchopneumonia similar grossly and histologically to that caused by *Pasteurella multocida*. *H. somnus* can cause a severe fibrinous pleuritis with or without a fibrinous pneumonia. Infection with bovine respiratory syncytial virus and infectious bovine rhinotracheitis virus have been reported to aggravate lung lesions caused by *H. somnus*. In the upper respiratory tract, *H. somnus* can cause laryngitis and tracheitis.

AFIP Diagnosis: Lung: Bronchopneumonia, fibrinonecrotic, subacute, diffuse, moderate, with interlobular edema and numerous coccobacilli, Holstein, bovine.

Conference Comment: *Haemophilus somnus* is a Gram-negative bacillus and a normal inhabitant and opportunistic pathogen of the bovine nasopharynx and urogenital tract. *H. somnus* is implicated in many bovine septicemic infections, including

thrombotic meningoencephalitis, pneumonia, pleuritis, myocarditis, reproductive failure, and arthritis. The initial lesion is widespread septic vasculitis and vascular necrosis, presumably mediated by the lipopolysaccharide endotoxin of *H. somnus,* leading to neutrophil and macrophage infiltration, initiation of the complement and coagulation cascades, and release of proinflammatory cytokines, including IL-1 and TNF-alpha.

In goats, *Haemophilus agni* causes respiratory and mammary infections, epididymitis, and infrequently septicemic infections. In pigs, *H. parasuis* causes fibrinous polyserositis and polyarthritis (Glasser's disease) and can be a secondary complication of viral bronchopneumonias. In chickens, *H. paragallinarum* causes an acute upper respiratory tract infection (infectious coryza).

Contributor: Department of Pathology and Microbiology, Faculty of Veterinary Medicine, University of Montreal, C.P. 5000, Saint-Hyacinthe, P. Quebec, Canada J2S 7C6

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Kathleen A. Ryan, DVM
Major, Veterinary Corps, U.S. Army
Wednesday Slide Conference Coordinator
Department of Veterinary Pathology
Armed Forces Institute of Pathology
Registry of Veterinary Pathology*

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