Joint Pathology Center
Veterinary Pathology Services

WEDNESDAY SLIDE CONFERENCE 2025-2026

Conference #11 — 12 November 2025

CASE I:

Signalment:
1-year-old, female, Brahma chicken (*Gallus gallus*)

History:
Found dead in the coop after sudden onset of inability to move with eyes closed and purple comb and wattle two days prior.

Gross Pathology:
The hen was covered in innumerable presumed mites. The heart had multifocal to coalescing regions of pallor. The liver had multifocal to coalescing regions of pallor with a focus of yellow, caseous material surrounded by green discoloration on the left lobe. The kidneys bilaterally had multifocal to coalescing regions of pallor.

Laboratory Results:
Aerobic bacterial culture of the liver: *Enterococcus faecalis*

Twort's tissue Gram stain: Cocci were gram-positive.

Microscopic Description:
Liver: Three sections of liver are examined. Within one section, there are multiple and coalescent, irregularly shaped granulomas replacing up to 60% of the tissue, multifocally blending in with the fibrous connective tissue of portal areas. Granulomas center around hypereosinophilic necrotic material mixed with

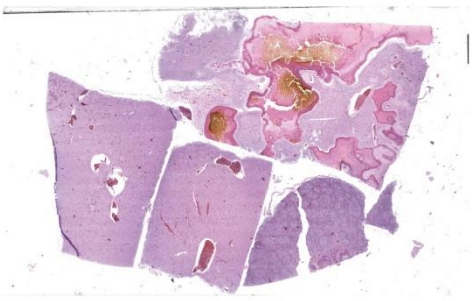

Figure 1-1: Liver and spleen, chicken. Three sections of liver and one section of spleen are submitted for examination. One section of liver demonstrates large geographic areas of necrosis. Similar but much smaller areas of necrosis are present at the bottom edge of the section of spleen. (HE, 10X)

relatively low to medium numbers of degenerate heterophils and cellular debris and multiple clusters of coccoid bacteria. Bordering the necrotic center is a layer of palisading macrophages with abundant eosinophilic and frequently vacuolated cytoplasm (epithelioid macrophages) and occasional multinucleated giant cells, which are further outlined by a robust layer of fibroblasts and collagen. Portal areas are variably expanded by medium to high numbers of lymphocytes, plasma cells, macrophages, including many laden with brown cytoplasmic granules, intermingled with numerous bile ducts (biliary hyperplasia), which extend into the adjacent parenchyma. In some portal areas, there are higher numbers of granulocytes with large, indented, vesiculate nuclei (interpreted as myeloid pre-

cursor cells and extramedullary hematopoiesis). Throughout all three sections of liver are individual necrotic hepatocytes to large regions of coagulative necrosis often centered around centrilobular veins, characterized by hepatocytes with shrunken, angular cell borders, hypereosinophilic cytoplasm and a pyknotic to karyorrhectic nucleus; larger areas of coagulative necrosis are frequently infiltrated by viable and non-viable heterophils. Within areas of necrosis and areas of viable hepatocytes are small clusters of coccoid bacteria within sinusoids.

Spleen: The splenic parenchyma is interrupted by a few, relatively smaller, coalescing granulomas centered around numerous viable and non-viable heterophils, pyknotic nuclei and cellular and karyorrhectic debris, which is separated by a collar of collagen and macrophages with the occasional multinucleated giant cells. Within these regions, there are multifocal cocci bacteria colonies. There are deposits of fibrin and serum protein present throughout the sinuses and around ellipsoids. Within these foci are few reticuloendothelial cells, red cells, low numbers of lymphocytes and macrophages, as well as pyknotic nuclei and karyorrhectic and cellular debris and colonies of coccoid bacteria.

Contributor's Morphologic Diagnoses:
Liver: granulomatous and necrotizing hepatitis, multifocal to coalescing, severe, with intralesional cocci and biliary hyperplasia

Spleen: granulomas, multifocal, marked, with intralesional and embolic cocci

Contributor's Comment:
Enterococci are non-motile, gram-positive, facultative anaerobic cocci bacteria that can appear in short and medium chains.[6] Unlike staphylococci and streptococci, toxins are not produced. Surface components that allow success for *Enterococci* include a polysaccharide capsule, adhesins, pili, and aggregation substance. *Enterococci* are able to produce biofilms, which allows for adherence, especially in nosocomial infections and contributes to antibiotic resistance. Virulence factors include bacteriocins, hemolysins, gelatinases, and serine proteases. Cell injury has been induced via production of toxic oxygen metabolites.[7] Unlike *Streptococcus* sp., these bacteria can tolerate bile salts and grow on MacConkey agar.[9]

Enterococcus sp. are considered normal flora in the gastrointestinal tract of poultry and other bird.[3,5,8] However, certain species that have been isolated in clinical disease include *E. avium, E. cecorum, E. durans, E. faecalis, E. faecium,* and *E. hirae*. Enterococcosis is a bacterial septicemia that has been reported in a variety of avian species. Birds can be afflicted via oral or aerosol routes (bedding, water, hatchery fluff) but can also arise from skin wounds.[5,8] There have been reports of vertical transmission through hens with salpingitis or peritonitis that continue to lay.[5] However, *Enterococcus faecium* has the potential to be a useful probiotic against other detrimental gastrointestinal disease in birds, such as colibacillosis, and improve feed efficiency.[3,10]

Across all ages, *Enterococcus faecalis* affects birds of all ages just as in this hen in this case, followed by *faecium*. Many birds die due to the rapid progression of disease and have vague clinical signs to include depression, lethargy, ruffled feathers, diarrhea, and decrease in egg production. Virulence factors that allow for infection include the collagen-binding protein (ace), aggregation substances

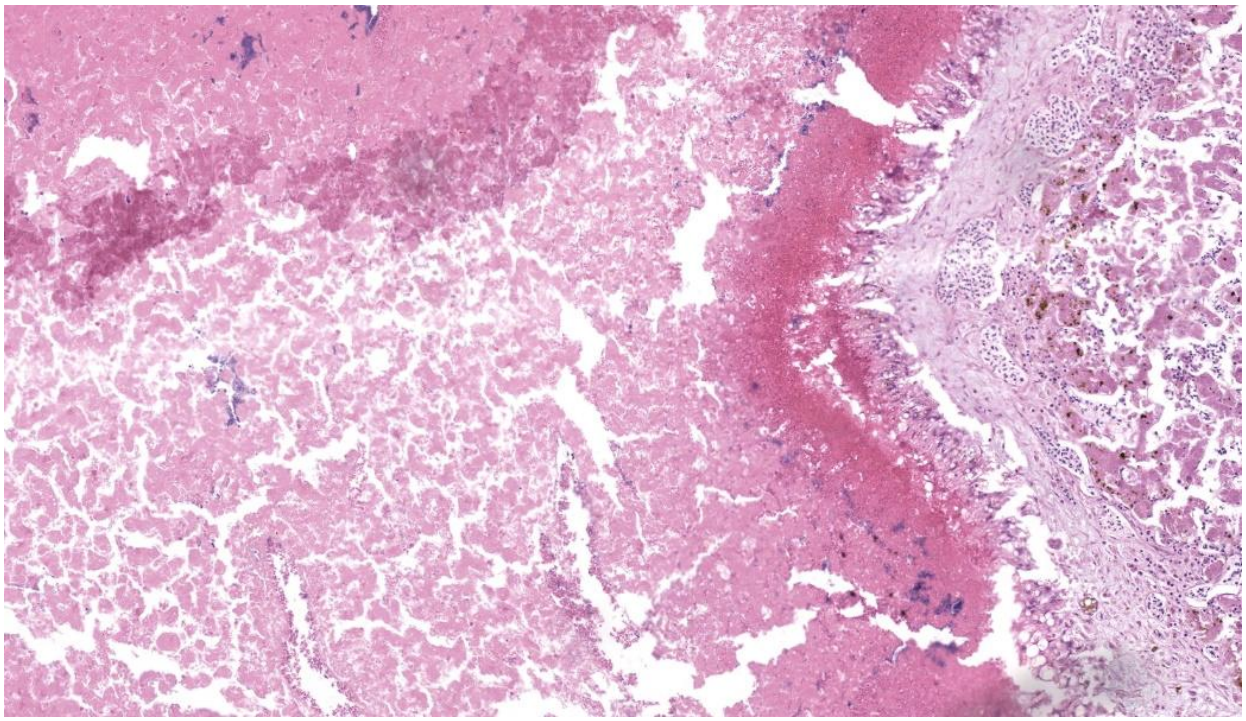

Figure 1-2: Liver, chicken. Areas of hepatocellular infarction contain large colonies of cocci, and are bounded by a thick eosinophilic rim of necrotic heterophils and cellular debris, and in turn by a layer of epithelioid and fewer foreign-body type macrophages and concentric lamellae of fibrous connective tissue. (HE, 125X)

(asa1), hemolysin activator (cylA), endocarditis antigen (efaA), surface protein (esp), gelatinase (gelE, and putative surface antigen EF0591.[5]

Enterococcus cecorum has become a significant disease in adult broiler chickens, causing femoral head necrosis, spondylitis, and arthritis. This disease is colloquially called "kinky back" when vertebral osteoarthritis occurs. The pathogenesis was recently described as requiring intestinal colonization that progressed to bacteriaemia prior to invading the skeletal tissue and demonstrated that intestinal disease itself was not required.[1,2]

In other species, Enterococci cause mastitis, enteritis, respiratory disease, endocarditis, and urinary tract disease as well as septicemia.[9] In humans, Enterococci cause 12% of nosocomial infections with E. faecalis and faecium being the most prevalent of the species.[6] Nosocomial infections frequently occurred through IV catheters, urinary catheters, aortic valve implantation, prosthetic joints, and other surgical sites. Occasionally, neurologic diseases, to include meningitis, do occur.[7]

Contributing Institution:

University of Connecticut Department of Pathobiology and Veterinary Sciences
Connecticut Veterinary Medical Diagnostic Laboratory
https://pathobiology.cahnr.uconn.edu/
https://cvmdl.uconn.edu/

JPC Diagnoses:

1. Liver: Hepatitis, necrotizing, heterophilic and granulomatous, chronic, multifocal to coalescing, severe, with numerous cocci.
2. Spleen: Splenitis, necrotizing, heterophilic and granulomatous, chronic, multifocal, moderate, with numerous cocci.

3. Liver: Extramedullary hematopoiesis, chronic, periportal, moderate.

JPC Comment:
The University of Pennsylvania's Dr. Nathan Helgert moderated this year's 11th conference. This is his first time moderating for the WSC, and participants thoroughly enjoyed his quick wit and engaged teaching style. He chose to focus on poultry and ruminant pathology, which participants are always grateful for. This first case was a classic entity with fantastic histologic lesions that, according to some conference goers, provided the perfect moment to make use of the term "geographic" to describe those dramatic areas of necrosis. They truly resemble some beautiful cartography.

Conference discussion focused on the diagnostic approach to cases like this one where additional diagnostics are required to "suss out" the etiologic agent. Participants were asked to take a figurative step back and develop a list of possible causes of bacterial sepsis in chickens that could lead to hepatic and splenic lesions like these. The list included *E. coli* (colibacillosis), *Salmonella typhimurium, Staphylococcus aureus, Enterococcus spp, Streptococcus spp., Erysipelothrix rhusiopathiae* (although this is more likely in turkeys and pheasants than in chickens), *Mycobacterium spp (*especially *M. avium),* and *Pasteurella multocida*, to name just a few. Some of these look nearly identical to one another both grossly and histologically, while others of these have more distinct features. Either way, culture and special stains will be needed.

As with every case of suspected bacterial infection, a simple Gram stain can provide crucial information. Of these above-mentioned

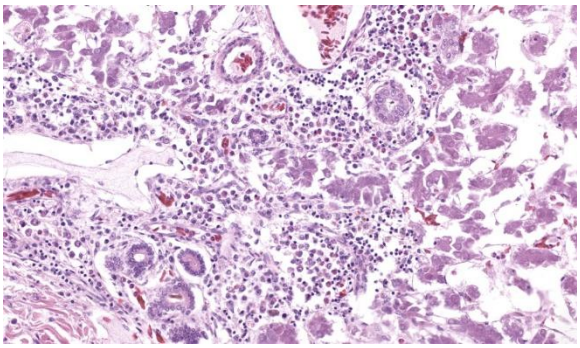

Figure 1-3: Liver, chicken. Portal areas are markedly expanded by extramedullary hematopoiesis. (HE, 406X)

organisms, several of them are gram-negative rods, which would make them less likely with the gram-positive staining seen in this case. *Mycobacterium spp*, which are best revealed with acid-fast stains due to the mycolic acid in their cell wall, were not present in this case. *Erysipelothrix rhusiopathiae* is a gram-positive rod, but the bacteria in this case were clearly cocci. Although it can sometimes be challenging to discern bacterial morphology, participants felt confident in this case calling these cocci both on the H&E and on the gram stain. This narrowed the field substantially to *Streptococcus, Staphylococcus,* or *Enterococcus*. The contributor was able to culture *Enterococcus faecalis* from an aerobic bacterial culture to confirm the identity of the offending organism in this case.

The contributor provides a succinct overview of *Enterococcus spp* in poultry, including the virulence factors that enable their pathogenesis. Infection by *Enterococcus spp* in chickens (and other birds) is considered opportunistic, and affected birds are generally older (>12wks) than those affected by *E.coli*, which typically affects younger birds. *Enterococcus faecalis* is normal flora of the chicken GI tract, whereas *Enterococcus cecorum,* which still requires intestinal colonization to occur prior

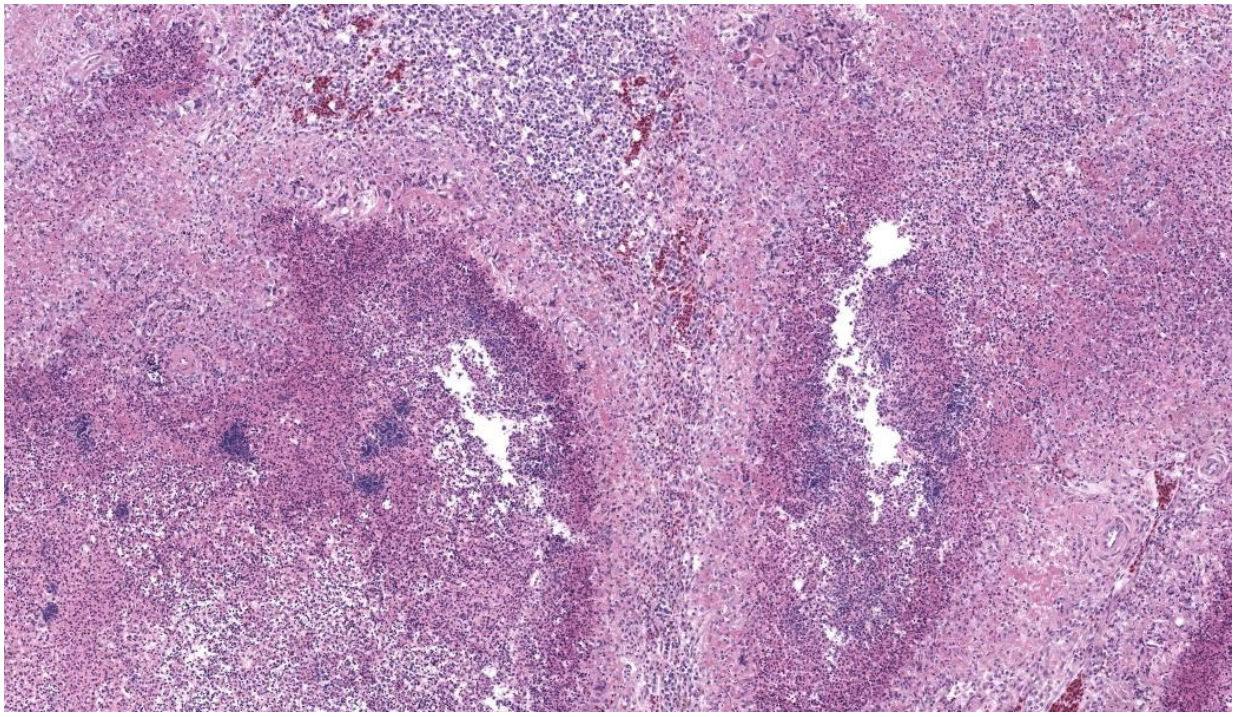

Figure 1-4: Spleen, chicken. Heterophilic granulomas, similar to those seen in the liver, are centered on areas of splenic necrosis with colonies of cocci.. (HE, 165X)

to septicemic spread, is not.[4,5] *E. cecorum* has a known predilection for bone, and primary sites of bone infection include the free thoracic vertebra (the synsacrum), the femoral head, and the hock.[2]

So why the free thoracic vertebrae? Predilection of *E. cecorum* for this site has been linked to osteochondrosis dissecans (OCD) of the free thoracic vertebrae, which is a common background lesion in broiler chickens.[2,4] The current hypothesis is that these OCD lesions result in clefts in the articular cartilage within these vertebrae that facilitate *E. cecorum* colonization and subsequent vertebral osteomyelitis.[2] Bacterial infection of bone results in a marked inflammatory response, coupled with edema and suppuration secondary to the actions of neutrophils and macrophages that are called in by pro-inflammatory cytokines. Additionally, there is subsequent osteoclast activation and bone resorption, which can result in pathologic fracture and collapse of the affected vertebrae.[2] This is one of the most common sequelae of this condition.[2,4] Following fracture, there is dorsal displacement of suppurative material and necrotic bone into the spinal canal, resulting in a sudden onset of ataxia and loss of proprioception to the hind limbs. Affected chickens will have a classic "motorcycle rider" or "hock-sitting" stance due to their inability to use their legs.[1,2.4] These birds will also have dirty wing edges due to "wing-walking" behavior as they attempt to ambulate with the support of their wings.

If you aren't sure what this "motorcycle rider" stance looks like in *Entercoccus*-infected birds, please do not google "motorcycle rider chicken" without the addition of "*Enterococcus*" unless you want to see photoshopped images of chickens riding actual motorcycles, or unless you want to learn all about "chicken

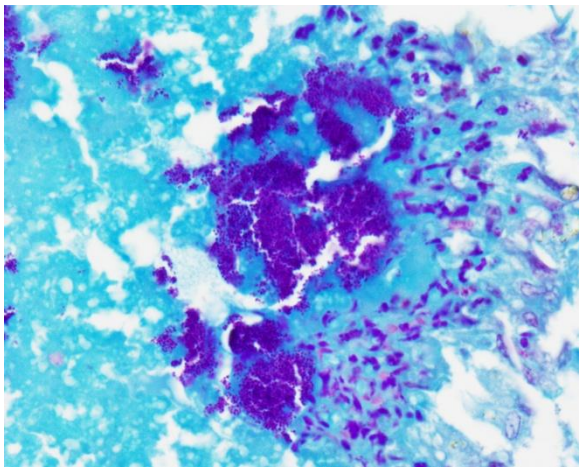

Figure 1-5: Liver, chicken. Colonies of cocci stain gram-positive. (Twort's, 400X) (Photo courtesy of: University of Connecticut Department of Pathobiology and Veterinary Sciences, Connecticut Veterinary Medical Diagnostic Laboratory, https://pathobiology.cahnr.uconn.edu/, https://cvmdl.uconn.edu/)

strips" in the motorcycle community, which refer to the unworn rubber on the outer edges of motorcycle tires. They are called "chicken strips" because they are usually seen on bikes of riders that are considered too nervous, or "chicken", to lean their bike over in sharp turns. Speaking from experience, being able to lean your bike over so far in a turn that you "get your knee down" to the pavement is considered to be an important rite of passage for motorcyclists, but one would have to imagine that chickens do not appreciate this comparison (*MAJ C. Culligan, personal communication*).

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CASE II:

Signalment:
78-day-old Chicken (*Gallus gallus*)

History:
The case is a chicken found dead on a Japanese native breed farm.

Gross Pathology:
The liver was enlarged and diffusely dark red. The spleen was moderately enlarged.

Laboratory Results:
DNA was extracted from the liver homogenate. PCR for detecting avian leukosis virus (ALV) subgroup B and endogenous subgroup E was positive.

Microscopic Description:
Round hematopoietic tumor cells strongly infiltrated the hepatic blood vessels and sinusoids. The hepatic sinusoids were diffusely expanded by tumor cell infiltration, with fewer normal erythrocytes and enlarged Kupffer cells which sometimes contained cellular debris. Most hepatocytes were shrunken. A few granulocytes were also found in the hepatic sinusoid. Small foci of granulocytic cells at different nuclear maturation stages were present around some hepatic triads. Tumor cells appeared round, oval, or polygonal in shape with a distinct cell border, amphophilic cytoplasm, anisocytosis, and anisokaryosis. Some tumor cells contained perinuclear pale areas known as halos. The nucleus was round and hyper

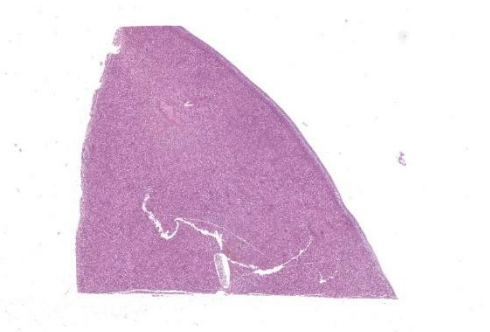

Figure 2-1: Liver, chicken. One section of liver is submitted for examination. (HE, 8X)

chromatic to pale, with one or two large nucleoli and coarsely clumped chromatin. Some binuclear tumor cells were also observed. There was significant mitosis and karyorrhexis of tumor cells. The cytoplasmic eosinophilic granules that are characteristic to myelocytic lineage cells were not present in tumor cells.

Immunohistochemical analysis revealed that tumor cells consistently exhibited cytoplasmic staining of hemoglobin antigen, with variable staining intensity, faint to strong, depending on the tumor cell. Hemoglobin was also detected in normal erythrocytes. Tumor cells were negative for CD3 (T cell marker), BAFF-R (B cell marker), and Iba-1 (macrophage/monocyte marker). Enlarged Kupffer cells were positive for Iba-1.

Tumor cells were observed in other organs, but only in the blood vessels. Some thrombi composed of necrotic tumor cells and fibrin were also observed in the vessels. The bone marrow was not histologically examined.

Contributor's Morphologic Diagnoses:
Avian erythroblastosis

Contributor's Comment:
Avian erythroblastosis (AE), also called erythroid leukosis, is a hematopoietic tumor of

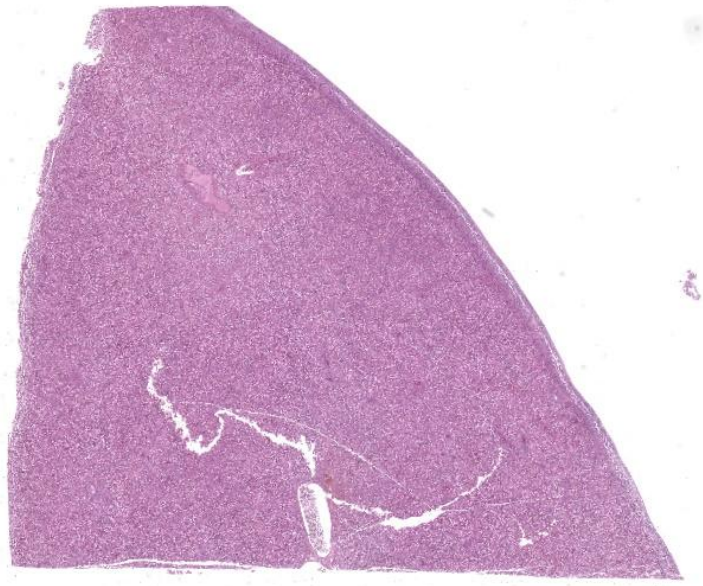

Figure 2-2: Liver, chicken. Hepatic sinusoids are filled with innumerable immature and neoplastic chicken erythrocytes. (HE, 738X). Hepatocytes are diffusely and mildly atrophic. There are numerous rhectic neoplastic cells and Kupffer cells often contain cellular debris.

erythrocytic lineage cells in birds.[2,7,9] Spontaneous occurrence of this tumor is rare in commercial chickens,[2] although there are several experimental reports of AE in chickens inoculated with AE virus (AEV) and some other viral strains in the avian leukosis/sarcoma group.[3,4,10,11,14,16,17] Experimentally, the viruses can induce AE and often other types of tumors, depending on the experimental conditions, such as the strain and dose of virus, inoculation route, and various host factors.[3,4,10,11,14,16,17] Historically, AEV has been used in research on viral oncogene and erythrocytic differentiation.[7,8,9] The relationship between the occurrence of AE and exogenous ALV infection is unclear in this case.

On the basis of the histologic and IHC findings, the hematopoietic tumor was diagnosed as AE. The chicken exhibited findings suggestive of AE, such as an enlarged, cherry red liver, intravascular nature of tumor cells, and round hematopoietic tumor cells with occasional perinuclear halo.[2,14] In addition, IHC detection of hemoglobin antigens in tumor cells was conclusive evidence of AE.

Hemoglobin is one of the markers useful for diagnosing erythrocytic tumors in humans and other mammals.[6,15,18] Past studies have reported that hemoglobin is present in transformed AE cells of chickens inoculated with AEV.[1,5] In past related studies conducting immunofluorescence assays of cultured AE cells transformed by AEV infection, the cells expressed a variety of avian erythrocytic markers, including hemoglobin, histone-5, erythroblast surface antigen, and erythrocyte surface antigen.[3,8] A commercial rabbit monoclonal antibody (clone EPR3608) against the human hemoglobin can cross-react with chicken erythrocytes and erythrocytic precursors in the

bone marrow on paraffin sections without nonspecific reactions.

Histologic differential diagnosis includes myeloid, lymphoid, and histiocytic tumors.[2,13] In addition, a concurrent tumor of mixed AE and myelocytoma components has been described.[2] A myeloid tumor can be differentiated from AE in that myeloid tumor cells replicate in both extra and intravascular space and often contain cytoplasmic granules.[2,14] In our case, small foci consisting of granulocytic cells in the liver were considered by size, distribution, and cellular morphology as foci of extramedullary granulopoiesis, which are often found in avian tissue.[2] Lymphoma was ruled out by negative IHC results by using anti-human CD3 and anti-chicken BAFF-R antibodies, which are the most appropriate commercial antibodies for detecting chicken T and B lymphocytes on FFPE sections.[12] The negative IHC results with this anti-human Iba-1 antibody indicate that tumor cells in our case were not macrophage/monocyte lineage cells.

Contributing Institution:
National Institute of Animal Health, NARO.
https://www.naro.go.jp/english/laboratory/niah/index.html

JPC Diagnoses:
1. Liver: Intravascular round cell neoplasm.
2. Liver: Extramedullary hematopoiesis, chronic, periportal, moderate.

JPC Comment:
This case proved to be challenging for participants given that the condition is relatively obscure and requires IHCs for definitive diagnosis. Leukemia and leukemic lymphoma were the top diagnoses considered by conference participants prior to case discussion. The contributor provides an excellent overview of and

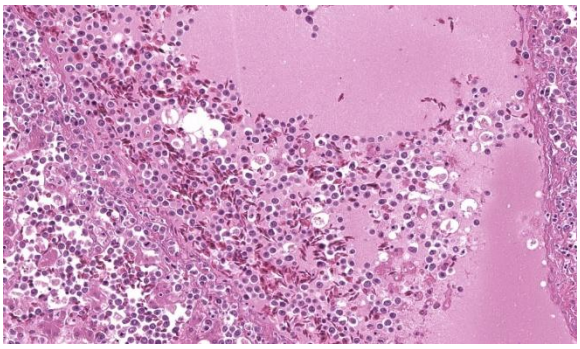

Figure 2-3: Liver, chicken. Neoplastic erythroblasts circulate within hepatic vessels. (HE, 738X).

a convincing diagnostic workup for the diagnosis of avian erythroblastosis in their comment. An in-house hemoglobin IHC at the JPC similarly revealed moderate cytoplasmic immunoreactivity for hemoglobin within the neoplastic cell population and no immunoreactivity of neoplastic cells for lymphocyte markers (CD3, CD20, PAX5, CD34). This entity, and its accompanying histologic findings, provided great discussion of oncogenic viruses and intravascular round cell neoplasms of avian species. “Intravascular round cell neoplasm” was ultimately the morphologic diagnosis that was favored by the JPC due to the inability to reach the diagnosis of erythroblastosis on the H&E slide alone (the JPC morphologic diagnosis is always based on the HE section, which is the only section provided in advance of the conference.)

Conference discussion focused largely on avian leukosis virus and its subtypes. Avian leukosis viruses (ALV) are alpharetroviruses that are usually slowly oncogenic. Subtype A is the most common, and subtypes A through E, as well as J, are known to infect chickens. Other subtypes affect numerous other species of birds. These viruses cause a variety of neoplasms by inserting themselves as promoters

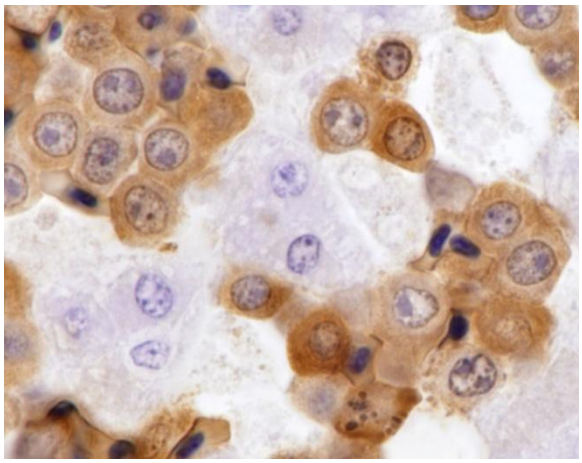

Figure 2-4: Liver, chicken. Neoplastic cells stain strongly positive for hemoglobin. (anti-HB, 1000X). (Photo courtesy of: Japanese National Institute of Animal Health, NARO, https://www.naro.go.jp/english/laboratory/niah/index.html)

into the affected chicken's genome near a cellular proto-oncogene, such as c-erbB, causing overexpression of the proto-oncogene. This overexpression leads to downstream dysregulation of cellular division and promotion of uncontrolled cell growth. *Et voila*, a neoplasm is produced! Such neoplasms include erythroblastosis, lymphomas (usually B-cell with IgM production), myelocytomatosis (subtype J), and various sarcomas.

Certain subtypes of ALV, such as subtype E, are endogenous to the DNA of chickens, where they live quietly and can be genetically inherited. These endogenous viral subtypes are considered to be non-oncogenic but can confound PCR results by producing false positives. As such, PCR for avian leukosis viruses is problematic and not generally reliable.

The subtypes of ALV that produce erythroblastosis, colloquially known as "avian erythroblastosis virus" (AEV), are unique among ALVs in that they stimulates rapid oncogenesis due to their genome containing its own potent oncogene (v-erbB).[11,13] This oncogene is a mutated and shortened version of the c-erbB proto-oncogene within chicken DNA that is associated with other ALVs.[13] The v-erbB oncogene results in the production of a mutated form of epidermal growth factor receptor (EGFR) protein, which is a type of tyrosine kinase receptor. This family of receptors is directly involved in cell signaling for growth and division. This receptor mutation results in loss of the ligand binding domain found in normal EGFR, as well as structural changes in its cytoplasmic regulatory regions. This enables the mutated EGFR to experience ligand-independent constitutive signaling activity and stimulate constant, transformative, cellular growth.[13] As such, this virus is able to directly cause erythroblastosis and fibrosarcomas, which have a much more rapid onset of disease, whereas most ALVs cause slow-growing neoplasms via an indirect route.[13] Chickens affected with avian erythroblastosis have a characteristically "cherry red" liver on gross examination.

Wrapping up the discussion of this fascinating and rare case was a quick review of other major oncogenic viruses in chickens, which included gallid herpesvirus-2 (causative agent of Marek's disease, which usually affects young birds and results in a classical T-cell lymphoma) and avian gammaretrovirus (causative agent of avian reticuloendotheliosis).

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CASE III:

Signalment:
4.5-year-old, female, Holstein-cow, *Bos taurus*

History:
The animal was slaughtered. The owner observed swellings of the limbs (not further specified) for one year prior to slaughter. At the slaughterhouse, the referring veterinarian submitted pieces of kidney, heart, muscles of the brisket and flank region to the Institute of Veterinary Pathology for further investigations.

Gross Pathology:
In all submitted tissues, multifocal to coalescing, miliary to nodular, whitish, coarsely textured foci were noted on the cut surface.

Laboratory Results: N/A

Figure 3-1: Heart, ox. Cut section of the heart muscle (left ventricular wall) with miliary white foci bulging from the cut surface. (Photo courtesy of: Institut für Veterinärpathologie, Vetsuisse-Fakultät, Universität Zürich, https://www.vetpathology.uzh.ch)

Microscopic Description:

Myocardium (left ventricular wall) and striated muscle (brisket): Affecting approximately 10-20% of the myocardial and skeletal muscle tissue, there is a marked intraluminal, haphazardly arranged, often glomeruloid, highly cellular proliferation of plump spindeloid cells within medium to large-size arterioles with partial to complete occlusion of the vascular lumina accompanied by a pronounced thickening of the corresponding tunica media (medial hypertrophy). These spindeloid cells have abundant, slightly granular, eosinophilic, occasionally vacuolized cytoplasm with indistinct cell borders containing oval to cigar-like shaped nuclei with inconspicuous nucleoli and coarsely stippled chromatin. There is moderate anisokaryosis and anisocytosis with infrequent multinucleated cells being present. Mitotic figures are rare or absent (<1/HPF).

There are frequent perivascular accumulations of variable numbers of hemosiderinloaden macrophages intermingled with a low number of inflammatory cell infiltrates consisting of lymphocytes and plasma cells as well as fewer neutrophils with rare small aggregates of extravasated erythrocytes. Few affected arterioles are infiltrated by a small to moderate number of eosinophils (not present on all slides). These inflammatory infiltrates also extend occasionally into the adjacent myocardial interstitium. The glomeruloid proliferations in the heart are surrounded by a moderate to marked deposition of collagen fibers (fibrosis) along with edema. Occasionally and affecting less than 5% of cardiomyocytes, there are intrasarcoplasmic protozoal cysts of approximately 100-200 µm in diameter containing numerous crescent-shaped bradyzoites. Perilesional myocytes of the brisket often display

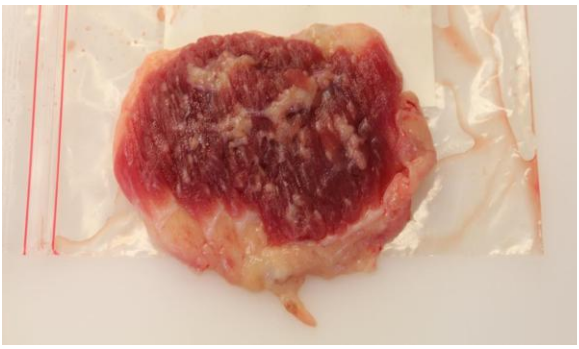

Figure 3-2: Skeletal muscle, ox. Similar gross changes are seen on a cut section of the brisket muscle. (Photo courtesy of: Institut für Veterinärpathologie, Vetsuisse-Fakultät, Universität Zürich, https://www.vetpathology.uzh.ch)

sarcoplasmic hypereosinophilia, swelling, loss of cross-striation and occasional fragmentation (hyaline degeneration and necrosis). Immunohistochemical labelling shows frequent cytoplasmic reactivity of the intralesional spindeloid cells for factor VIII/von Willebrand factor (vWF) and smooth muscle actin (SMA).

Contributor's Morphologic Diagnoses:
Myocardium of the left ventricular wall and striated muscle (brisket): Severe multifocal arteriolar intraluminal endothelial and pericyte proliferation with intraand perilesional hemosiderosis as well as hemorrhages accompanied by diffuse media hypertrophy (consistent with reactive angioendotheliomatosis) and mild eosinophilic arteriolitis Heart (myocardium): Moderate to marked, multifocal to coalescing interstitial lymphoplasmacytic myocarditis and myocardial fibrosis with occasional intrasarcoplasmic protozoal cysts (most likely *Sarcocystis sp*.) Striated muscle (brisket): Mild multifocal degeneration and necrosis of myocytes

Contributor's Comment:
In human medicine, the term angioendotheliomatosis includes either a malignant or a benign variant. The latter, also termed as reactive angioendotheliomatosis (RAE), is characterized by intravascular endothelial as well as pericyte proliferation and is mainly restricted to the skin.[9,16] Associations between this condition and type 2, 3, or 4 hypersensitivity diseases were hypothesized, including autoimmune diseases, such as thrombotic thrombocytopenic purpura (TTP), underlying subacute systemic infections, or organ transplantation.[8,11,14,16] The malignant angioendotheliomatosis (MAE) commonly refers to a rare type of angiotropic large cell lymphoma but may also apply to intravascular disseminated angiosarcoma.[9,16]

In veterinary medicine, cases of MAE in the form of intravascular angiotropic lymphoma have been documented in dogs and to a lesser extent in cats.[7,10] All previously published cases had concurrent involvement of the central nervous system and, to a lesser extent,

other organs of the digestive, endocrine, respiratory, and urogenital systems of which the liver, lung, small intestine, and kidney are frequently represented. The veterinary cases mostly resembled human reports except for humans mainly being affected by a B-cell lineage neoplasm.[10]

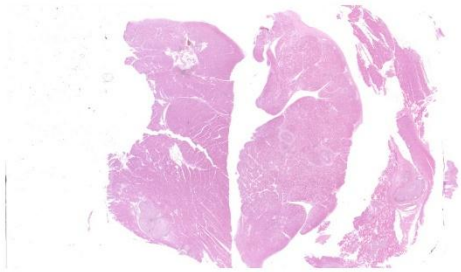

Figure 3-3: Heart, ox. Sections from various areas of the heart are submitted for examination and all are similar. Within each section, arteriolar walls are profoundly thickened. (HE, 10X)

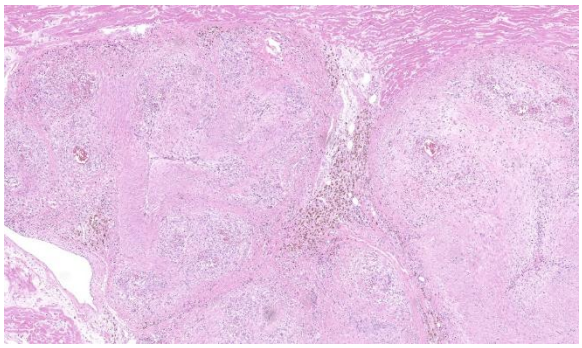

Figure 3-4: Heart, ox. Within the ventricular wall, arterioles are markedly tortuous with numerous small branches. Each arteriole has a markedly thickened wall which often compromises the lumen, and spindle cells profoundly expand the arteriolar wall. There is fibroplasia surrounding these arterioles which extends into the adjacent myocardium. At the periphery of some of the affected arterioles, there are numerous hemosiderin laden macrophages, indicating previous hemorrhages. (HE, 92X)

Contrary to humans in which RAE is mainly benign, the feline counterpart feline systemic reactive angioendotheliomatosis (FSRA) is a rare fatal multisystemic disease of unclear origin with few documented cases.[3,12,13,16] Affected animals often present with cardiorespiratory symptoms due to the heart being the main affected organ. Other organs in which lesions were frequently observed include the kidney, spleen, intestine, and lymph nodes, followed by others, but to a lower degree.[3,11] In most of these cases, the cause remained unidentified. One cat was diagnosed with TTP, to which the lesions were presumably attributed.[2]

Previously, there has been one report in which such proliferative lesions were observed in a 2-year-old Corriente steer. The lesions resembled FRSA and were termed systemic reactive angioendotheliomatosis-like syndrome.[2] The authors believed that the animal was persistently infected with the bovine viral diarrhea virus (BVDV) since they detected corresponding intralesional antigen by immunohistochemistry. The authors hypothesized that a TTP-like condition due to a BVDV infection was present.[2] Formalin-fixed paraffin-embedded tissues (FFPE) of this animal plus other species suffering from vascular proliferative disorders, including cats with FSRA, were subjected to molecular analysis yielding the isolation of *Bartonella sp*.-DNA in all specimens. In addition, the authors demonstrated in vitro evidence for *Bartonella vinsonii sp. berkhoffi* being capable of inducing the transcription factor hypoxia-induced factor-1 (HIL-1) with subsequent production of the endothelial mitogen vascular endothelial growth factor (VEGF) in human cells (HeLa 229).[1] The results led to the conclusion that there might be an association between *Bartonella sp*.-infections and the vascular proliferative disorders. However, these results need to be interpreted with caution as there is a likelihood of false-positive PCR results for *Bartonella spp*. in FFPE-specimens due to cross-contamination during necropsy or histology processing.[15]

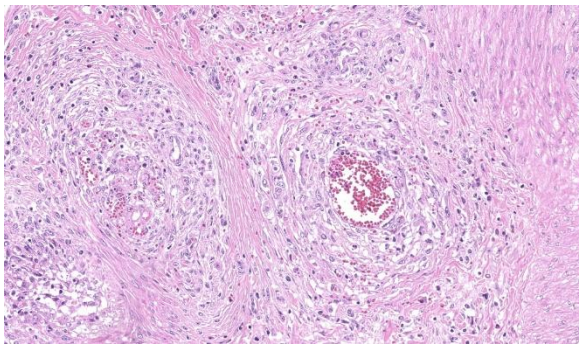

Figure 3-5: Heart, ox: High magnification of several affected arterioles demonstrating their tortuosity, proliferation of a variety of spindle cells (endothelium, smooth muscle and fibroblasts, luminal compromise, formation of numerous smaller arteriolar branches, wand in some areas, endothelial loss hemorrhage , and extrusion of plasma proteins into the wall. (HE 468X)

The findings of the present case are consistent with the case report of Breshears et al., and the diagnosis of a systemic reactive angioendotheliomatosis-like syndrome was made. The glomeruloid proliferation of endothelial cells and pericytes staining positive for factor VIII/von Willebrand factor (vWF) and smooth muscle actin (SMA), respectively, is in concordance with the previous literature on RAE and FSRA.[2,3,10,16,17] Without exception, these lesions were present in all submitted tissue samples including the kidney and flank muscle (not shown). No evidence for the presence of BVDV antigen was detected by immunohistochemical labeling using the C42 and 15C5 monoclonal antibodies against the viral protein Erns (envelope protein, RNase, secreted) of which one is specifically directed against BVDV while the other is detecting pestiviruses, respectively.[4] Furthermore, no intralesional argyrophilic microbial structures could be found.

The occasionally seen intra-sarcoplasmic protozoal cysts are most likely bradyzoites of a Sarcocystis sp. In brief, this is a highly prevalent heteroxenous coccidian parasite, including around 90 species, which can infect a wide range of species, including humans. Its lifecycle consists of gametogeny (sexual stages) in the definitive host and schizogony (asexual stages) in the intermediate host. Coincidentally, the schizogony partially takes place within endothelial cells of arterioles and capillaries before its final stage in the musculature.[6] On some slides, we noticed a mild eosinophilic intralesional inflammatory component which are most likely due to the protozoal infection. However, no additional investigation has been attempted in this case, as the significance of this infection is mostly clinically irrelevant.

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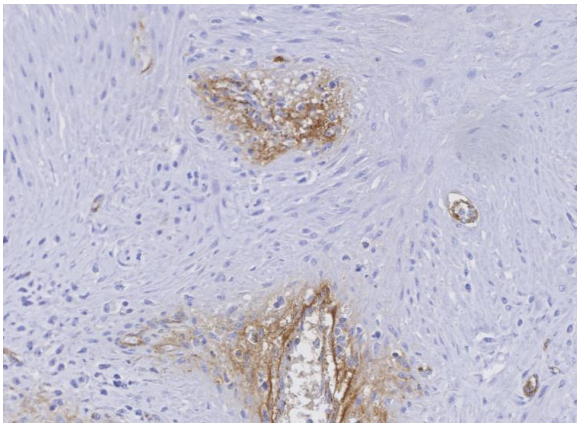

Figure 3-6: Heart, ox:. Proliferating cells within the walls of affected arterioles demonstrate moderate cytoplasmic immunoreactivity for von-Willebrand's factor. (anti-VWF, 400X). (Photo courtesy of: Institut für Veterinärpathologie, Vetsuisse-Fakultät, Universität Zürich, https://www.vetpathology.uzh.ch)

JPC Diagnoses:

1. Heart and skeletal muscle, arterioles: Atypical endothelial and pericyte proliferation (angioendotheliomatosis), chronic, diffuse, severe, with medial hypertrophy and mural and adventitial fibrosis.
2. Heart, myocytes: Sarcocysts, multiple. Another unique condition in its first WSC iteration in this species, this case also proved to be diagnostically challenging for participants. The contributor provided an excellent write-up summarizing the current literature on this condition across species. Similar cases of systemic reactive angioendotheliomatosis and SRE-like syndrome have been seen before in the WSC (Conference 21, Case 3, 2014, Conference 13, Case 4, 2019, and Conference 9, Case 1, 2020), all of which have had great write-ups and similar immunohistochemical staining patterns with vWF and smooth muscle actin (SMA) to those that were performed in this case, but were all in cats.
3. The contributor's comment covered all pertinent aspects of conference discussion, from the comparison between human and veterinary forms of this condition, to the current hypotheses on this syndrome's pathogenesis, to the possible associations of this condition with TTP and certain systemic infections (i.e. *Bartonella spp.* in cats and bovine pestivirus in cattle). Although this condition is rare, a recent 2024 paper found that systemic reactive angioendotheliomatosis in cats can mimic hypertrophic cardiomyopathy both clinically and on echocardiogram and should be considered as a differential for cats that have symmetrical left ventricular wall thickening.[5]

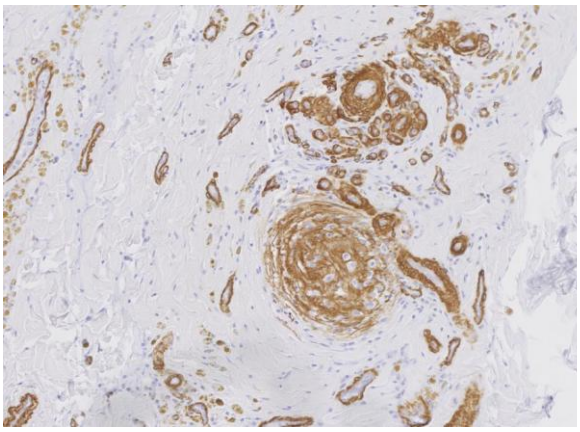

Figure 3-7: Heart, ox. Proliferating cells within the walls of affected arterioles demonstrate moderate cytoplasmic immunoreactivity for smooth muscle actin. (anti-SMA, 400X). (*Photo courtesy of:* Institut für Veterinärpathologie, Vetsuisse-Fakultät, Universität Zürich, https://www.vetpathology.uzh.ch)

JPC Comment:

Another unique condition in its first WSC iteration in this species, this case also proved to be diagnostically challenging for participants. The contributor provided an excellent write-up summarizing the current literature on this condition across species. Similar cases of systemic reactive angioendotheliomatosis and SRE-like syndrome have been seen before in the WSC (Conference 21, Case 3, 2014, Conference 13, Case 4, 2019, and Conference 9, Case 1, 2020), all of which have had great write-ups and similar immunohistochemical staining patterns with vWF and smooth muscle actin (SMA) to those that were performed in this case, but were all in cats.

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cattle). Although this condition is rare, a recent 2024 paper found that systemic reactive angioendotheliomatosis in cats can mimic hypertrophic cardiomyopathy both clinically and on echocardiogram and should be considered as a differential for cats that have symmetrical left ventricular wall thickening.[5]

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CASE IV:

Signalment:
Five-month old, male, Japanese black, bovine (*Bos taurus*)

History:
The present calf was transferred to a farm for fattening at the age of 4-month old and vaccinated with the mixed live vaccines, including bovine infectious rhinotracheitis virus, bovine viral diarrhea virus (BVDV) type 1, bovine parainfluenza virus type 3, bovine respiratory syncytial virus, and bovine adenovirus (BAV) type 7. The calf developed respiratory signs such as coughing and was administered with florfenicol, cefazolin and dexamethasone. The calf died at the age of 5-month-old. The other calves in the farm did not show any apparent clinical signs.

Gross Pathology:
At necropsy, a small amount of bloody feces was attached to the anal area. The lung showed multiple consolidation with caseonecrotic foci. The abomasum had multiple erosions and ulcers in the pyloric part of mucosa. From the duodenum to rectum, the mucosa was dark red and covered with dark red, watery or fibrinous contents. The thymus, both the cervical and thoracic parts, was membranous, showing to be atrophic. The gallbladder was almost empty of bile and had streaks of dark red mucosa.

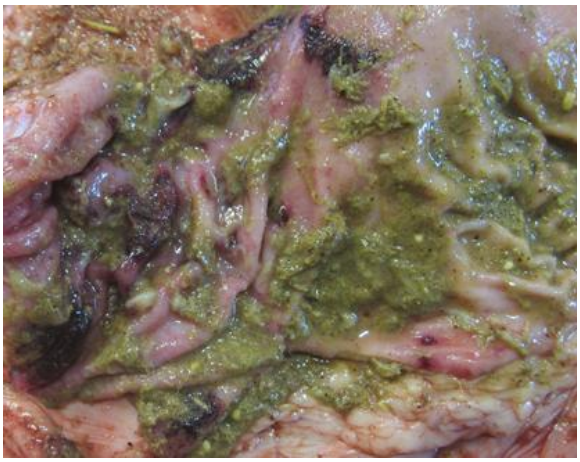

Figure 4-1: Abomasum, Japanese black calf. The abomasum has multiple erosions and ulcers in the pyloric part of mucosa. (Photo courtesy of: National Institute of Animal Health, http://www.naro.affrc.go.jp/english/niah/index.html)

Laboratory Results:
No bacteria were isolated from liver, spleen, kidney, heart, lung, or brain. Neither *Salmonella* nor *Clostridium perfringens* were isolated from cecal and jejunal contents, respectively. PCR tested positive for *Mycoplasma bovis* from the lung, negative for BVDV from the kidney, and positive for BAV from the liver, kidney, heart, lung, and cecal content. BAV was isolated from the liver, kidney, heart, lung, and cecal content. The isolate was identified to be BAV type 5 by sequencing the hexon gene.

Microscopic Description:
In the abomasum, focally extensive hemorrhage and edematous swelling were present in the lamina propria mucosa and in the submucosa, respectively. In the lamina propria mucosa, the capillary blood vessels and small veins showed severe congestion and hemorrhage. The endothelial cells of these vessels and arterioles had basophilic to amphophilic

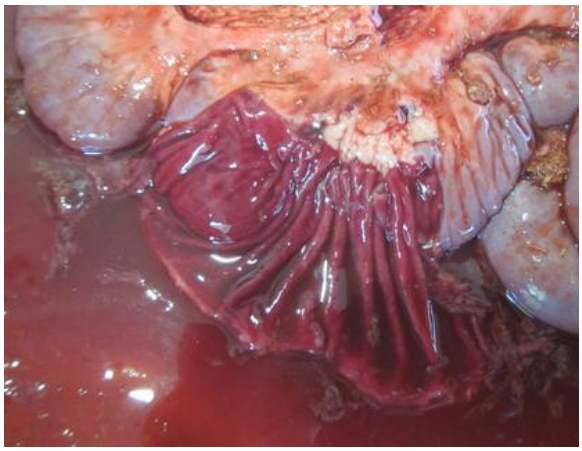

Figure 4-2: Abomasum, Japanese black calf. From the duodenum to rectum, the mucosa was dark red and covered with dark red, watery or fibrinous contents (Photo courtesy of: National Institute of Animal Health, http://www.naro.affrc.go.jp/english/niah/index.htm)

intranuclear inclusion bodies, of either full type or Cowdry type A. Occasionally, focal areas of necrotic mucosal epithelium were accompanied by neutrophil infiltration. In the submucosa, the endothelial cells of blood vessels had the same intranuclear inclusion bodies. Fibrinous and proteinous or serous materials were accumulated in some parts of the submucosal tissue. Neither bacteria nor fungi were detected by Gram and Giemsa stain, and by periodic acid-Schiff and Grocott methods, respectively.

Contributor's Morphologic Diagnoses:
Abomasum: abomasitis, hemorrhagic, focally extensive, with endothelial intranuclear inclusion bodies.

Contributor's Comment:
The present case was characterized pathologically by adenoviral hemorrhagic gastroenteritis and mycoplasmal caseonecrotic bronchopneumonia. The endothelial intranuclear inclusion bodies were detected histologically in the gastrointestinal tract (abomasum, duodenum, jejunum, ileum, cecum, colon, and rectum), liver, gallbladder, spleen, kidney and lung. The forestomach and brain contained no endothelial intranuclear inclusion bodies. In the abomasum, focal ulceration was associated with hemorrhagic abomasitis (No ulceration in the submitted sections). In the ileal Peyer's patch, lymphocytes were severely depleted. Epitheliotropic BAV inclusion bodies were not observed in any organs. By immunohistochemistry, the endothelial intranuclear inclusion bodies showed positive cross-reaction to anti-BAV type 7, weak cross-reaction to anti-BAV type 1, but negative for anti-BAV type 3 antisera. By transmission electron microscopy, the endothelial cells of hepatic sinusoids had paracrystalline arrays of adenovirus-like particles, 60-80 nm in diameter, in their nuclei.

BAV belong to the family *Adenoviridae*, genera *Mastadenovirus*, and *Atadenovirus*.[8] The serotypes of BAV-1, -2, -3, -9 and -10 belong to the genus *Mastadenovirus*, and the serotypes of BAV-4, -5, -6, -7, and -8 belong to the genus *Atadenovirus*.[1,2,3,4,5,6,7,10] Serotypes 3, 4, 7, 10 have been associated with enteric disease.[4,7,8] BAV, including serotypes 3, 7 and 10 has also been associated with respiratory disease.[2,4,5,6] BAV-5 was isolated from a calf

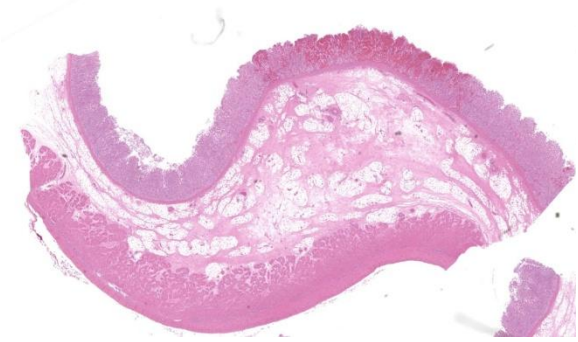

Figure 4-3: Abomasum, Japanese black calf. A section of abomasum with a focally extensive area of mucosal necrosis and hemorrhage is submitted for examination. There is marked edema and thickening of the submucosa. (HE, 12X).

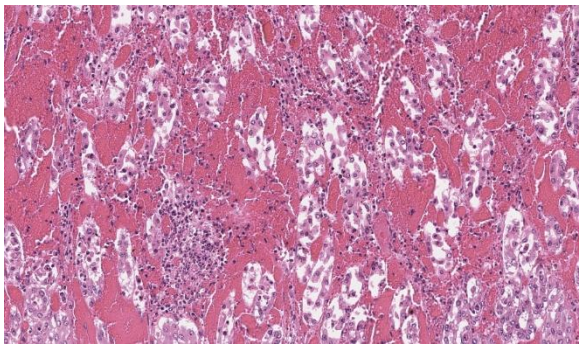

Figure 4-4: Abomasum, Japanese black calf. Higher magnification of the acute hemorrhage, glandular necrosis and aggregates of neutrophils within the mucosa. (HE, 381X).

with weak calf syndrome, but not have been fully associated with severe gastroenteric disease.[1]

Adenovirus infections in animals appear, in general, to be subclinical, and disease seems to occur more commonly in immunologically compromised individuals.[8] In the present calf, the stress and debilitation caused by transportation and by mycoplasmal pneumonia might have caused immunosuppression, followed by systemic BAV-5 infection and gastroenteritis.

The pathogenesis of adenoviral gastroenteritis in calves is not fully clarified. It appears that after an initial viremic stage, the virus localizes in the endothelial cells of vessels in a variety of organs, resulting in thrombosis with subsequent focal areas of ischemic necrosis.[8] Especially, in the bovine gastrointestinal tract, it appears that the endothelial cells of capillary and small veins are highly susceptible to cytopathic effect of the BAV-5 strain. Severely swollen and necrotic endothelial cells may impede the blood circulation through the lamina propria, leading to severe congestion, followed by hemorrhage per diapedesis and per rhexis.

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JPC Diagnoses:
Abomasum: Abomasitis, necrohemorrhagic, acute, focally extensive, severe, with submucosal edema and endothelial intranuclear viral inclusions.

JPC Comment:
This was a beautiful example of a classic entity that served as a nice little dessert to wrap the conference up. The endothelial intranuclear viral inclusions (and their ubiquitous distribution) in this case are textbook-worthy (have you ever considered how many histologic images in veterinary pathology texts come from the WSC?)

As some participants struggled minimally with tissue identification in this case, a quick review of abomasal microanatomy is in order, as not all regions of the abomasum are identical. Chief and pyloric cells are only found in

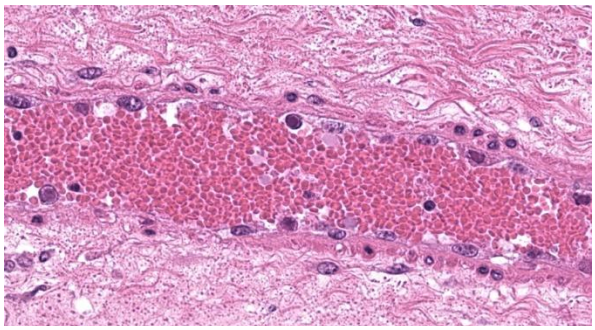

Figure 4-5: Abomasum, Japanese black calf. Endothelial cells lining a submucosal vein contain intranuclear adenocarcinoma inclusions. (HE,1181X).

the fundic portion of the abomasum, whereas the pylorus and cardia lack these. Additionally, there are no goblet cells. The lack of goblet cells in this section immediately rules out large intestine, Other helpful hints include the tortuosity of gastric pits, whereas intestinal crypts are straight. Adipose tissue is not found in the intestinal submucosa but can be seen in the submucosa of the ruminant abomasum and in the equine cecum. Lastly, the degree of autolysis can also be used as a clue. The intestines tend to have a high degree of autolysis due to the milieu of bacterial flora that reside within. The stomach, on the other hand, is a borderline sterile environment that very few bacteria can tolerate due to the level of acidity (unless you are *Helicobacter* spp…), so there is generally little autolysis.

The contributor's write-up of bovine adenoviruses covered much of what was discussed in conference about this ubiquitous and relevant viral family. While the pathogenesis is not well-understood, the abomasum in this case had a significant, wedge-shaped hemorrhagic infarct on the H&E slide that tied in well to the current hypothesis on the pathogenesis of this virus. It is thought that viral targeting of endothelial cells and subsequent endothelial viral inclusions may disrupt blood flow to some degree, leading to turbulence and increased incidence of thrombosis of smaller vessels that can lead to ischemic infarcts.[9] There was conversation on whether this should be morphed as an abomasitis or a vasculitis due to the endothelial targeting. It was ultimately the opinion of participants that this would not classify as true vasculitis due to the lack of inflammation in vessel walls.

Conference concluded with a quick review of the viruses that form paracrystalline arrays on

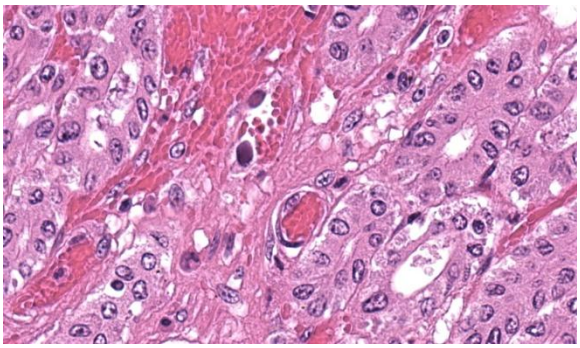

Figure 4-6: Abomasum, Japanese black calf. Adenoviral inclusions also are present within capillary endothelium within the hemorrhagic mucosa (HE, 1205X).

electron microscopy, which include adenovirus, polyomavirus, papillomavirus, picornavirus, circovirus, iridovirus, birnavirus, and flavivirus and a brief overview of a few pertinent adenoviruses in other species that would likely qualify as important boards-fodder. The main one on that list was canine adenovirus-1, which causes infectious canine hepatitis usually in puppies less than 10 days old and can also cause "blue eye" secondary to the corneal edema sometimes seen with this virus. The other notable mentions were avian adenovirus serovars 4 and 8, which cause inclusion body hepatitis and hydropericardium syndrome in poultry, and type II avian adenovirus, which causes hemorrhagic enteritis and marble spleen disease in turkeys.

References:

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