Joint Pathology Center
Veterinary Pathology Services

WEDNESDAY SLIDE CONFERENCE 2026-2027

Conference #9 — 21 October 2026

CASE I:

Signalment:
3-year-old, intact female, Boer goat (Capra hircus)

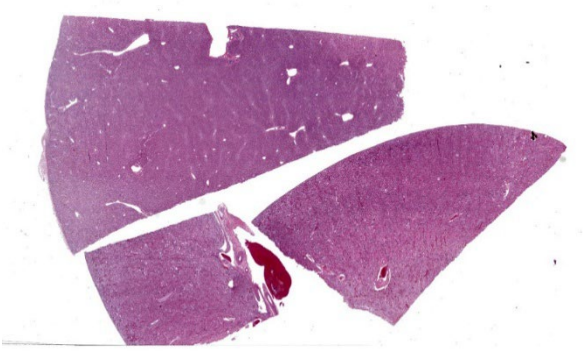
History:
Animal initially presented to the teaching hospital for weight loss, intermittent diarrhea, and dull hair coat. Physical exam showed dull flaky coat with no ectoparasites, pink mucous membranes with a slightly increased FAMACHA score of 2/5 and a BCS 1.5/5. She was being fed high-quality alfalfa and timothy hay and pellets. Bloodwork at this time showed a moderately high eosinophilia, moderate hypoalbuminemia, and mild hyperglobulinemia. A thoracic and abdominal ultrasound were performed and considered within normal limits. Fecal flotation showed no evidence of parasites. Dewormed with moxidectin and Albon despite negative fecal results, and recommended mineral block. Test for valley fever and Johne's disease was sent out. The goat seemed to slightly improve over 2 weeks. Valley fever titer came back positive and Johne's testing was negative. Bloodwork now showed marked hypoalbuminemia, mild thrombocytosis, moderate eosinophilia, and a mild neutrophilia. Goat was offered starter feed, started on Prednisolone, and recommended starting a



1-1. Liver, goat: The liver is light to medium pink to orange-red and friable. (*Photo courtesy of:* Midwestern University College of Veterinary Medicine Diagnostic Pathology Laboratory, https://www.mwuanimalhealth.com/diagnostic-pathology-center)



1-2. Liver, goat: The kidneys are dark brown-red, symmetrical, and grossly unremarkable. (*Photo courtesy of:* Midwestern University College of Veterinary Medicine Diagnostic Pathology Laboratory, https://www.mwuanimalhealth.com/diagnostic-pathology-center)



1-3. Liver, goat: Three sections of liver are submitted for examination. (HE, 7X)

multivitamin. Owners saw over the course of a month weight gain on prednisolone but lost weight again when weaned off. Bloodwork now showed a marked eosinophilia, mild hypoalbuminemia, and moderate to marked increase in liver enzyme values. The goat passed away before further diagnostics or treatment could be performed.

Gross Pathology:
The goat was submitted for necropsy and had a poor body condition, extremely thin with marked muscle wasting and easily palpable bony prominences.

There is mild serosanguinous pleural effusion. The liver is light to medium pink to orange-red and friable. The kidneys are dark brown-red, symmetrical, and grossly unremarkable. The urinary bladder is contracted and empty.

Laboratory Results:
The liver was stained with rhodanine, in which approximately 10% of the hepatocytes contained red-brown cytoplasmic (copper) granules, which is also within the cytoplasm of most Kupffer cells (Figures 3 & 4).

Trace mineral panel was submitted on formalin fixed kidney and liver samples.

Test: Trace Mineral Panel (ICP/MS)

Specimen: Renal Cortex: Fixed

Cobalt (ICP/MS) (1015) Dry Wt Basis No Reference Range 0.24 ug/g

Copper (ICP/MS) (1016) Dry Wt Basis Toxic 2614.62 ug/g

Iron - Feed or Tissue (ICP/MS) (1041) Dry Wt Basis No Reference Range 1626.24 ug/g

Manganese (ICP/MS) (1045) Dry Wt Basis No Reference Range 7.33 ug/g

Molybdenum (ICP/MS) (1048) Dry Wt Basis No Reference Range 0.73 ug/g

Selenium (ICP/MS) (1058) Dry Wt Basis No Reference Range 7.64 ug/g

Zinc (ICP/MS) (1074) Dry Wt Basis No Reference Range 169.55 ug/g

Test: Trace Mineral Panel (ICP/MS) **Specimen:** Liver :: Fixed

Cobalt (ICP/MS) (1015) Dry Wt Basis None Detected, < 0.11 ug/g

Copper (ICP/MS) (1016) Dry Wt Basis Toxic 3502.46 ug/g

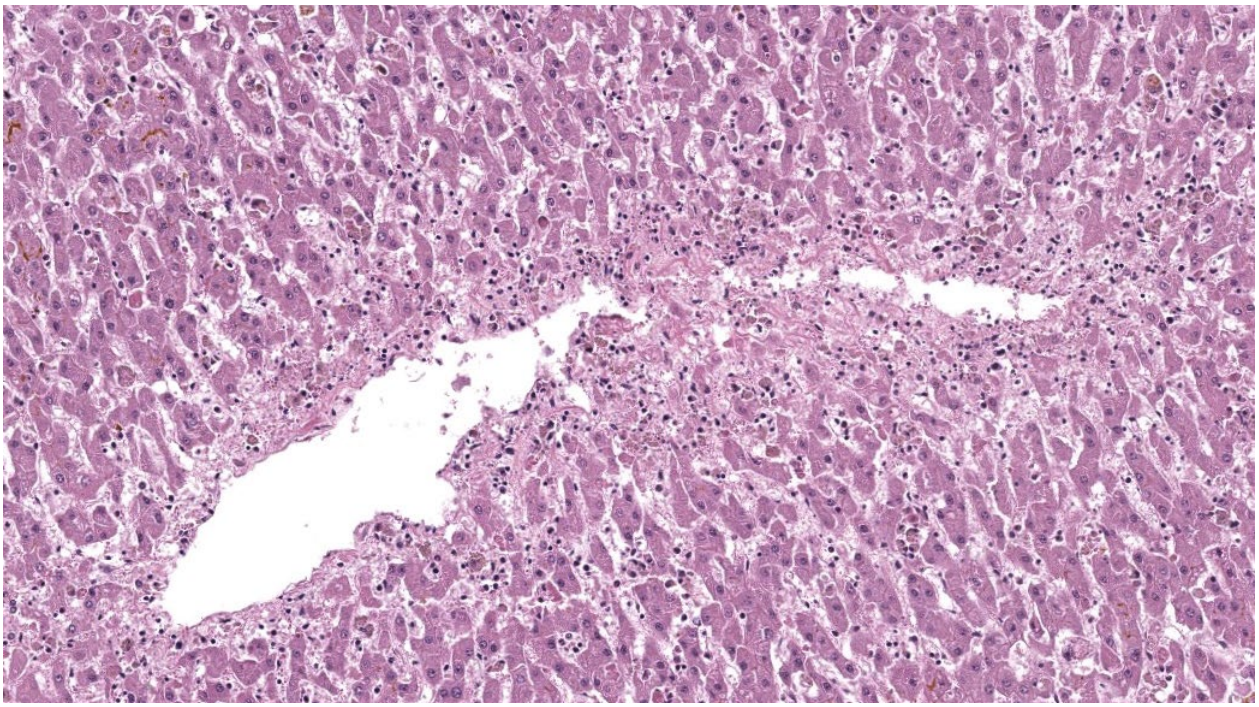
Iron - Feed or Tissue (ICP/MS) (1041) Dry Wt Basis Normal 306.82 ug/g

Manganese (ICP/MS) (1045) Dry Wt Basis Normal 9.91 ug/g

Molybdenum (ICP/MS) (1048) Dry Wt Basis None Detected, < 0.15 ug/g

Selenium (ICP/MS) (1058) Dry Wt Basis Normal 1.43 ug/g

Zinc (ICP/MS) (1074) Dry Wt Basis Normal 158.28 ug/g



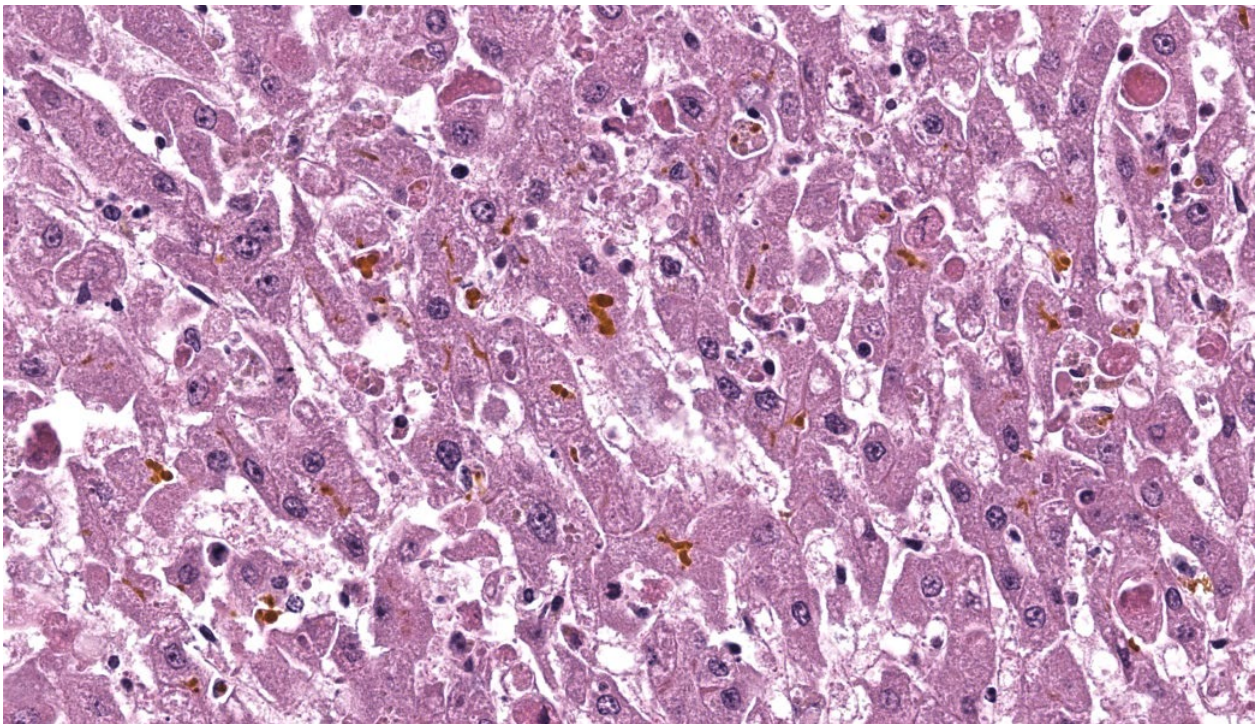
1-4. Liver, goat: Diffusely, there is necrosis of centrilobular hepatocytes. Centrilobular hepatocytes are lost, and granular debris, apoptotic hepatocytes, and debris- and pigment-laden macrophages are present within this region of the hepatocellular lobule. (HE, 260X)

Microscopic Description:
Liver: Predominately affecting centrilobular hepatocytes and to a lesser extent the midzonal and portal hepatocytes, there is loss of hepatocytes, dissociation of hepatic cords, cellular debris, fibrin, and hypereosinophilic, shrunken, pyknotic individual hepatocytes (necrosis). There are often small aggregates or individual Kupffer cells in areas with loss and necrosis that sometimes contains bright pink to orange to light brown intracytoplasmic material. Small numbers of lymphocytes, plasma cells, and fewer neutrophils are also sometimes in necrotic areas. The remaining hepatocytes in these areas occasionally have vacuolated cytoplasm, slightly swollen (degeneration) and/or contain orange to pink intracytoplasmic granular material. Multifocally and frequently the canaliculi contain bile casts.

Kidney: Many multifocal tubules with the cortex and medulla are ectatic and contain bright red granular material (hemoglobin casts) or pale eosinophilic globular to amorphous material (cellular casts and protein). There tubules are sometimes lined by attenuated epithelium. There is multifocal tubular degeneration and necrosis, primarily of the proximal convoluted tubules, characterized by hypereosinophilic shrunken epithelium with pyknotic or absent nuclei, complete loss; or sloughing with karyorrhectic cellular debris and hypereosinophilic basement membranes.

Contributor's Morphologic Diagnoses:
Liver: Moderate subacute centrilobular to random hepatocellular necrosis, degeneration, and with intralesional copper and bile stasis

Kidney: Marked acute multifocal to coalescing tubular necrosis with hemoglobin and cellular casts



1-5. Liver, goat: There is diffuse cholestasis with marked canalicular dilation in all regions of the lobule. In this midzonal region in this field there are scattered apoptotic hepatocytes and few debris-laden macrophages. (HE, 694X)

Contributor's Comment:

This is a case of copper toxicosis in a goat with evidence of intravascular hemolysis, acute tubular necrosis, hepatocellular necrosis with affinity for centrilobular area, and cholestasis. Excessive copper was confirmed through mineral panel testing on the liver and kidneys. This testing was performed on formalin fixed tissues. Previous studies have shown that formalin fixation can alter mineral levels to varying degrees depending on the mineral of interest. However, concentrations of copper and zinc have not shown a significant difference between fresh or frozen and formalin-fixed liver samples[1].

While this is a goat, sheep, especially lambs, are the species most susceptible to copper toxicity, which is suspected to be in part due to lower biliary and urinary copper excretion[2,3,4]. Copper toxicosis is uncommon in adult goats; however, it has been suggested that meat breeds may be more susceptible than dairy breeds[3]. Intravascular hemolysis was not seen in a report of copper intoxication over a large number of dairy goats, but has been reported in Boer goats.[3,4] This suggests that dairy breeds may at least be more resistant to the hemolytic component.

There are two forms of copper toxicosis, acute and chronic, which describe the length of time of exposure and not duration of clinical signs. Acute copper toxicosis is associated with a severe gastroenteritis. Hepatic necrosis, intravascular hemolysis, and hemoglobinuria are more often associated with the chronic form, but can occur in the acute form if the animal survives the gastroenteritis[2]. The chronic form is considered more common.

Copper toxicity can occur not only due to ingesting excessive copper, but also depending on copper antagonists, and hepatic disease decreasing copper excretion. Copper antagonists

compete with copper for absorption and utilization, and elements include molybdenum, iron, zinc, and sulfur. Low intake of these antagonists can lead to chronic excessive copper accumulation in the liver. Copper is stored lysosomes, in which if their storage is exceeded will lead to unbound copper in the nucleus and cytosol. Copper functions in oxidation-reduction catalysis, in which free radicals are produced which cause oxidative damage. Unbound copper will cause oxidative damage that can damage hepatocytes to the point of necrosis, which releases copper into the bloodstream. The free copper in the blood will oxidize hemoglobin in red blood cells causing intravascular hemolysis. This then leads to hemoglobinuria with acute renal tubules damaged by ischemic events and copper accumulation[2]. The cause of copper toxicity was not found in this case.

Contributing Institution:
Midwestern University
College of Veterinary Medicine
Diagnostic Pathology Laboratory
5725 W. Utopia Road
Glendale, Arizona 85308
https://www.mwuanimalhealth.com/diagnostic-pathology-center

JPC Diagnoses:
1. Liver: Hepatocellular necrosis, centrilobular, diffuse, with moderate diffuse cholestasis.

2. Kidney, tubular epithelium: Degeneration and necrosis, multifocal to coalescing, moderate with tubular proteinosis and pigment casts.

JPC Comment:
This week's moderator is an alumnus of the JPC/AFIP DOD Veterinary Pathology Residency program, and a previous staff member of the AFIP Department of Veterinary Pathology, LTC (Ret.) Luann McKinney. Dr. McKinney's impressive body of work also includes being staff pathologist at the Walter Reed Army Institute of Research, director of the Registry of Toxicologic Pathology for Animals, Pathologist, instructor and Deputy Directory of the European Center for Toxicologic Pathology, and for the last 15 years, a pharmacologist and reviewer for the FDA's Center for Drug Evaluation and Research. Her resume in laboratory animal pathology and toxicologic pathology is impeccable, and we are extremely happy that she has decided to rejoin the department in her "retirement:"

Copper toxicosis (not "copper toxicity", which refers to the inherent ability of copper to cause damage) has made a number of appearances in the WSC years, it has popped up relatively rarely in sheep (WSC 2024, conference 12, case 3), in a cat (WSC 2023, conference 11, case 1), in a dog (WSC 2017, conference 10, case 3) and in a goat (WSC2010, conference 14, case 1). In the older WSC conference archive, it was an extremely popular condition with 22 separate WSC cases between 1975 and 2001, including one case in a fish (WSC 1987, conference 23, case 3).

The contributor has provided a concise yet thorough explanation of copper toxicosis in ruminants, which results in cyclic waves of necrosis of copper-laden hepatocytes, release of copper into the peripheral circulation, oxidation of erythrocytes, which results in ischemia and a second centrilobular hepatocyte death (and so on and so on) Centrilobular hepatocytes typically live "on the razor's edge of hypoxia" in the normal state, as they are the last cells in the body to be oxygenated. Any loss of the oxygen-carrying ability of erythrocyte mass in these animals results in additional loss of centrilobular hepatocytes. This vicious cycle of ischemia and progressive release of

copper into the circulation may result in death of affected sheep within as little as 12 hours. A more extensive review of the pathogenesis of copper toxicosis in ruminants and other species is available within case write-ups previous years of the in WSC or in the JPC's Veterinary Systemic Pathology Online.

This allows us to turn our attention to a species which has been rarely discussed in these write-ups, namely humans (which we don't often consider when discussing syndromes of copper toxicosis). Both acute and chronic copper intoxication syndromes are documented in people. Acute cases typically are the result of accidental ingestion of increased amounts of copper or suicide attempts via ingestion of copper sulfate. Chronic syndromes associated with overload of copper over a long period of time include Wilson's disease and Indian childhood cirrhosis.[5]

The recommended amount of copper for adults is 0.9 to 1.3 mg of copper per day. Ingestion of 8 to 10 mg of copper per kg body weight will result in acute copper toxicity. Copper does not need to be ingested and may be inhaled (they are widely used in fireworks and fungicides) or absorbed through the skin (they are widely used in ointments and creams, particularly burn ointments). Syndromes of acute copper toxicosis in people do not differ significantly in their clinical presentation from what we see in domestic animal species - vomiting, gastrointestinal bleeding, acute renal and hepatic damage, hemolytic anemia, and cardiac dysrhythmia. In acutely intoxicated adult humans, the first 24 to 48 hours is typically associated with hemolysis, with liver failure ensuing between 40 and 72 hours, and kidney failure on the 4th day.[5]

The most common cause of chronic toxicosis in humans is Wilson (not Wilson's) disease, resulting from a mutation in chromosome 13 at the locus of the ATP7B gene. This genetic abnormality results in copper overload in the liver, resulting in the development of chronic hepatitis, cirrhosis, and ultimately acute liver failure. Mutated variants of the ATP7B gene are many and varied and may have a shortened half-life, incorrect conformation, or may improperly localize within the cell. Mutated ATPase7B is also unable to interact properly with other proteins that are important for proper copper metabolism.[6] It does not appear that mutations in this gene are all that are involved in manifestations of Wilson disease, but other genetic and epigenetic factors likely further complicate this picture.[6]

In Wilson disease, copper also accumulates in the brain, particularly in the thalamus and putamen, causing encephalitis with white matter degeneration and neuronal loss, ultimately resulting in cerebral atrophy and *hydrocephalus ex vacuo*. The disease received its name from Dr. S.A.K. Wilson, who described the changes in the putamen and globus pallidus, and the significant neuropsychiatric symptoms associated with the disease for which he is remembered. Neural symptoms of Wilson disease are movement disorders, tremors, and rigidity mimicking Parkinsonism; psychiatric symptoms include cognitive impairment, affective disorders, and psychosis. Another "brush with celebrity" associated with Wilson disease is that the first reports of two forms of large astrocytes in the brain of a Wilson disease patient was reported by von Ostlin and Alzheimer in 1912. These cells were officially named Alzheimer type 1 and 2 cells (or "Alzheimer glia" cells) eight years later in 1920 by another researcher.

While the slow accumulation of copper and the ability of the liver to cope with large loads of it result in clinical signs of Wilson disease

typically manifesting in the fourth decade of life,[5] Indian childhood cirrhosis, first diagnosed in the 1880s in Calcutta (now Kolkata) is a disease of massive copper accumulation in the liver of children typically less than 5 years of age (although cases in children as old as 12 years have been documented). While attributed to excess ingestion of copper for many years, that idea has been largely discarded, and a true cause in these children remains a mystery.[7]

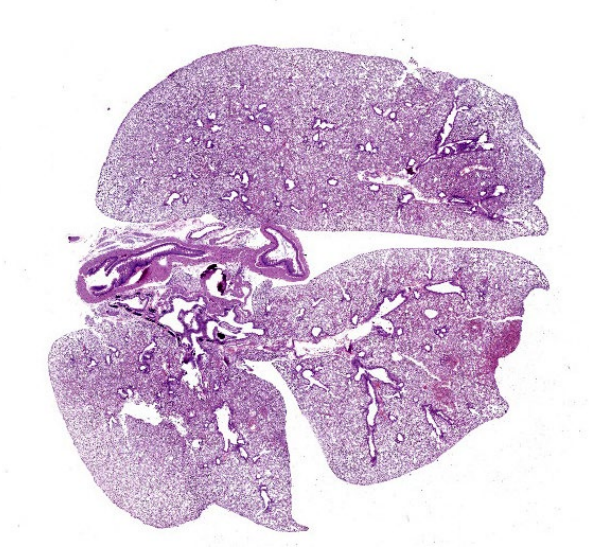
References:

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2. Borobia M, Villanueva-Saz S, Ruiz de Arcaute M, et al. Copper Poisoning, a Deadly Hazard for Sheep. Animals (Basel). 2022;12(18):2388.
3. Bozynski CC, Evans TJ, Dae YK, et al. Copper Toxicosis with Hemolysis and Hemoglobinuric Nephrosis in Three Adult Boer Goats. J Vet Diagn Invest. 2009;21(3):395-400.
4. Cornish J, Angelos J, Puschner B, et al. Copper toxicosis in a dairy goat herd. J Am Vet Med Assoc. 2007;231(4):586-589.
5. Sailer J, Nagel J, Akdogan B, Jauch AT, Engler J, Knolle PA, Zischka H. Deadly excess copper. Redox Biol. 2024 Sep;75:103256. doi: 10.1016/j.redox.2024.103256. Epub 2024 Jun 28. PMID: 38959622; PMCID: PMC11269798.
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7. Nayak NC, Chitale AR. Indian childhood cirrhosis (ICC) & ICC-like diseases: the changing scenario of facts versus notions. Indian J Med Res. 2013 Jun;137(6):1029-42. PMID: 23852284; PMCID: PMC3734708.

CASE II:

Signalment:
16 week old, male, MISTRG6* mouse (*Mus musculus*)

*Standardized mouse strain nomenclature:
C;129S4-
Rag2$^{tm1.1Flv}$*Csf1*$^{tm1(CSF1)Flv}$*Csf2/Il3*$^{tm1.1(CSF2,IL3)Flv}$*Thpo*$^{tm1.1(TPO)Flv}$*Il2rg*$^{tm1.1Flv}$*Sirpa*



2-1. Lung, immunodeficient mouse: Subgross magnification of submitted section through the lung, esophagus, and trachea. (HE, 10X).

tm1(SIRPA)Vlcg$Il6^{tm2(IL6)Vlcg}$

History:
At 4 weeks of age the mouse was administered busulfan intravenously, followed 24 hours later by intravenous administration of CD34+ human hematopoietic stem cells. At 14 weeks of age, the mouse was presented to veterinary services for unilateral swelling and dark red discoloration of the left pinna. Meloxicam was administered for a week but the lesion did not resolve and progressed to more severe swelling, at which point the mouse was euthanized and submitted for complete necropsy.

Gross Pathology:
The left pinna was diffusely swollen and discolored dark red. No other external or internal gross changes were observed.

Laboratory Results:
None available

Microscopic Description:
Lungs. Diffusely, alveolar spaces contain abundant, variably sized, round to oval aggregates of a dense, homogeneous, eosinophilic extracellular material. Multifocally, alveolar spaces also contain small to moderate numbers of red blood cells. Alveolar walls are multifocally expanded by an infiltrate composed of macrophages with an abundant pale brown, coarsely granular intracytoplasmic pigment (compatible with hemosiderin), and occasional intracytoplasmic red blood cells.

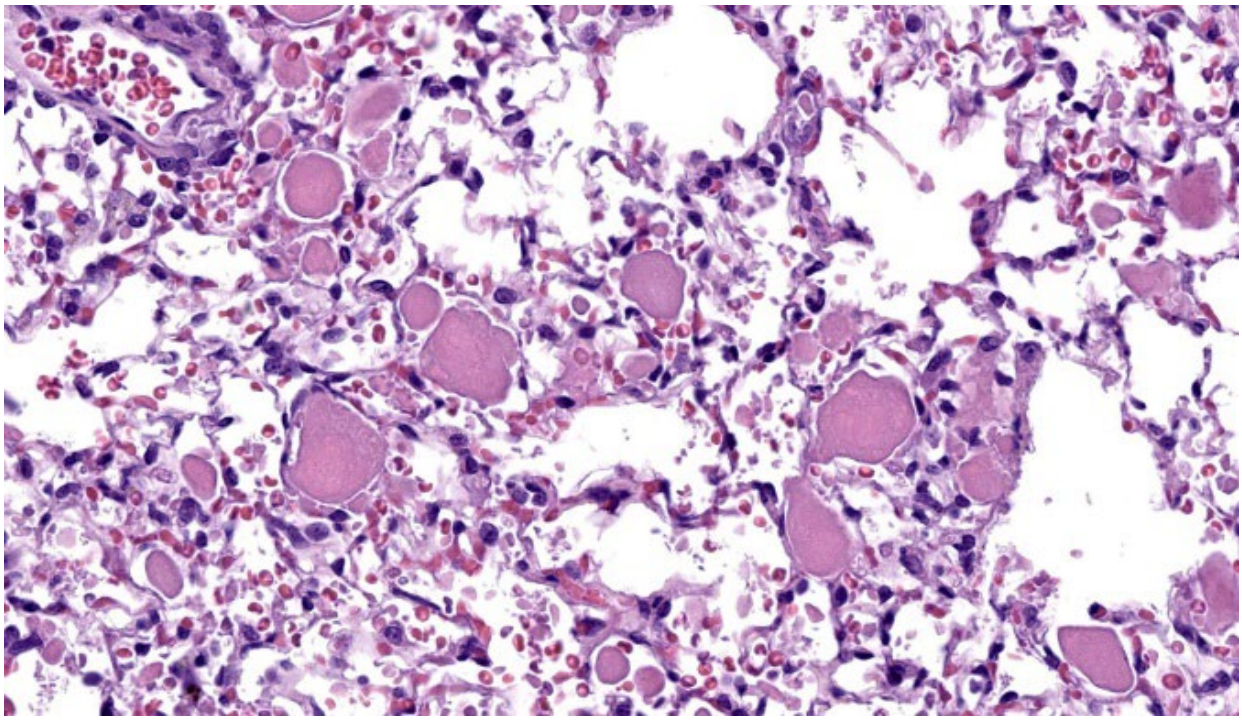
Contributor's Morphologic Diagnoses:
Lungs:

1. Alveolar proteinosis, diffuse, marked.
2. Interstitial histiocytic infiltrate with hemosiderosis and erythrophagocytosis, multifocal, mild.

Contributor's Comment:
The MISTRG6 mouse strain is severely immunodeficient due to inactivation of the Rag2 and Il2rg genes resulting in a lack of T, B, and NK cells, and expresses knocked-in human alleles for 6 cytokine genes: M-CSF (CSF1), IL3, GM-CSF (CSF2), SIRP alpha, thrombopoietin, and IL6. The immunodeficient phenotype and expression of human cytokines allow the efficient engraftment, proliferation and differentiation of human hematopoietic stem cells, resulting in a humanized immune system. This model is valuable in several research areas including cancer and infectious diseases. However, this and other humanized immunodeficient mouse strains expressing human cytokines, are prone to develop unique lesions which may limit their usefulness, as they may confound research results and result in unexpected morbidity and mortality during the course of experiments. Two of these lesions are demonstrated in this case.

This mouse was presented to veterinary services due to unilateral swelling and discoloration of the pinna. This lesion was histologically consistent with a cutaneous hemangioma (not shown on submitted slide), composed of vascular spaces lined by endothelial cells positive for mouse CD31 and negative for human CD31 on IHC, consistent with a spontaneous tumor of mouse endothelial cell origin. While cutaneous hemangioma has not been reported to our knowledge in MISTRG6 mice, its occurrence is not surprising as this strain is on a BALB/c genetic background, and hemangiomas have been described to occur spontaneously with a low incidence in wild type BALB/c mice.

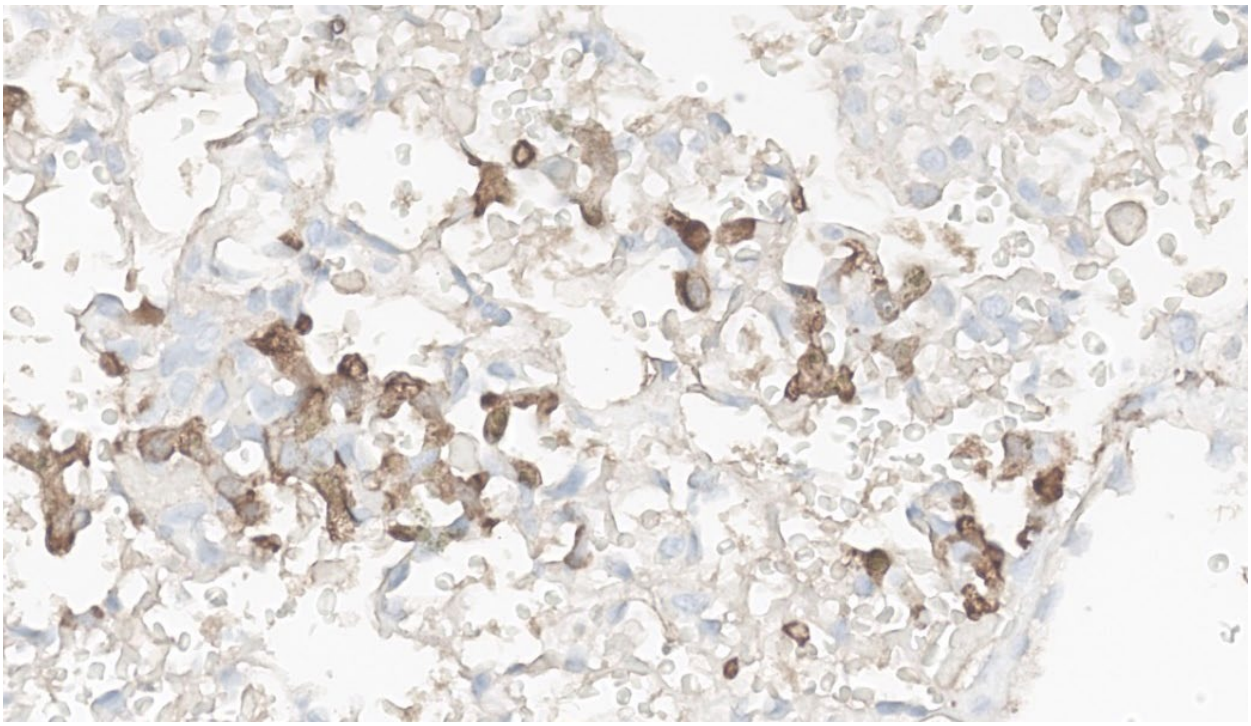
Examination of other organs revealed two additional lesions unrelated to the presenting clinical complaint: pulmonary alveolar pro-



2-2. Lung, immunodeficient mouse: Alveolar spaces contain variable combinations and concentrations of globular eosinophilic lipoprotein, alveolar macrophages, and rare hemorrhage. Alveolar macrophages contain small amounts of brown granular cytoplasmic pigment (likely iron). (HE, 750X).

teinosis (PAP) in the lungs, and hemophagocytic lymphohistiocytosis / macrophage activation syndrome (HLH/MAS) in the liver, spleen, and lungs.

PAP is a disease caused by accumulation of surfactant proteins in alveoli. Three classes are recognized in humans, based on pathogenesis: acquired, congenital, and secondary. The acquired form has been associated with the presence of circulating anti-GM-CSF antibodies leading to inhibition of GM-CSF activity. Among its multiple functions, GM-CFS upregulates surfactant clearance by alveolar macrophages, as initially demonstrated by the unexpected finding that GM-CFS knock out mice develop PAP[1]. MISTRG6 mice have a knocked-in human GM-CSF allele: the mouse GM-CSF gene is replaced by human GM-CSF. This results in the same phenotype as in GM-CSF knock out mice, as there is a loss of mouse GM-CSF and human GM-CSF fails to stimulate mouse alveolar macrophages[2]. Once these mice receive human hematopoietic stem cells, the development of human alveolar macrophages results in a partial resolution of the PAP phenotype. Human congenital PAP, a fatal disease of newborns, has been associated with mutations of GM-CSF, GM-CSF receptor beta chain, and other genes. Secondary PAP has been associated with various primary diseases of humans, including inhalational conditions, immunodeficiencies, malignancies, and hematopoietic disorders. PAP is characterized by extracellular accumulation of an amorphous material that is PAS positive (confirmed on PAS stain in this case but not shown). Other common conditions resulting in accumulation of eosinophilic material in pulmonary alveoli in mice, and that must be differentiated from PAP, include acidophilic macrophage pneumonia and pneumocystosis. Acidophilic macrophage pneumonia results from accumulation of YM1 and YM2 chitinase proteins and is characterized histologi-



2-3. Lung, immunodeficient mouse: An IBA-1 stain demonstrates aggregates of macrophages at the periphery of alveolar lumina and within the alveolar septa. (IBA-1, 282X).

cally by the accumulation of eosinophilic needle to rhomboid-shaped crystals in alveolar macrophages and extracellular alveolar spaces. Pneumocystosis is a disease of immunodeficient mice caused by the fungal organism *Pneumocystic murina*, and is microscopically manifested by the presence of foamy eosinophilic material with punctate organisms (fungal cysts that can be better visualized on PAS or GMS stain), variably associated with an inflammatory infiltrate.

HLH/MAS, also termed myeloid cell hyperactivation, is a hemophagocytic disorder that has been described in multiple immunodeficient mouse strains expressing human cytokines genes and administered human hematopoietic stem cells: the NSG-SGM3, NOG-EXL, and MISTGR6 strains[3,4]. The lesions of HLH in these models are characterized by multisystemic infiltrates composed of human macrophages (human CD68+ on IHC) with erythrophagocytosis and hemosiderin accumulation, and the mice develop anemia. This disorder occurs with high frequency in these models, in which it can be life-limiting, and is believed to be caused by stimulation of human macrophages by human cytokines, of which GM-CSF has been suggested to be the most significant.

The development of complex genetically engineered mouse strains and the humanization of their immune system by administration of human hematopoietic cells have allowed improved modeling of human diseases, but these models are associated with the development of unique lesions that may confound research outcomes. Veterinary pathologists working with these models must become familiar with these lesions, two of which are illustrated by this case.

Contributing Institution:
Memorial Sloan Kettering Cancer Center, https://www.mskcc.org/research-programs/comparative-medicine-pathology

JPC Diagnoses:

1. Lung: Alveolar lipoproteinosis, chronic, multifocal, marked.
2. Lung, septa: Histiocytosis, multifocal, mild, with erythrophagocytosis and hemosiderosis.

JPC Comment:

The contributor has provided a very thorough and comprehensive review of alveolar lipoproteinosis in genetically engineered mice, humans, and differential diagnoses for this lesion in mice.

Pulmonary alveolar proteinosis (PAP), an alveolar filling disorder in which the alveolar space is filled by pulmonary surfactant and granular debris, was first described in humans by Rosen et al in 1958,[5,6] who described a disease in which alveoli are filled by lipid-rich PAS-positive material. The true nature of the material was not identified until later, however.

PAP is not a singular disease, but a syndrome resulting from many different causes. The most common clinical form of PAP, referred to as autoimmune PAP, is the most common clinical form of PAP and accounts for 90% of cases. It is the result of alveolar macrophage dysfunction due to a high level of GM-CSF autoantibody in the lungs, which results in disruption of GM-CSF signaling.[5] Elevated serum levels of GM-CSF autoantibody is used as a biomarker in disease diagnosis.

Genetic mutations of GM-CSF associated gene ("primary PAP") is the least common form, and are thought to result in less than 1% of human cases. Finally, "secondary PAP" results from a wide variety of infectious agents, inhalation toxicities (including smoking), and hematologic diseases and results in about 8-9% of all cases. Hematologic diseases and malignancies are thought to account for the majority of cases of PAP.[6]

Whole lung lavage (WLL) has been the standard therapy for PAP since the 1960s.[6] This procedure is performed under general anesthesia using a double lumen endotracheal tube to maintain ventilation in one lung while repeatedly filling and aspirating the other with up to 50L of saline to physically remove accumulated surfactant.[6]

References:

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2. Willinger T, et al. Human IL-3/GM-CSF knock-in mice support human alveolar macrophage development and human immune responses in the lung. Proc Natl Acad Sci USA 2011, 108: 2390-2395.

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CASE III:



3-1. Presentation, calves. Four affected calves (right) show marked growth retardation compared with an unaffected calf (left) of the same age. (*Photo courtesy of:* Universidade Federal do Rio Grande do Sul, Setor de Patologia Veterinária, http://www.ufrgs.br/patologia)

Signalment:
2-month-old, female, Holstein-Friesian calf (Bos taurus).

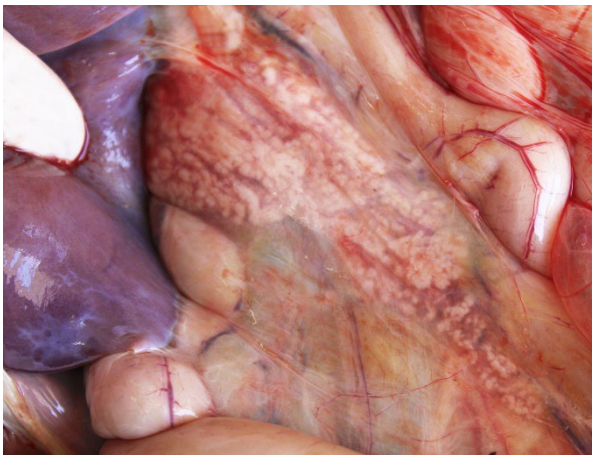
History:
On four different dairy farms, Holstein-Friesian calves of both sexes, ranging from 60 to 120 days of age, were reported to exhibit marked growth retardation despite maintaining a good appetite. The stunting was severe, with calves reportedly gaining only 2 kg over a 33-day period. All affected calves were lethargic, and some also exhibited mild diarrhea.

On all farms, calves were transitioned to a milk replacer shortly after colostrum intake, at approximately four days of age. Producers reported that younger calves fed whole milk weighed approximately 10–20 kg more than older calves receiving the milk replacer.

On one of the farms, 25 calves received the milk replacer, of which 20 became clinically affected (80% morbidity) and nine died (45% case fatality). Four calves that died were necropsied.

Gross Pathology:
Four affected calves were necropsied. On gross examination, the pancreas was markedly reduced in size, diffusely firm, and beige to chalky white in all calves. No significant gross lesions were observed in the remaining organs.

Laboratory Results:
A complete blood count was performed on blood samples from five affected calves (Calves 1-5) and one unaffected calf (Calf 6) from the same farm (Table 1). The main hematologic abnormalities included anemia in calves 1, 2, and 4, with erythrocyte counts of 3.62, 4.21, and 3.50 x 10^6/µL, respectively (reference range: 5-10^6 x 10/µL).[1] Calves 1 and 2 also had increased mean corpuscular volume (MCV; 71.82 and 68.88 fL, respectively; reference range: 40-60 fL), consistent with macrocytosis.[1] Calf 4 had low hemoglobin (6 g/dL; reference range: 8-15 g/dL) and hematocrit levels (18%; reference range: 24-46%).[1] In addition, neutrophilia was observed in calves 1-3 and 5), with neutrophil counts of



3-2. Pancreas, calf. Upon opening the abdominal cavity, the pancreas is markedly reduced in size. (*Photo courtesy of:* Universidade Federal do Rio Grande do Sul, Setor de Patologia Veterinária, http://www.ufrgs.br/patologia)

Table 1. Complete blood count results of affected calves (1-5) and of an unaffected calf (6).

Parameter	Reference interval[a]	Calf					
		1	2	3	4	5	6*
RBC (x10⁶/µL)	5-10	3,62	4,21	6,84	3,5	6,3	8,06
Hemoglobin (g/dL)	8-15	8,6	9,6	11,6	6	10,9	13,2
Hematocrit (%)	24-46	26	29	35	18	33	39
MCV (fL)	40-60	71,82	68,88	51,7	51	52	48,39
MCHC (g/dL)	30-36	33,08	33,1	33,14	33	33	33,85
Total protein (g/dL)	5.8-8	5,6	6,5	65	5,2	5,8	8,5
Platelets (/µL)	100,000-800,000	200,000	752,700	747,000	255,000	130,000	800,000
Total leucocytes (cell/µL)	4,000-12,000	9,300	9,900	10,800	5,722	8,138	9,600
Band neutrophils (cell/µL)	0-100	0	0	0	0	0	0
Segmented neutrophils (cell/µL)	600-4,000	5,580	5,445	5,940	2,346	1,139	6,432
Lymphocytes (cell/µL)	2,500-7,500	3,162	3,960	4,428	3,204	6,754	2,304
Monocytes (cell/µL)	0-800	558	495	432	114	163	864
Eosinophils (cell/µL)	0-2400	0	0	0	57	81	0
Basophils (cell/µL)	0-200	0	0	0	0	0	0

*Unaffected calf. [a]Thrall et al. 2022.[1]

5,580, 5,445, 6,432, and 5,940 cells/µL, respectively (reference range: 600-4,000 cells/µL).[1]

Serum samples were collected from calves 1-3 and 6. All four calves had increased gamma-glutamyl transferase (GGT) activity (202, 80, 193, and 52 U/L, respectively; reference range: 10-26 U/L).[1] In addition, calves 1-3 had elevated serum zinc (Zn) concentrations 532.7, 432.7, and 551.1 µg/dL, respectively; reference value: 145 ± 11 µg/dL).[2]

Microscopic Description:
Pancreas: There is marked proliferation of fibrous connective tissue (fibrosis) dissecting pancreatic lobules and acini and surrounding pancreatic ducts, as highlighted by Masson's trichrome stain. The fibrosis is associated with moderate to marked acinar atrophy and intra- and interlobular ductular hyperplasia. Mild inflammatory infiltrates composed of lymphocytes, plasma cells, macrophages, and neutrophils are multifocally present within the fibrotic stroma. In addition, moderate exocrine pancreatic necrosis is observed, characterized by acinar cells with hypereosinophilic cytoplasm and pyknotic, karyolytic, or absent nuclei, accompanied by cellular debris and mild to moderate neutrophilic infiltration.

Contributor's Morphologic Diagnoses:
Pancreas: pancreatic fibrosis, marked, diffuse, chronic, with acinar atrophy, ductular hyperplasia, mild lymphoplasmohistiocytic and neutrophilic inflammation, and multifocal exocrine pancreatic necrosis.

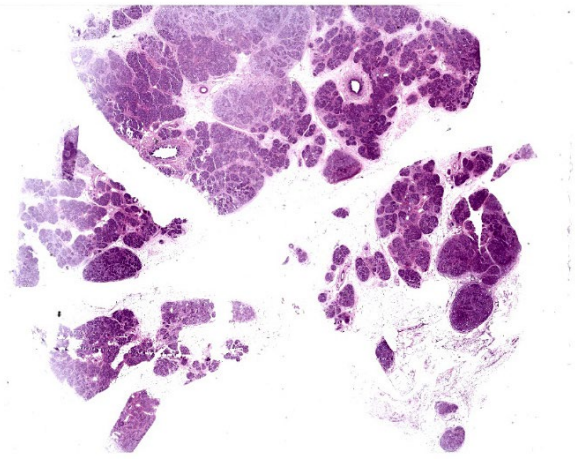
Contributor's Comment:
All four affected farms used the same commercial milk replacer. Following necropsy and the identification of marked pancreatic fibrosis, chronic Zn toxicosis was suspected. Consequently, the milk replacer was analyzed for Zn concentration and contained 1,838.36 mg/kg, exceeding the concentration declared on the product label (1,400 mg/kg). According to the National Research Council, milk replacers should contain approximately 40 mg Zn/kg of product.[3] However, the commercial milk replacer fed to the calves in these cases greatly

exceeded this recommended concentration. For Holstein-Friesian calves, the maximum tolerable Zn intake has been estimated at 3.5 mg/kg body weight/day.[4] Based on the estimated body weight and daily milk replacer consumption of the affected calves, their Zn intake was approximately 40.85 mg/kg body weight/day. This exposure exceeded the proposed maximum tolerable intake by more than 11-fold. In addition to elevated serum Zn concentration (551.1 U/L; reference value: 145 ± 11), the necropsied calf had increased hepatic and renal Zn concentrations. Zn analysis revealed liver and kidney concentrations of 261.7 mg/kg and 171.81 mg/kg, respectively, compared with reference values of 88-130 mg/kg for the liver and 18-25 mg/kg for the kidneys.[5] All these findings, along with the gross and histological lesions, supported a diagnosis of chronic Zn toxicosis.[6]

Zinc toxicosis is uncommon in ruminants, but when cases are reported, they are characterized by chronic intoxication. The first documented case in ruminants occurred in 1968 caused by accidental Zn contamination of



3-3. Pancreas, calf. The pancreas is diffusely and markedly firm, with a white, chalky discoloration. (*Photo courtesy of:* Universidade Federal do Rio Grande do Sul, Setor de Patologia Veterinária, http://www.ufrgs.br/patologia)



3-4. Pancreas, calf. Sections of pancreas are characterized by regional pallor of lobules (top center) and expanded interstitium at subgross magnification. (HE, 12X)

feed.[7] Subsequent reported described outbreaks in calves, including one in which the source of Zn contamination could not be identified and another associated with the consumption of forage harvested near a steel pipe galvanizing facility.[8,9] More recently, Zn toxicosis was reported in cattle from farms in New Zealand that used the same mineral pellet, which contained 97,000 mg/kg of Zn.[10] Also in New Zealand, chronic Zn intoxication has been sporadically reported following excessive prophylactic Zn supplementation, administered as ruminal boluses or through drinking water, for the prevention of facial eczema (sporidesmin poisoning) in cattle.[11,12]

The pancreas may be particularly susceptible to Zn toxicity because it represents a major route of Zn excretion. However, the exact mechanisms underlying the development of pancreatic lesions remain poorly understood. The main clinical syndrome observed in affected ruminants of different age groups, including calves, heifers, and lactating cows is reduced weight gain or substantial weight loss, resulting in poor body condition.[9-12] Decreased appetite and diarrhea have also been

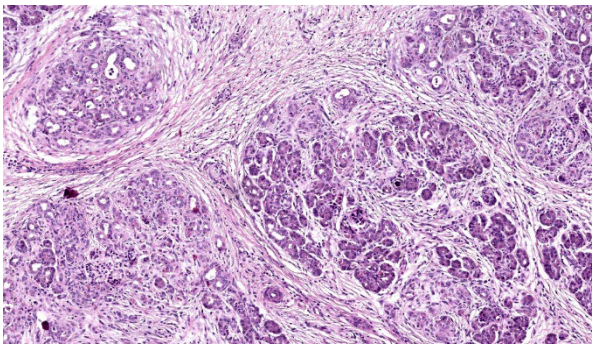
described in cattle with chronic Zn intoxication, which are common clinical manifestations of exocrine pancreatic insufficiency.[9,10,12,13] Anemia is another clinical sign commonly reported.[9,10,12] Although the underlying mechanism is not fully understood, it may involve the direct hemolytic effects of excessive Zn exposure or secondary nutritional deficiencies.[7,10,12,14] Additionally, the interaction between Zn and copper metabolism has been suggested as a potential contributing factor in the development of anemia.

At necropsy and histological examination, the characteristic lesion of chronic Zn intoxication is marked, irreversible fibrosis, with ductular components reportedly affected first in ruminants.[13] This lesion pattern is associated with the limited regenerative capacity of the pancreas after exocrine acinar cell necrosis. Following injury to the exocrine pancreas, regeneration is minimal, and the predominant response consists of fibrosis, along with ductular proliferation and lobular atrophy.[15]

Following the farm visits and diagnosis, the commercial milk replacer was removed from the calves' diet, after which no additional cases were observed. However, previously affected calves continued to have poor growth performance.

Contributing Institution:
Faculdade de Veterinária
Universidade Federal do Rio Grande do Sul
Setor de Patologia Veterinária
http://www.ufrgs.br/patologia

JPC Diagnoses:
Exocrine pancreas: Degeneration, necrosis, and atrophy, lobular, chronic, multifocal to coalescing, severe, with ductal hyperplasia and diffuse fibrosis.

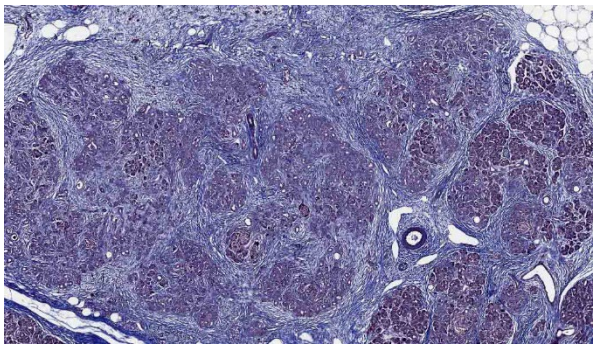


3-5. Pancreas, calf: There is marked degeneration, attenuation, and loss of acinar epithelium, with some lobules only containing remnant ducts. There is marked fibrosis of the interstitium. (HE, 173X)

JPC Comment:
The contributor provides a comprehensive explanation of zinc toxicosis in cattle. Four additional cases of zinc-induced pancreatic necrosis have been submitted to the Wednesday Slide Conference over the years, not to include a single case associated with zinc phosphide, an uncommonly used pesticide whose ingestion results in intoxication with phosphine gas and a microvesicular steatosis leading to liver failure.

Zinc is a trace element which has been shown to produce toxic effects in multiple species including humans, dogs, sheep, cattle and many wildlife species.[8] In ruminants, zinc toxicity may result from administration of zinc as protection against sporidesmin toxicity.[8] In other animals, zinc toxicity typically results from dietary indiscretion, and may be caused by the ingestion of zinc-coated U.S. pennies (a particular hazard for zoo species due to the proclivity of Americans to throw pennies into any body of water, even those containing zoo animals), batteries, paint, hardware, creams, and automotive parts.[13,15,16]

In ruminants, initial effects are produced within ductal epithelium within the exocrine pancreas with subsequent changes in acinar



3-6. Pancreas, calf: A Masson's trichrome demonstrates the severity of fibrosis within affected lobules. (Masson's trichrome, 67X)

cells. [8,17,18] The initial reported lesions include vacuolar degeneration, necrosis and regeneration with a pronounced lobular distribution. As seen in this case, the distribution of the lesion is lobular, with affected lobules bordering intact, morphologically normal. It is hypothesized when injury of a duct occurs, drainage is impeded causing damage to the that lobule.[17] This is supported by the fact that cattle, which have a dual exocrine pancreatic drainage via an accessory duct, do not show a discrete lobular pattern despite having other similar histopathological changes.[17] With prolonged zinc intoxication, pancreatic necrosis exceeds the rate of regeneration, with fibrosis and atrophy becoming the predominant findings.[8,17,18] The endocrine pancreas is not affected.[17]

Additionally, excessive zinc induces hemolytic anemia with production of Heinz bodies of which the exact mechanism is unknown. Possible mechanisms include hapten-induced immune-mediated destruction, direct cell membrane damage, or erythrocyte enzyme inhibition.[18] Hemoglobin release from damaged hepatocytes may result in acute renal tubular injury, in addition to hypoxic injury caused by anemia and reduced renal blood flow.[19]

In our last discussion in the WSC regarding exposure to toxic levels of zinc[18], we brought you "metal fume fever" a disease of foundry workers and welders of galvanized steel.[18, 20] in which inhaled zinc oxide gases result in serious pulmonary inflammatory disease. Today, in the interest of obscure diseases with interesting names, we bring you "white monkey syndrome." This disease has been reported in a number of primate species, and was best described by Frost et al.[22] in young baboons kept in galvanized steel cages. Over 23 months, clinical signs of zinc toxicosis was diagnosed in 35 baboons aged 5-12 months including reduced pigmentation of hair, skin, and mucous membranes (whiteness), alopecia, cachexia, dermatitis, diarrhea and, in six cases, severe gangrenous dermatitis of extremities. The syndrome was characterized by pancytopenia, elevated zinc and low copper serum concentrations, and atypical myelomonocytic proliferation of bone marrow. A similar condition was reported in nursing wild savannah baboon infants by Markham et al., who attributed the whitish discoloration of the baboon's coats to copper deficiency, which they opined was related to dietary zinc excess.[22]

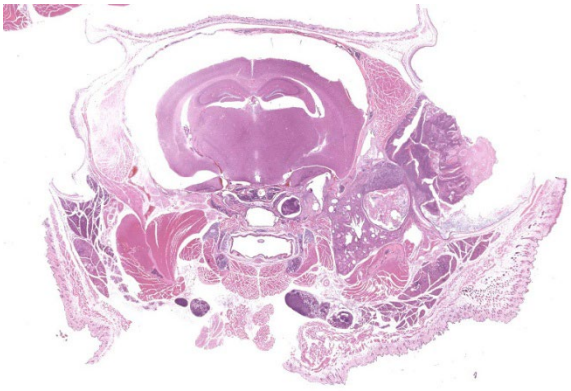
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CASE IV:

Signalment:
28-month-old male mouse (C57B46N Cre)



4-1. Zymbal's gland, mouse: An infiltrative neoplasm expands the Zymbal's gland and infiltrates the adjacent soft tissues of the head. (HE, 10X)

History:
Experimentally naïve mouse with 3 week history of dermatitis of the right shoulder, neck and thickening of the right ear base that progressed to serous, watery discharge from the right ear canal. Topical antibiotic therapy once daily was administered, but the ear exudate persisted on subsequent rechecks. Euthanized due to developed of focal cartilage exposure at the caudal aspect of the right ear base.

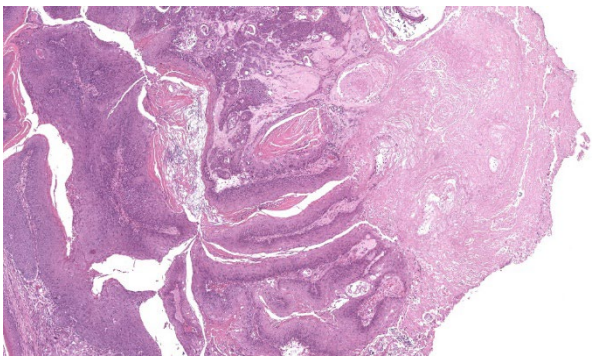
Gross Pathology:
Approximately 2mm of circumferential fur loss (alopecia) surrounding the opening of the right external ear canal and pinna. A two mm linear region of flaky and dark pink skin extends ventrally from the right intertragal notch. The antitragus is diffusely pink with a 1-2 mm section of white cartilage exposed near the intertragal notch. The right external ear canal contains a moderate amount of light white, watery discharge.

Laboratory Results:
None Available

Microscopic Description:
Extending through the ear canal is a large, infiltrative, unencapsulated, well-demarcated, multilobular, densely cellular neoplasm. The neoplasm is composed of papillary projections of squamous epithelium supported by a moderate fibrovascular stroma. There is moderate multifocal to coalescing hyperkeratosis and multifocal cystic cavities within central portions of the neoplasm containing keratinocytes, necrotic cells and leukocytes. Neoplastic cells are pleomorphic with variably distinct cell borders, contain a moderate amount of eosinophilic cytoplasm and round to oval central nuclei with one to two nucleoli. There is moderate anisocytosis and anisokaryosis. Mitotic figures average 5 per 40x field. There is local invasion into the dermis, striated muscle and middle ear in multiple sections. There are multifocal areas of mild erosion, ulceration, necrosis and hemorrhage admixed with neutrophils, histiocytes and fewer lymphocytes throughout the neoplasm, ear canal exudate, and extending to adjacent dermis of external ear.

Mesenteric lymph node (not shown): Metastatic carcinoma.

Lung (not shown): Multifocal perivascular carcinoma metastases and intravascular tumor emboli. Mild multifocal eosinophilic macrophage pneumonia, hemorrhage and lightly eosinophilic amorphous material expanding pulmonary vessels and pulmonary parenchyma



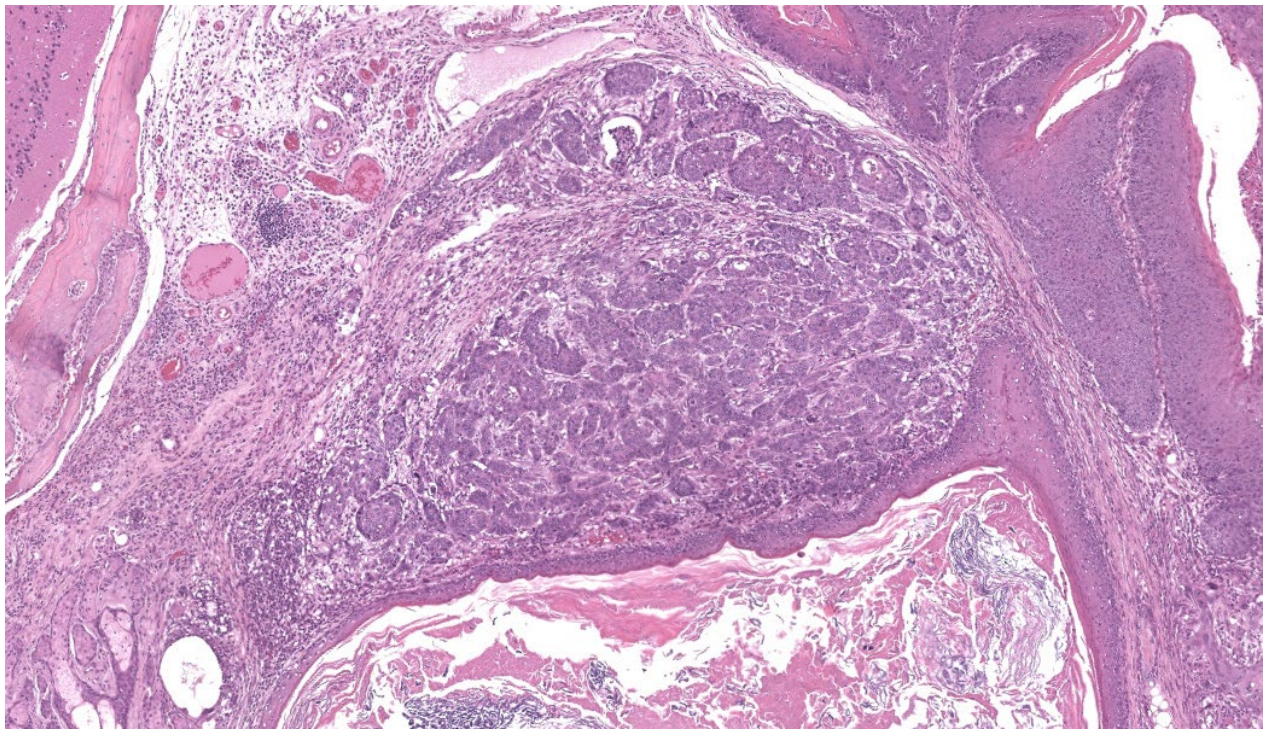
4-2. Zymbal's gland, mouse: The majority of the tumor is composed of long papillary projections of squamous epithelium which are capped by equally long fronds of lamellated keratin. (HE, 84X)

Contributor's Morphologic Diagnoses:
1. Ear: Carcinoma, Zymbal's gland, mouse.

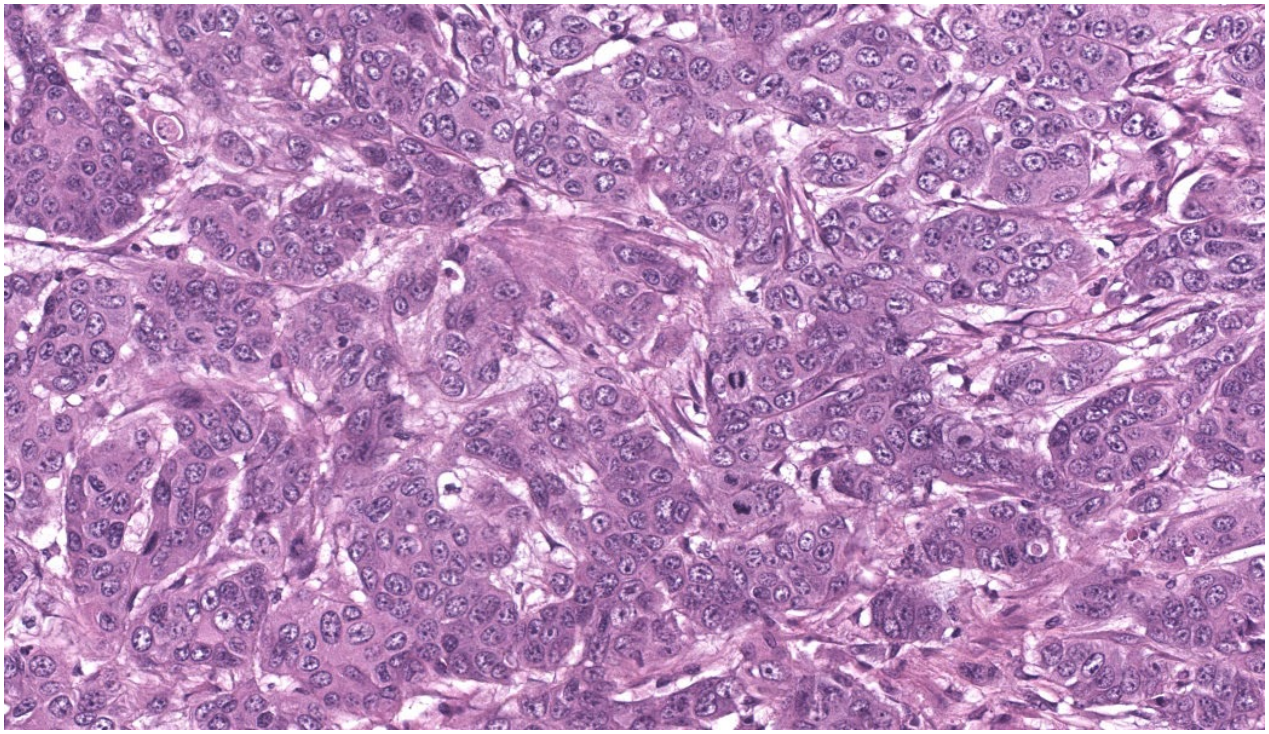
Contributor's Comment:
Histologic evaluation of sections of right ear canal revealed an invasive Zymbal's gland tumor. In laboratory rats and mice, tumors of these modified sebaceous glands surrounding the external ear canal commonly occur with chemically induced carcinogenesis, and less commonly form spontaneously, as in this case of an experimentally naïve mouse.[1,3,5,6]

Neoplasms arising from the Zymbal's gland may be adenomas, squamous papillomas, or carcinomas.[4,5] While tumors are often not large enough to be detected on macroscopic exam, local ulceration, necrosis and exudation from affected ear canals may be seen, notably with Zymbal's gland carcinomas. [2,3,4] Thus the outcome of the ventral ear lesion in this case is suspected to have been most likely related to neoplasm induced necrosis of the tissue. Other notable histologic findings in this case include local invasion and metastasis to the lungs and lymph node. While local invasion may occur as a feature of Zymbal's gland carcinomas, metastasis is uncommon.[3,4]

Contributing Institution:
University of Washington
Dept of Comparative Medicine
Seattle, WA
https://www.washington.edu/compmed/



4-3. Zymbal's gland, mouse: At the deepest aspect of the tumor, trabeculae and nests of squamous epithelium infiltrate the adjacent soft tissues. (HE, 108X)



4-4. Zymbal's gland, mouse: High magnification of the infiltrative component of the tumor with a high mitotic rate (justifying the diagnosis of carcinoma in this case. (HE, 576X)

JPC Diagnoses:

1. Zymbal's gland: Carcinoma.
2. Haired skin, head: Dermatitis, ulcerative, subacute, focally extensive, moderate.

JPC Comment:

This classic neoplasm of laboratory rats and mice has been a frequent flyer in the Wednesday slide conference over the last 30 years, with seven previous accessions. In the field of toxicologic pathology, evaluation of the Zymbal's gland (as well as the preputial and clitoral glands) in laboratory rodents has been a standard practice for the evaluation of xenobiotics for many years.

This gland, which typically sits at the base of the ear in laboratory rats and mice, was first described by Dr. Zymbal in 1933. The gland has intermingled squamous and sebaceous portions, each of which can give rise to benign and malignant tumors with varied and often confusing histologic morphologies, which may be made additionally more confusing by patient trauma. The term "Zymbal's gland tumor" is appropriate for gross inspection, and histologic examination is required for further determination of benignancy or malignancy. In this particular case, in the deeper aspects of the tumor, there is an infiltrated section of the squamous portion of this tumor. In this region, a brisk mitotic rate further cements a diagnosis of carcinoma.

A less commonly seen differential diagnosis is squamous papilloma of the Zymbal's gland (WSC 2015-2016, Conference 22, Case 3.) These neoplasms arise from the main duct epithelium and have a complex arborizing structure with maturing squamous epithelium overlying fibrous cores. Squamous papilloma of the Zymbal's gland lacks evidence of cellular atypia, infiltration of the adjacent of tissues

as well as sebaceous differentiation within the neoplastic portions.[4,7]

The INHAND projects categorization of proliferative and non-proliferative lesions of the mammary, Zymbal's, clitoral, and preputial glands[4] also lists a range of hyperplastic and degenerative changes in this gland, in addition to criteria for differentiating the various types of benign and malignant tumors that may arise from it. This document, and all of the other INHAND documents (which cover all systems and organs of laboratory rodents), should be at the ready for trainees and practicing pathologists who encounter any laboratory rodents in their daily caseload.

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