Joint Pathology Center
Veterinary Pathology Services

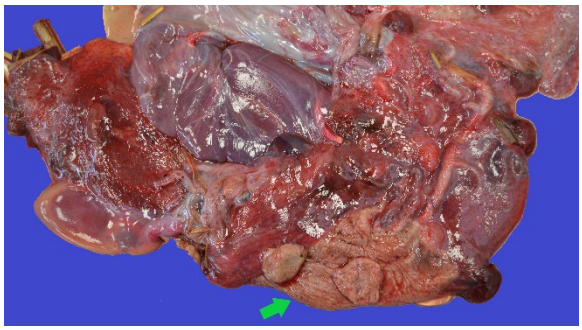
WEDNESDAY SLIDE CONFERENCE 2024-2025

Conference #22 — 2 April 2025

CASE I:

Signalment:
Late-term aborted, female lamb from lowland sheep (*Ovis aries*).

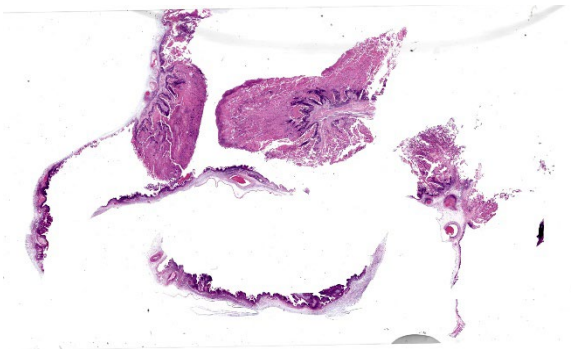
History:
Eight aborted lambs from six abortions were submitted for necropsy. Twenty-two late-term abortions had occurred in a group of 230 lowland ewe lambs (1-year-old) over an 8-day period. The ewe lambs were due to start lambing approximately 1 week later. Twin pregnancies had been particularly affected and occasionally one twin was born alive and survived. The ewe lambs had been kept outdoors on grass only, with no access to silage or concentrates, appeared in good body condition and had been vaccinated against toxoplasmosis and ovine campylobacteriosis, but not against ovine enzootic abortion (syn. enzootic abortion of ewes (EAE)).



Placenta, sheep: There is a focally extensive area of moderately thickened, non-translucent, slightly dry and brown intercotyledonary tissue and similarly dry and brown cotyledons (Photo courtesy of: Department of Pathobiology and Population Sciences, Royal Veterinary College, Hawkshead Lane, North Mymms, Hertfordshire, United Kingdom, AL9 7TA. The website address is www.rvc.ac.uk)

Gross Pathology:
Six out of the eight submitted aborted lambs were received with all or part of their placentas. Three placentas were grossly unremarkable. In the other three placentas, there was a focally extensive area of moderately thickened, non-translucent, slightly dry and brown intercotyledonary tissue and similarly dry and brown cotyledons. Large adjacent areas were moderately edematous with injected blood vessels. The aborted lambs were well-preserved with no evidence of maceration or mummification. Some aborted lambs had small amounts of serosanguinous fluid in the abdominal cavity and occasional subcutaneous or perirenal bruising.

Laboratory Results:
Laboratory testing was carried out on four of the six abortions. Culture of fetal stomach contents from three cases revealed a very heavy pure growth of hemolytic Gram-positive rods that were identified as *Listeria ivanovii*. Enriched culture was negative for *Campylobacter* spp. Placental smears stained with modified Ziehl-Neelsen were negative for *Brucella* spp., *Chlamydia* spp. and *Coxiella*



Placenta, sheep: Sections of cotyledon and intercotylendonary placenta are submitted for examination. (HE, 6X)

spp. PCR for *Toxoplasma gondii* and border disease virus were both negative.

Microscopic Description:
Chorioallantois, cotyledons and intercotyledonary tissue: The cotyledons and intercotyledonary tissue are extensively necrotic, expanded by edema and multifocal fibrin deposits and infiltrated by high numbers of viable and degenerate neutrophils, fewer macrophages and several prominent colonies of short, Gram-positive, rod-shaped bacteria (bacilli), measuring 0.5–2 µm in length (*Figure 2*). Multifocally, there are degenerate and necrotic trophoblasts, some of which contain intracytoplasmic Gram-positive bacilli. Several blood vessel walls, mainly arteries, contain intraluminal fibrin thrombi and the blood vessel walls are moderately to markedly infiltrated and expanded by high numbers of viable and degenerate neutrophils and fibrin.

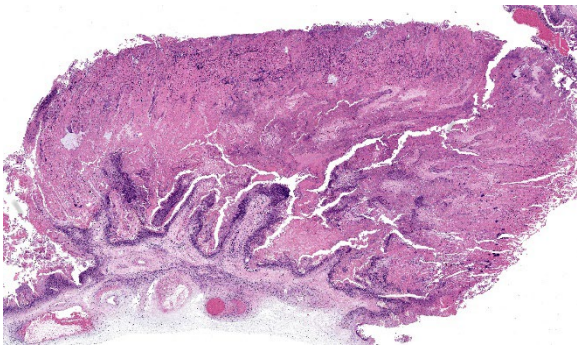
Contributor's Morphologic Diagnosis:
Chorioallantois, cotyledons and intercotyledonary tissue; acute, focally extensive, marked, necro-suppurative placentitis with large numbers of intralesional Gram-positive bacilli and multifocal, marked, necrotizing and neutrophilic vasculitis with acute intraluminal fibrin thrombi

Contributor's Comment:
The microscopic findings in the chorioallantois and the pure growth of *Listeria ivanovii* from fetal stomach contents support this abortion outbreak to be the result of listerial infection.

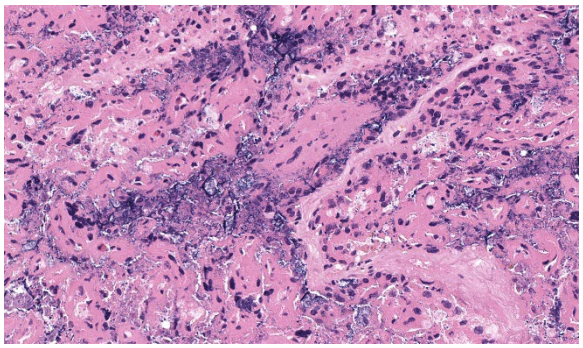
L. ivanovii, formerly known as *L. monocytogenes*, serotype 5 [8] is a recognized cause of ovine,[1,6,9] caprine[5] and bovine[3] abortions, but rarely causes other conditions. It appears to be especially pathogenic for sheep but is less commonly isolated than *L. monocytogenes*.[7]

The most common lesions in abortions caused by *L. monocytogenes* are necro-suppurative cotyledonary and intercotyledonary placentitis, autolysis of aborted fetuses, miliary foci of necrosis in the liver and spleen, and marked necrotizing enteritis,[4,7] whereas less is known about typical lesions in abortions caused by *L. ivanovii*.

The present case had necro-suppurative placentitis and fibrino-suppurative vasculitis, which has not been previously described in cases of ovine abortions due to *L. ivanovii*,[1,6,9] but has been described in a case of caprine abortion.[5] Interestingly, only rare, microscopically evident, necrotic foci in the liver were identified in this case, even though grossly apparent necrotic hepatitis is commonly described in ovine and bovine abortions due to



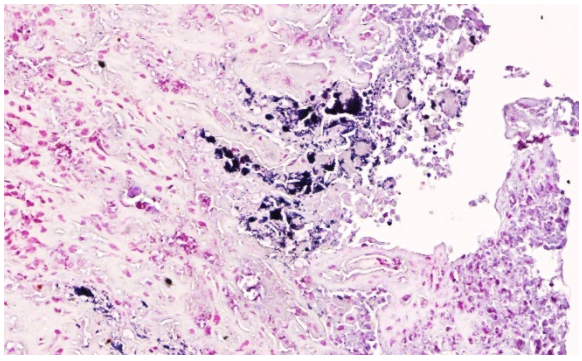
Placenta, sheep: There is diffuse coagulative and lytic necrosis of the cotyledon. (HE, 33X)



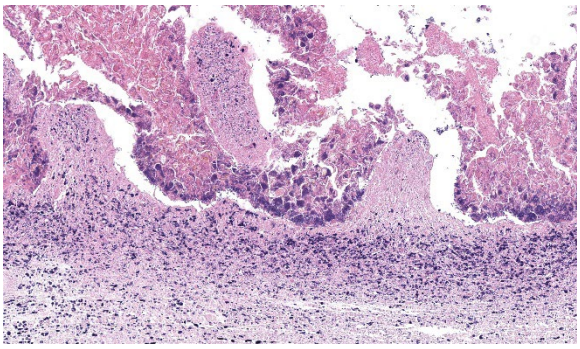
Placenta, sheep: There are innumerable bacteria within the necrotic cotyledon. (HE, 608X)

L. monocytogenes [7] and also in previous cases of ovine abortions due to *L. ivanovii*.[1,6,9] Also, the lungs had moderate neutrophilic bronchopneumonia which was likely the result of inhaled amniotic fluid with admixed listerial bacteria. Similarly, bronchopneumonia has been described in an ovine,[6] caprine[5] and bovine[3] abortion case caused by *L. ivanovii*.

In abortion outbreaks caused by *L. monocytogenes,* infection most often spreads by ingestion of food or water contaminated by feces, urine, placenta or vaginal discharge from affected ewes. Also, consumption of contaminated poor-quality silage is a well-known and important source of infection with *L. monocytogenes*.[7] Previously reported ovine abortion outbreaks caused by *L. ivanovii* often coincided with periods of cold and wet weather[1,6,9] and feeding of spoiled hay[9] or moldy hay and barley.[6] In the herein described abortion outbreak, the ewe lambs had only been on grass, suggesting that *L. ivanovii* infection may have been directly acquired from the pasture environment. This route of exposure has been proposed in a case series of weaned lambs in the United Kingdom with visceral *L. ivanovii* infections.[2] Interestingly, in this submission, the farmer reported that some abortions consisted of one dead lamb and one live unremarkable lamb including one of those submitted from which *L. ivanovii* was isolated. This is in contrast to previous reports.[1,6,9]



Placenta, sheep: The bacilli within the necrotic cotyledon are gram-positive. (Gram, 400X) (Photo courtesy of: Department of Pathobiology and Population Sciences, Royal Veterinary College, Hawkshead Lane, North Mymms, Hertfordshire, United Kingdom, AL9 7TA.)



Placenta, sheep: There is necrosis of the intercotyledonary epithelium and the trophoblasts are swollen with intracytoplasmic bacilli. (HE, 308X).

The present case highlights the importance of testing for common as well as less common abortion pathogens and sampling of several tissues for histology to confirm isolated pathogens microscopically.

Contributing Institution:
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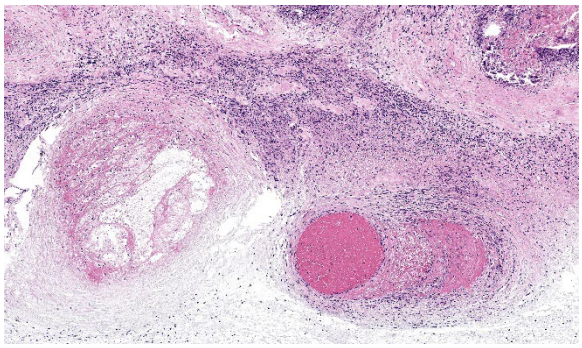

Placenta, sheep: There is necrotizing vasculitis and thrombosis of the endometrial vessels. (HE, 308X).

JPC Diagnosis:
Placenta: Placentitis, necrosuppurative, subacute, diffuse, severe, with vasculitis, thrombosis, and numerous extracellular and intratrophoblastic bacilli.

JPC Comment:
This week's moderator was Dr. Maggie Highland from the University of Wisconsin Veterinary Diagnostic Laboratory. Dr. Highland emphasized the diagnostic workup of small ruminant abortion in her pre-conference lecture and revisited these concepts in this first case which we excerpt again here.

From subgross magnification, tissue identification of the placenta in this case is facilitated by recognition of ruminant cotyledonary structure. Although there is marked coagulative (and subsequently lytic necrosis) present in this tissue, the state of tissue preservation is representative of typical abortion cases. The major diagnostic features present include vasculitis and innumerable intratrophoblastic cytoplasmic bacilli which provide a clear mechanism for abortion (interruption of blood flow and placental insufficiency). Conference participants considered several possible etiological agents including *Chlamydia* (which would also have vasculitis and intracytoplasmic bacteria) as well as *Brucella* (vasculitis) and *Coxiella* (lacks vasculitis, but centered on trophoblasts).[7] Other potential rule outs for small ruminant abortion include Border disease virus (and BVDV) as well as toxoplasmosis, though the latter is associated with cotyledonary necrosis without vasculitis.[7]

Our Gram stain was helpful for resolving *Listeria* as the probable agent given the size and slight curvilinear shape – we noted large numbers of gram-positive bacteria both free and within trophoblasts. Conference participants wondered if the large number of organisms present on this slide represented a particular tropism/niche (and corresponding fitness) of *L. ivanovii* for placenta. Likewise, we speculate that *Listeria* hitting twins harder than singleton lambs reflects a decreased placental reserve for twins over singletons. Although not performed at the JPC, Giemsa and/or Gimenez stains to enhance visualization of trophoblastic organisms is a helpful part of the diagnostic workup.[7] Culture of fetal abomasal contents may prove vital in instances where the placenta lacks diagnostic information. Dr. Highland emphasized reporting PCR/culture results as "not detected" or cultures as "no growth: rather than 'negative' in both instances– this distinction carries some weight in animals previously treated with antibiotics and precludes potential client misinterpretation of "negative" results.

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3. Gill PA, Boulton JG, Fraser GC, Stevenson AE, Reddacliff LA. Bovine abortion caused by *Listeria ivanovii*. *Aust Vet J*. 1997;75(3):214.
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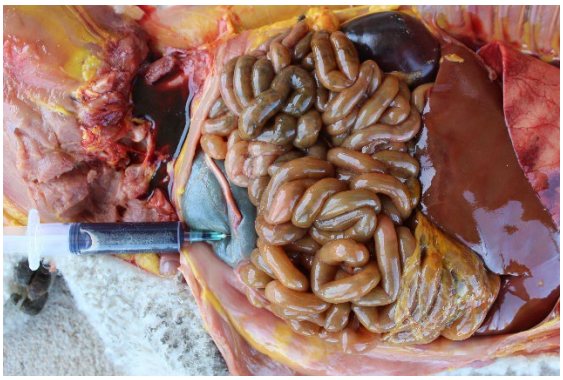
CASE II:

Signalment:
<30-day-old (neonate), female, Texel lamb, *Ovis aries*

History:
Death of 20, <30-day-old lambs was reported in a flock of 450 nonvaccinated Texel sheep in a farm in the department of Rivera, Uruguay, in October 2023 (spring season in the Southern Hemisphere). The flock was grazing natural grassland on a low terrain that used to be used for the cultivation of rice, and following a severe flooding event, the affected lambs exhibited severe apathy and hemoglobinuria, progressing to death within 24-48 hours.



Liver, lamb: There is diffuse dark red discoloration of the right kidney and dark red urine (hemoglobinuric nephrosis). The adipose and subcutaneous tissues are yellow (jaundice), and the skeletal muscles are pale pink (consistent with anemia). (Photo courtesy of Instituto Nacional de Investigación Agropecuaria (INIA), La Estanzuela, Colonia 70006, Uruguay. www.inia.uy)

Gross Pathology:
The main gross findings included yellowish discoloration of the subcutaneous and adipose tissues (jaundice), diffuse bilateral dark-red discoloration of the kidneys with dark-red urine filling the urinary bladder (hemoglobinuria), pale skeletal muscles (anemia) (Figure 1), dark pink to red mottled lungs with rubbery/meaty texture and intraluminal bronchial and tracheal froth (pulmonary edema).

Laboratory Results:

	Tissues	
Tests for detecting *Leptospira*	**Liver**	**Kidney**
Immunohistochemistry*	Positive	Negative
qPCR for pathogenic	Positive	Positive

Leptospira spp. (targeting the *lipL32* gene)		
PCR targeting the 16S rDNA gene followed by sequencing for species identification	*L. kirschneri*	*L. kirschneri*

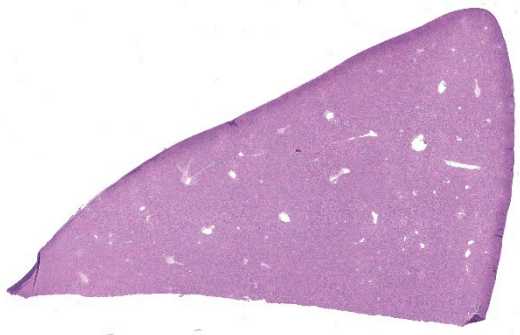
*Using *Leptospira* multivalent fluorescent antibody conjugate (LEP-FAC) as primary antibody.

Microscopic Description:
Liver: diffusely there is disruption of the histoarchitecture of hepatic cords in the centrilobular (periacinar) areas with a bridging pattern. Within these regions hepatocytes are frequently dissociated and individualized from the hepatic cords and are either swollen with vesicular nucleus (hydropic degeneration) or shrunken with angular cell borders and hypereosinophilic cytoplasm and nuclear pyknosis or karyorrhexis (necrosis) (Figure 2). In these areas there is multifocal infiltration of neutrophils, lymphocytes and histiocytes, occasionally grouping around necrotic hepatocytes, although similar inflammatory infiltrates are present in the sinusoids of the midzonal and periportal regions where hepatocytes are preserved. Portal tracts are moderately and multifocally expanded by inflammatory cells, notably histiocytes, lymphocytes and rare neutrophils, and/or fibroblasts embedded in a loose extracellular collagenous matrix (fibrosis/fibroplasia).

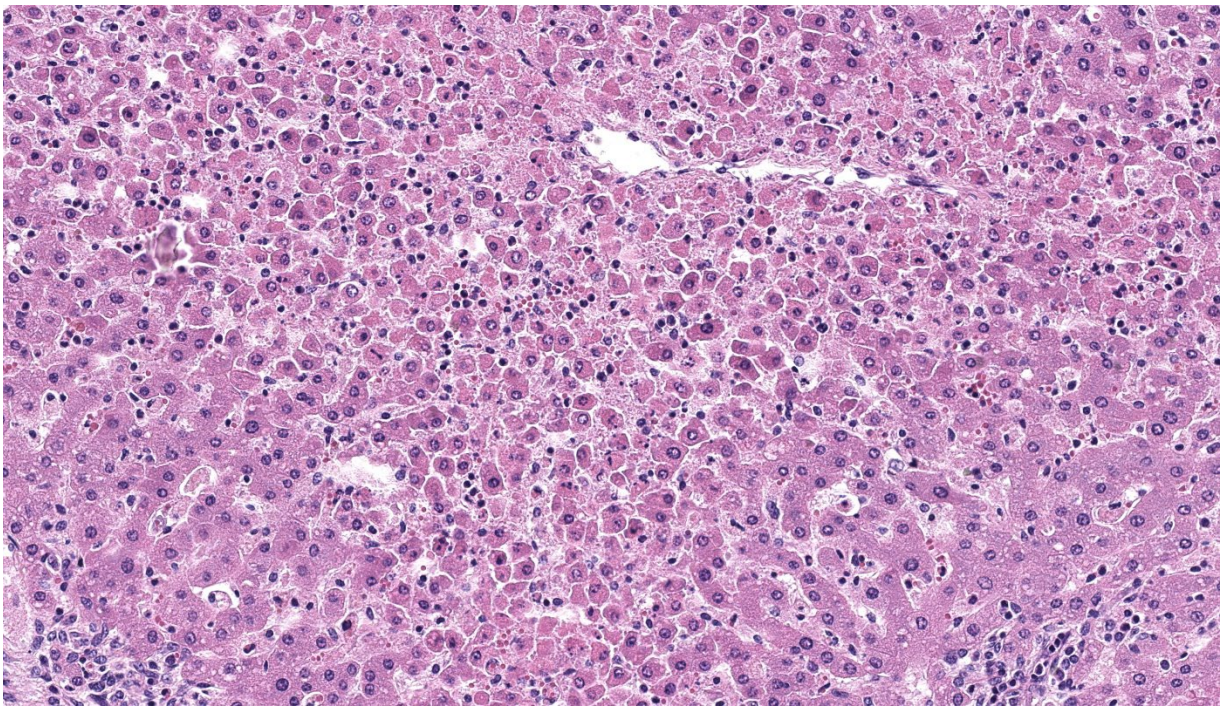
Contributor's Morphologic Diagnosis:
1. Liver: multifocal random neutrophilic and lymphohistiocytic hepatitis with severe diffuse acute periacinar hepatocellular necrosis, lamb.
2. Liver: hepatitis, portal, lymphocytic and histiocytic, with fibrosis, lamb

Contributor's Comment:
The clinical signs and gross pathological findings in this lamb were highly suggestive of acute (likely intravascular) hemolysis. Differential diagnoses include "yellow lamb disease" (a poorly characterized enterotoxemia presumably caused by *Clostridium perfringens* alpha toxin), *Mycoplasma ovis* infection, and toxic plants causing hemolysis (i.e. *Allium* spp., *Brassica* spp., *Indigofera* spp., *Urochloa arrecta*).[2,3,8,9] In older sheep, chronic copper toxicity is characterized by similar clinical and pathological findings.[2] In this case, an etiologic diagnosis of leptospirosis was established based on intralesional identification of *Leptospira* spp. antigen by immunohistochemistry in the liver (Figure 3), and molecular identification of *Leptospira kirschneri* in the liver and kidney (see laboratory results section).

The nature and distribution of the microscopic lesions in the liver of the lamb, notably diffuse acute periacinar hepatocellular degeneration/necrosis, suggest that they probably resulted, at least in part, from hypoxia perhaps secondary to hemolytic anemia. However, a direct action of leptospiral invasion and multiplication in the liver, as high-



Liver, lamb: One section of liver is submitted for examination with no obvious changes at subgross magnification. (HE, 7X)



Liver, lamb: Within centrilobular and midzonal areas, there is disassociation of hepatic plates with individualization and rounding up of hepatocytes. (HE, 381X)

lighted immunohistochemically, probably contributed to the inflammatory and necrotizing lesions seen in the hepatic parenchyma. It was not clear whether the portal lesions in this case were due to *Leptospira* infection or a pre-existing incidental finding. No *Leptospira* antigen could be clearly identified in the portal tracts or bile ducts. Notably, despite the jaundice seen grossly, no significant bile stasis was observed histologically in the liver, suggesting pre-hepatic jaundice probably resulting from hemolysis.

Leptospirosis is a zoonotic disease of worldwide distribution caused by spirochetes in the genus *Leptospira*. The taxonomy of the genus has evolved enormously in recent years, and now contains several pathogenic species such as *L. interrogans*, *L. borgpetersenii*, *L. noguchii*, and *L. kirschneri*, within which more than 350 serovars have been identified.[4] While a wide range of wild and domestic animal species can be infected by a wide range of serovars, some serovars are adapted to a given animal species (maintenance hosts) and cause disease in another species (incidental hosts).[1] The major host-adapted serovars are Hardjo in cattle and sheep, Icterohaemorrhagiae and Copenhageni in rats, Ballum in mice, Canicola in dogs, and Pomona and Bratislava in pigs. Dogs, cattle, pigs, and horses are the main incidental domestic animal hosts and suffer from the disease in diverse degrees from asymptomatic to lethal.[4]

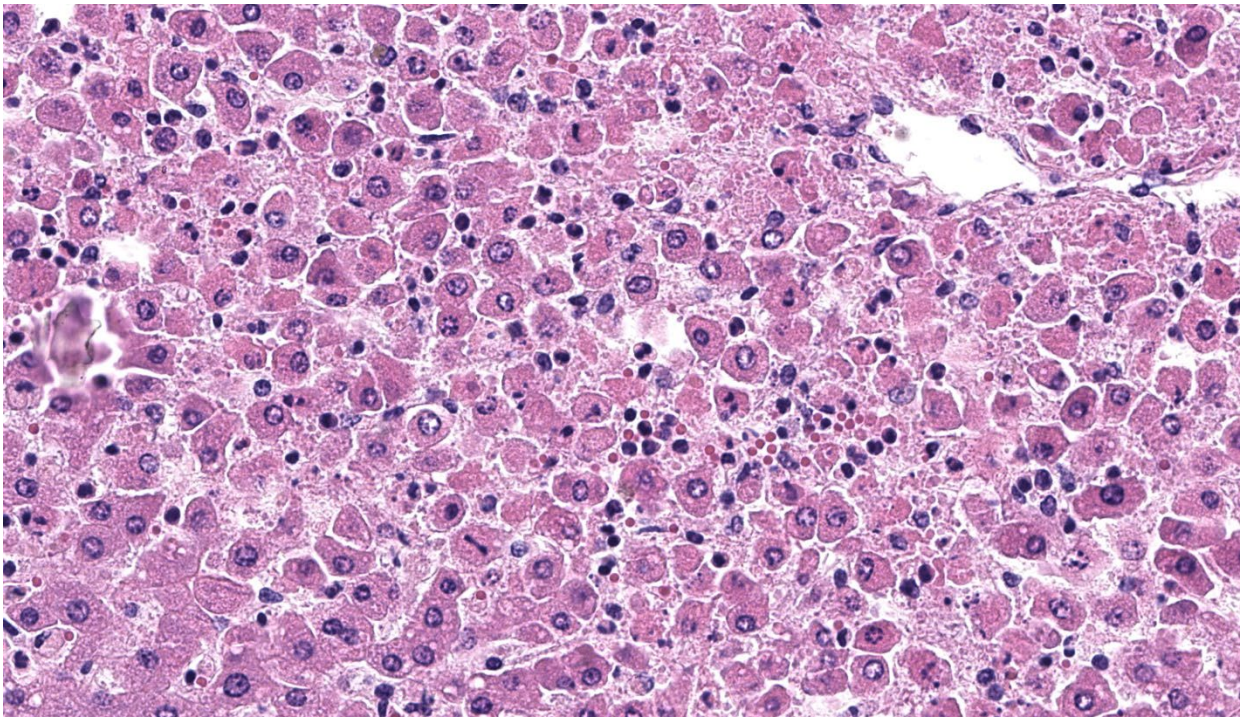
The natural niche of pathogenic *Leptospira* spp. are the proximal renal tubules and the genital tract in certain maintenance hosts. Transmission might be direct through contact with urine, lochia, milk, genital mucosa (venereal transmission), or transplacental. Infection of incidental hosts is usually indirect, via environmental contamination by urine of carrier animals. Under ideal wet, warm, and neutral to slightly alkaline conditions leptospires may survive for weeks or months in water-logged soil or water. Thus, in temperate climates leptospirosis occurs especially in the wet season and the risk of exposure and infection is increased by heavy

rainfall, agricultural irrigation and/or flooding. In tropical and subtropical areas, the disease can occur year-round.[1,4]

In incidental hosts, infection may cause severe acute or subacute systemic disease during bacteremia (leptospiremic phase), particularly in young animals. After leptospiremia has ceased, chronic disease can manifest as abortion, stillbirth, infertility, or recurrent uveitis. The acute/subacute systemic disease is clinically characterized by fever, jaundice, hemolytic anemia, hemoglobinuria, pulmonary congestion, and occasional meningitis.[1]

Leptospira genomes encode many proteins of unknown or poorly defined function and the molecular bases for virulence are poorly understood. Adhesion to host cells and components of the extracellular matrix likely plays a role in virulence. Flagellar motility, notably controlled by chemotaxis, is key to *Leptospira* virulence, as are several mechanisms allowing the bacteria to escape or resist the host immune response. How the lipopolysaccharide (LPS) contributes to virulence is still poorly known, but mutations that alter the LPS structure attenuate virulence. Pathogenic *Leptospira* spp. also produce sphingomyelinase-like enzymes with phospholipase C, hemolytic, and apoptotic activities. As these are absent in the saprophytic *Leptospira* spp. they are thought to contribute to virulence.[4]

Leptospirosis is a complex disease; its pathogenesis has not been fully elucidated and varies for different serovars in different animal species.[1] Leptospires entry to the body through mucous membranes (conjunctival, oral, genital) or via damaged or compromised skin, without inducing notable lesions at the point of entry.[4] The mechanisms used to enter the bloodstream through endothelial cells are not well understood; however, motility seems to be essential for pathogenic *Leptospira* spp. to cross tissue barriers, which is thought to occur through intracellular

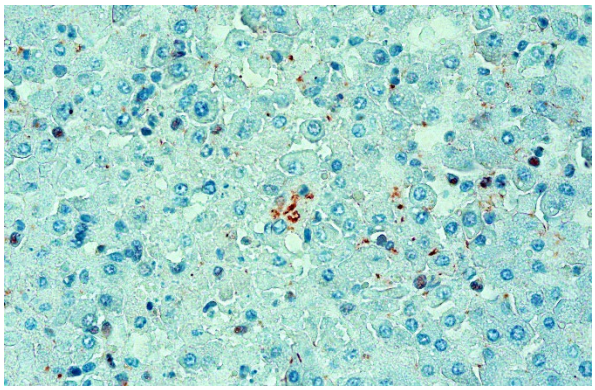


Liver, lamb: Individualized hepatocytes demonstrate granular eosinophilic cytoplasm with variable pyknosis and karyorrhexis. Hepatocytes are surrounded by abundant granular eosinophilic debris which fills sinusoids; there are few intact hepatocytes. (HE, 721X).

translocation. During the leptospiremic phase (hematogenous dissemination), which can last up to 7 days, the main symptom is fever, while clinicopathological findings frequently include leukocytosis and thrombocytopenia. Hemorrhages in the liver, kidneys, and/or lungs can develop in the acute phase of the disease, at which stage inflammation is usually absent.

After rapid hematogenous spread, leptospires interact through adhesins with a range of host tissue proteins in different organs.[4] The pathogen multiplies especially well in the liver, kidney, lungs, placenta, mammary gland, and cerebrospinal fluid (CSF).[1] *Leptospira* have developed strategies to evade host defenses and resist the complement system. Although generally considered an extracellular pathogen, it is also able to penetrate host cells and survive inside macrophages and other phagocytes involved in the innate immune response. Leptospires have also developed strategies to escape recognition by pattern-recognition receptors of the innate immune system that recognize microbe-associated molecular patterns (i.e. Nod-like and Toll-like receptors). However, the innate immune system can detect *Leptospira* and activate an immune response and the expression of cytokines.[4] After tissue colonization, hepatitis, and hepatocellular death (apoptosis/necrosis) can be seen early in the disease associated with leptospiral invasion. In the kidneys, interstitial nephritis is seen, but can be quite discrete, whereas hemoglobinuria can occur in ruminants.[4] Development of agglutinating and opsonizing antibodies after approximately 6-7 days clears the agent from most organs except from immunoprivileged sites such as the proximal tubules of the kidneys, the CSF, and the vitreous humor of the eyes. Certain serovars can also survive and establish chronic infection in the genital tract of maintenance hosts.[1]

In sheep, *Leptospira* infection is usually asymptomatic, although severe disease



Liver, lamb. There is scattered strong granular to linear immunoreactivity for leptospiral antigen within Kupffer cells. (anti-Leptospira spp., 400X) (Photo courtesy of Instituto Nacional de Investigación Agropecuaria (INIA), La Estanzuela, Colonia 70006

occurs sporadically in young animals. In neonate lambs, leptospirosis is usually characterized by leptospiremia with hemolysis, anemia, and death. There is little information on the species and serovars involved in fatal cases of leptospirosis in sheep. In Uruguay, sporadic outbreaks of acute fatal leptospirosis in lambs associated have been associated with *L. interrogans* serogroup Pomona serovar Kennewicki.[5] *L. kirschneri*, the species detected in the case described herein, has been identified as one of the dominant *Leptospira* species (along with *L. interrogans*) associated with human leptospirosis in central Malaysia.[7]

Regardless of the acting species, it is important to determine the serovars involved in outbreaks of leptospirosis and/or infecting animals and humans in different geographic regions, so that circulating serovars can be included in vaccines, considering that immunity is serovar specific. Unfortunately, the serovar involved in the ovine case presented here could not be identified as attempts to culture and isolate this labile and fastidious organism were unsuccessful. Of note, the serovar Kennewicki which has been isolated from sheep,[5] cattle[10] and humans[6] in Uruguay is not included in the locally available commercial vaccines for livestock.

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JPC Diagnosis:
Liver: Hepatitis, necrotizing, acute, diffuse and centrilobular, moderate, with hepatocellular disassociation.

JPC Comment:
The contributor provides an excellent summary of leptospirosis that weaves in some of the salient features of this case. Histologic changes were apparent even from low-magnification and we agree with the contributor that the underlying pathogenesis is acute centrilobular hepatitis that is probably augmented by hypoxic effects. Although anemia is more of a clinical diagnosis than a histologic one, we could not help but notice the paucity of erythrocytes within sinusoids that corresponds to the intravascular hemolysis characteristic of this agent. Dissociation (individualization) of hepatocytes was another important feature of this case which has been attributed to hepatic infectious with several species of *Leptospira*.[11] These bacteria can infiltrate the space of Disse and cause dissociation of hepatocytes through physical disruption and breakdown of intracellular tight junctions. A second consequence of the loss of tight conjunctions is leakage of bile from the canaliculus – this is a form of intrahepatic cholestasis that lacks dilatation of bile canaliculi.[11] In this case, the lack of bile plugs despite systemic icterus fits with this interpretation.

We also ran a Masson's trichrome stain to evaluate liver structure and concurrent pathology. We differed from the contributor in that we did not observe hepatic fibrosis, to include within centrilobular regions with hepatocyte loss. This argues against a prolonged event, to include secondary hypoxic changes and/or sinusoidal outflow obstruction (see Conference 12, Case 2 of this year for a relevant example). Finally, we debated the relevance of periportal cellular infiltrates. While some participants considered oval cell hyperplasia, the group consensus was for extramedullary hematopoiesis given the age of this animal and concurrent loss of erythrocytes necessitating demand.

The lack of histologic renal changes in this young lamb likely reflected a very acute course of disease and an insufficient time course for bacteremia to bring the agent to the lumina of renal tubules via the renal vasculature. That stated, the positive qPCR result in the kidney is intriguing, and we wonder whether the detection of nucleic acid therein could reflect cross-contamination.

References:

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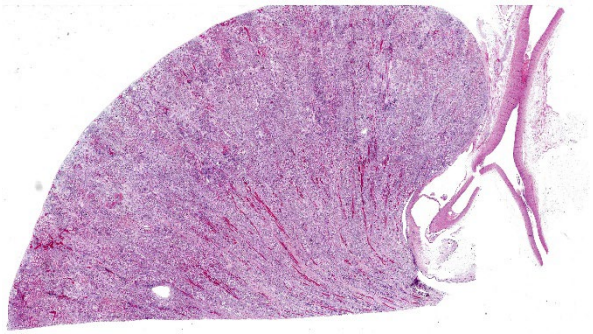
<u>CASE III</u>:

Signalment:
3-year-old, male, Merino X, *Ovis aries*, ovine

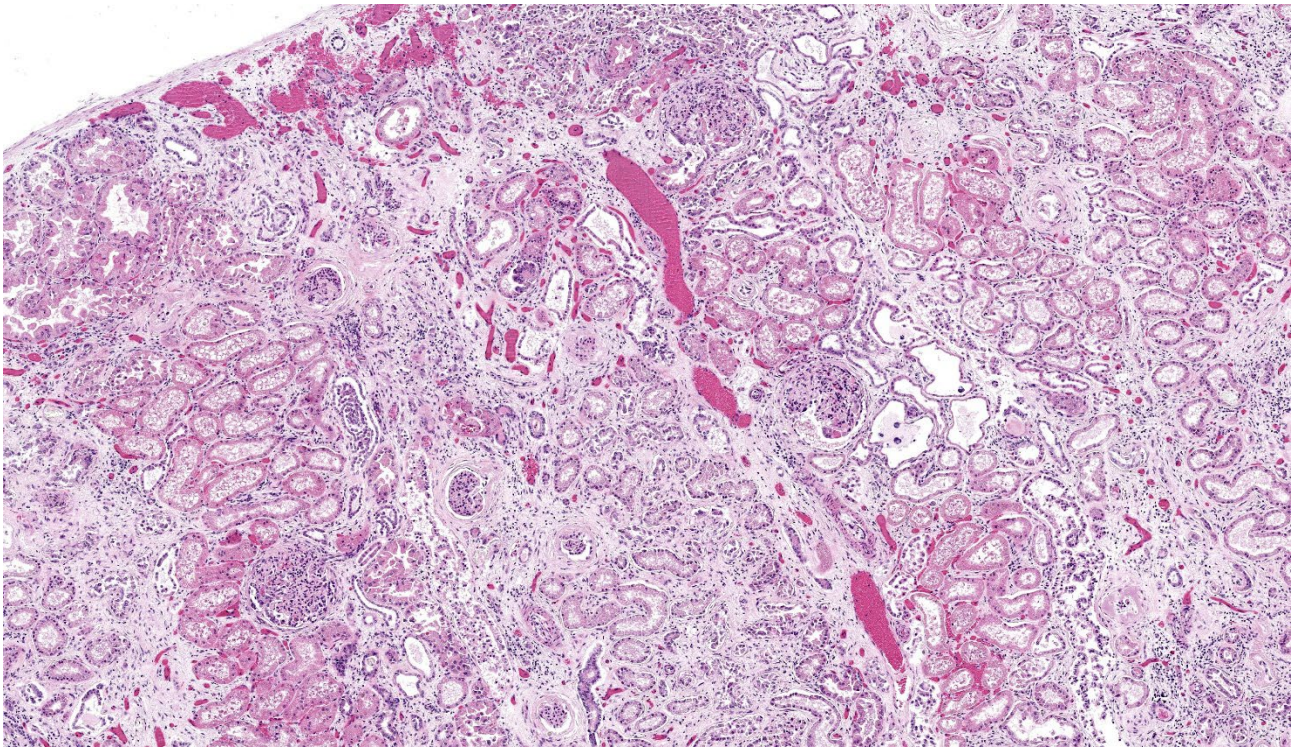
History:
Animal found dead two weeks after moved onto a paddock with a predominance of soursobs (*Oxalis cernua*) in pasture.

Gross Pathology:
Post-mortem performed by referring veterinarian. Post mortem findings included heart petechial haemorrhages, leathery appearance of renal capsules and mild hepatomegaly.

Microscopic Description:
There is moderate multifocal predominantly cortical and less often medullary tubular loss, interstitial fibrosis and mild multifocal interstitial infiltrates of lymphocytes and plasma cells. Remnant tubules are often lined by degenerate, necrotic or attenuated epithelium. Bowman's capsules and glomerular mesangium are thickened by fibrosis, with frequent synechia and scattered obsolescent glomerular tufts. Tubules are frequently ectatic, expanded up to 6 times normal diameter and filled with amorphous translucent eosinophilic material (protein), occasional sloughed epithelial cells and clear-yellow to lightly basophilic refractile crystals. Crystals are com



Kidney, sheep: A section of kidney is submitted for examination. (HE, 8X)



Kidney, sheep: Within the cortex, there is loss of tubules, marked interstitial fibrosis, mild lymphoplasmacytic inflammation, and various glomerular changes including variation in size, hypercellularity, and periglomerular fibrosis. (HE, 71X)

posed of radiating angular shards of variable size and shape and are birefringent under polarised light (calcium oxalate).

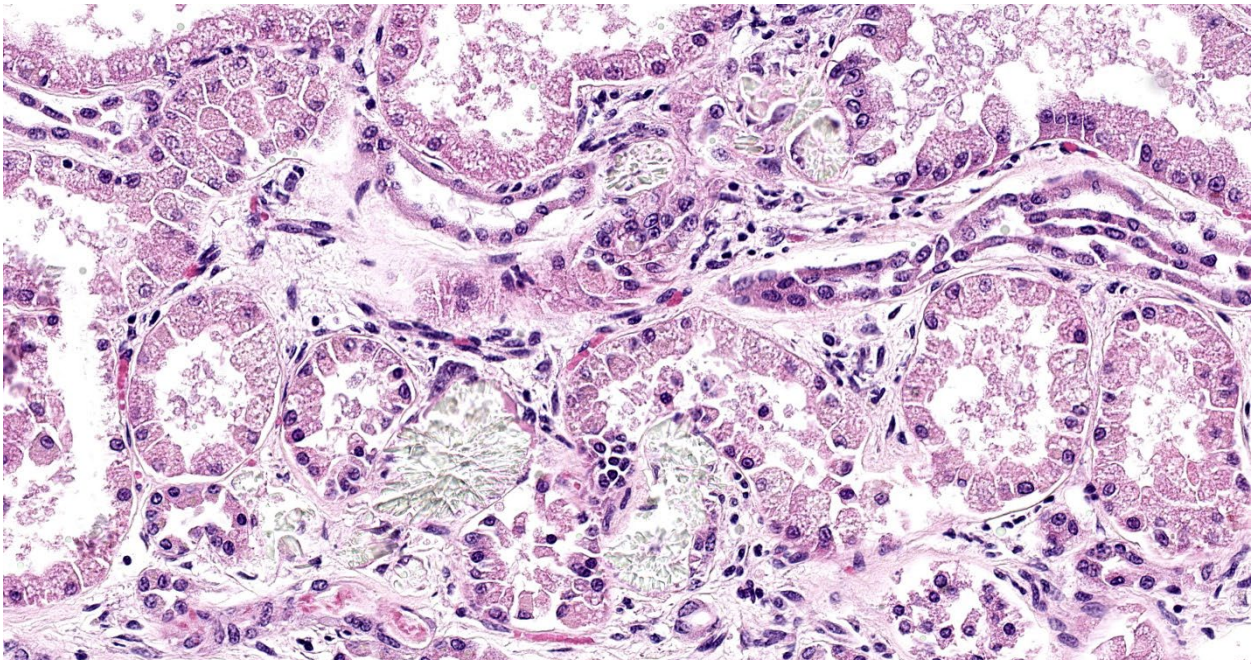
Contributor's Morphologic Diagnosis:
Lymph nodes, spleen and liver: T-cell lymphoid hyperplasia, severe, diffuse
Liver: Pericholangitis and perivasculitis, mild, multifocal, lymphoplasmacytic with erythrophagocytosis and extramedullary hematopoiesis

Contributor's Comment:
Oxalate nephrosis is the outcome of excessive calcium oxalate accumulation within renal tubules, forming insoluble crystals and resulting in tubular obstruction and acute renal failure.[5] Tubular epithelial injury may also result from inflammation-mediated free-radical damage and interference with oxidative phosphorylation; however there is conjecture over the concentrations required to elicit these changes.[5,12] Oxalate is the ionic form of oxalic acid and is derived from a number of sources.[4] Endogenous production occurs in the liver via oxidation of glycolate to form glyoxalate or via the metabolism of hydroxyproline, a component of collagen. This is followed by conversion to oxalate by the action of lactate dehydrogenase.[4] Primary hyperoxaluria (PH) is the predominant cause of oxalate toxicity in humans, caused by increased endogenous production due to defective enzyme activity.[4] This may involve defects in alanine glyoxalate aminotransferase (PH1), glyoxalate/hydroxypyruvate reductase (PH2), or mitochondrial 4-hydroxy 2-oxoglutarate adolase (PH3).[4] Primary hyperoxaluria is rare in domestic species, but has been reported in cats, dogs, and Beefmaster cattle, and is suspected in Australian wildlife species Gilbert's potoroo (*Potorous gilbertii*) and koalas (*Phascolarctos cinereus*).[1,5,6,13]

Secondary oxaluria predominates in domestic and non-domestic species, caused by increased intestinal absorption or increased intake of oxalates or oxalate precursors such as ethylene glycol or ascorbic acid (vitamin C).[1,4] In ruminants, oxalate toxicity is most commonly caused by ingestion of plants containing soluble oxalates, usually in the form of sodium or potassium oxalate. [3,5,10] This includes a vast range of plant species but is most commonly reported following ingestion of *Halogeton glomeratus* (halogeton), *Sarcobatus vermiculatus* (greasewood), *Rheum rhaponticum* (rhubarb), *Oxalis* spp. (soursobs) and *Rumex* spp. (sorrel, dock), *Portulaca oleracea* (purslane), *Chenopodium album* (lamb's quarter), *Bassia hyssopifolia* (bassia), *Amaranthus* spp. (pigweed), *Salsola tragus* (Russian thistle) and *Beta vulgaris* (sugar beets).[3,5,10] Oxalate concentration in these plants is dependent on a number of factors and varies between species. Higher concentrations are found in leaves rather than stems and seeds, and young plants commonly have higher concentrations than aged plants.[5,10] Concentration is also known to decrease as the plant dries; however, plants with extremely high concentrations may be potent enough to cause intoxication even after a dry summer.[5,10]

After ingestion, soluble oxalates are rapidly absorbed from the gastrointestinal tract, resulting in acute disease as soon as 2 hours post-ingestion.[9] In plasma, oxalates complex with calcium, causing hypocalcemia and precipitation of calcium oxalate within renal tubules and the vascular lumens of various tissues, resulting in vascular necrosis, haemorrhage and acute renal failure.[5,10] The kidneys are the most severely affected due to their primary role in oxalate excretion.[9] Ruminants are more tolerant of ingested oxalates than monogastrics due to the action of ruminal microbes such as *Oxalobacter formigenes,* which degrade oxalate to produce carbon dioxide and formate.[5,11]

Clinical signs of acute toxicity are caused largely by hypocalcemia and include ruminal stasis and subsequent bloat; twitching and



Kidney, sheep: Within the cortex, there is loss of tubules, marked interstitial fibrosis, mild lymphoplasmacytic inflammation, and various glomerular changes including variation in size, hypercellularity, and periglomerular fibrosis. (HE, 71X)

tetany which may progress to seizures; and weakness and bradycardia.[9] Animals that survive acute hypocalcemia may succumb within a number of days to acute renal failure, characterised by anorexia, depression, weight loss and diarrhoea.[9] Sheep are more commonly affected than cattle, however both species are equally susceptible under experimental conditions, suggesting that differing grazing patterns may contribute to differences in natural susceptibility.[5] The characteristic clinical and pathological findings of acute oxalate intoxication in sheep include hypocalcemia, azotemia, and nephrosis associated with precipitation of birefringent calcium oxalate crystals in renal tubules.[3,7,8]

Ruminal oxalate-degrading bacteria increase with gradual exposure to higher concentrations of oxalate, allowing adapted animals to consume greater quantities.[2,3,11] The development of acute toxicity also varies depending on rate of consumption, the availability of water and other feed and the total amount consumed.[10] Therefore, management relies on limiting availability of oxalate-containing plants and providing access to other feed sources.[9]

Contributing Institution:
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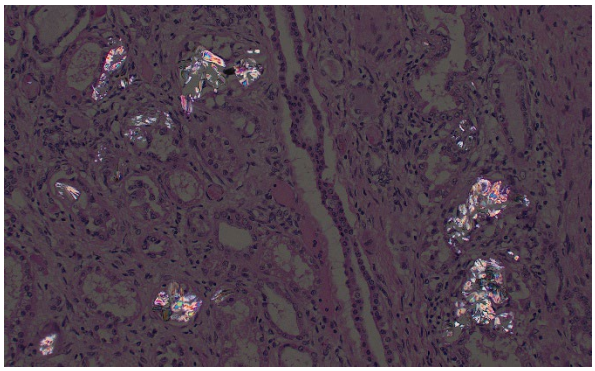
https://www.adelaide.edu.au/vet/about-us/pathology

JPC Diagnosis:
1. Kidney: Tubular degeneration, necrosis, and loss, diffuse, with proteinosis, tubulorrhexis, and numerous oxalate crystals.
2. Kidney: Nephritis, interstitial, lymphoplasmacytic, chronic, diffuse, moderate, with glomerular synechiae and periglomerular and interstitial fibrosis

JPC Comment:
This third case prompted intense discussion among participants. The contributor provides a outstanding histologic section to accompany a quality summary of oxalate toxicosis. We homed in on the disparity between acute and chronic changes on the slide, aided by Masson's trichrome, Jones methenamine silver, and PAS stains. We agree that the tubular changes, tubulorrhexis and leakage of the urinary filtrate into the interstitium, where it mimics edema fluid) reflect a primary process of a subacute time course, though we could not agree that the chronic interstitial nephritis followed from this same tubular obstruction. Masson's trichrome showed marked interstitial and periglomerular fibrosis that does not fit with the relatively short time course between introduction to pasture and death of this animal. To satisfy these concepts for this case, we created two separate morphologic diagnoses and interpreted this case as superimposed acute renal failure on a background of chronic subclinical renal insult.



Kidney, sheep: Oxalate crystals are birefringent with polarized light. (HE 400X)

Some participants also commented on the possibility of calcium carbonate uroliths given that the morphology of some crystals did not completely fit with oxalates. Calcium carbonate uroliths are also common in ruminants, particularly when calcium availability is high. Habituation of *Oxalobacter* in the rumen to oxalate-containing forage presents one such opportunity as breakdown of calcium oxalate increases free calcium significantly.[11] It is also worth noting that oxalate crystals can also be a normal finding in the urine of ruminants, especially when concentrated.[11] In the present case, there is clear association with tubular changes to include tubulorrhexis that is outlined clearly with JMS and PAS stains.

There are other considerations for this case that were briefly entertained by the contributor already. Primary hyperoxaluria has been described in sheep breeds, to include the Zwartbles (a Dutch breed).[14] The condition is autosomal recessive and involves a loss of function missense mutation in the gene encoding for alanine-glyoxylate aminotransferase (Type 1 hyperoxaluria). The associated nephropathy is severe and heterozygous sheep may still develop histologic changes within the kidney.[14] That this animal was cross bred raises the possibility of a similar gene interaction. Finally, production of oxalates by fungi such as *Aspergillus* remain an uncommon possibility. Nephrosis following ingestion of contaminated feed has been previously described.[15] It is possible that this case reflects a multifactorial pathogenesis that leaves conference participants satisfied not matter their prevailing theory of the case.

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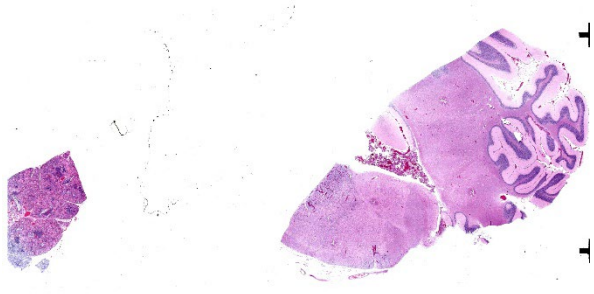
CASE IV:

Signalment:
2-month-old, female, Toggenburg goat (*Capra aegagrus hircus*)

History:
Presented with clinical complaints of vomiting and lethargy. Huge amount of fluid in peritoneal cavity (ascites). No abnormalities found on echocardiac examination and blood examination. Laparascopy performed: suspicion of encapsulating peritoneal sclerosis. Died at night.



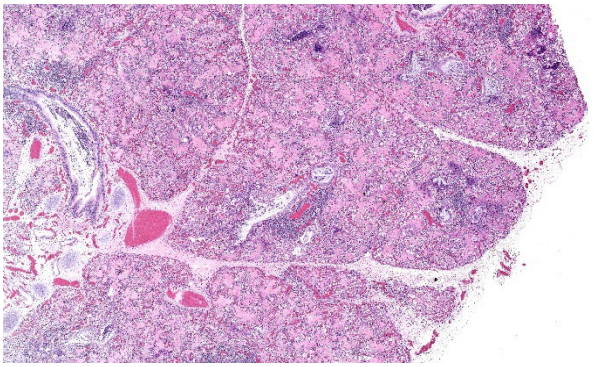
Lung and brainstem/cerebellum, goat: There is diffuse atelectasis and foci of hypercellularity in the lung at subgross magnification. (HE, 8X)

Gross Pathology:
A 2-month-old female Toggenburg goat kid presented for nystagmus, incoordination, and inability to ambulate. Several days prior, this kid's sibling was euthanized for similar severe neurologic signs.

Laboratory Results:
Immunohistochemical staining for Caprine Arthritis and Encephalitis Virus was positive on brainstem and lung tissue (Michigan State University, Veterinary Diagnostic Laboratory).

Aerobic culture grew few colonies *Streptococcus infantarius, Streptococcus equinus,* and coagulase negative *Staphylococcus* spp. *Mycoplasma spp.* PCR was negative.

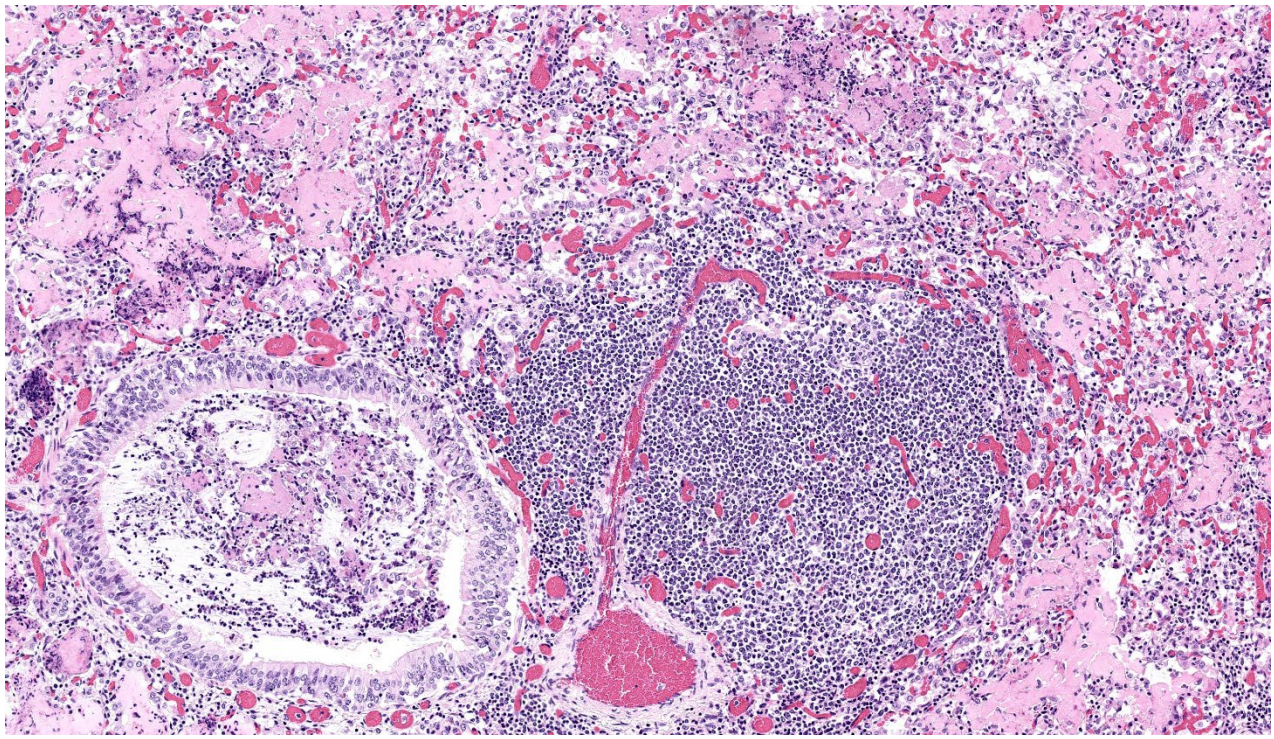
(Ohio Department of Agriculture, Animal Disease Diagnostic Laboratory).



Lung, goat. There is marked BALT hyperplasia, and airway lumina contain a cellular infiltrate with abundant mucus. Alveoli are filled with brightly eosinophilic edema fluid and fibrin and a cellular exudate. (HE, 43X)

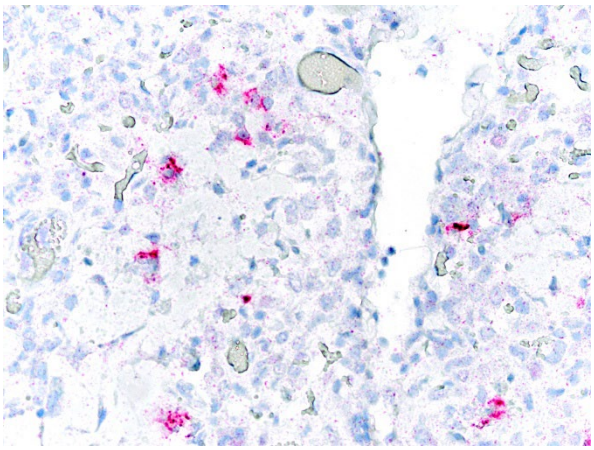
Microscopic Description:
Brainstem and cerebellum: Regionally affecting the brainstem white matter along the midline is an area of neuropil loss and replacement by numerous macrophages with foamy eosinophilic cytoplasm with eccentrically placed nuclei (gitter cells) and mild to moderate numbers of reactive astrocytes, microglia, and admixed lymphocytes and fewer plasma cells. Myelin sheaths are frequently replaced by gitter cells and are rarely dilated with either swollen hypereosinophilic axons (spheroids) or macrophages (digestion chambers). Scattered throughout the affected region is abundant eosinophilic cellular debris. Virchow Robin's spaces are multifocally expanded by numerous lymphocytes, histiocytes, and fewer plasma cells (perivascular cuffs).

Lungs: Diffusely alveoli are filled with large amounts of eosinophilic amorphous proteina-



Lung, goat. There is marked BALT hyperplasia, and airway lumina contain a cellular infiltrate with abundant mucus. Alveoli are filled with brightly eosinophilic edema fluid and fibrin and a cellular exudate. (HE, 43X)

ceous fluid (alveolar proteinosis) and multifocal admixed foci of necrotic cellular and



Lung, goat. Multifocally, mononuclear cells demonstrate strong cytoplasmic immunolabeling for CAEV. (anti-CAEV, 400X) (Photo courtesy of The Ohio State University College of Veterinary Medicine, Department of Veterinary Biosciences, https://vet.osu.edu

nuclear karhyorrhectic debris. Multifocally, alveoli are lined by plump type II pneumocytes (type II pneumocyte hyperplasia). Vari ably, alveolar septa are expanded by moderate numbers of lymphocytes, histiocytes and

fewer plasma cells. Bronchi and large bron chioles contain abundant degenerate neutrophils admixed with eosinophilic cellular and karyorrhectic debris and moderate amounts of basophilic mucin. Lymphoid tissue surrounding bronchi and bronchioles is moderately hyperplastic, with frequent prominent germinal centers.

Contributor's Morphologic Diagnosis:
Brainstem: Severe, focally extensive, lymphohistiocytic leukoencephalitis with axonal degeneration and neuropil necrosis

Lungs:

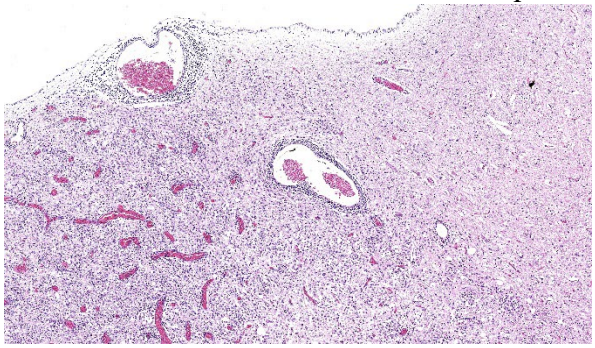
a. Marked, diffuse, chronic, lymphohistiocytic interstitial pneumonia with type II pneumocyte hyperplasia and alveolar proteinosis

b. Moderate, multifocal, acute, suppurative bronchopneumonia

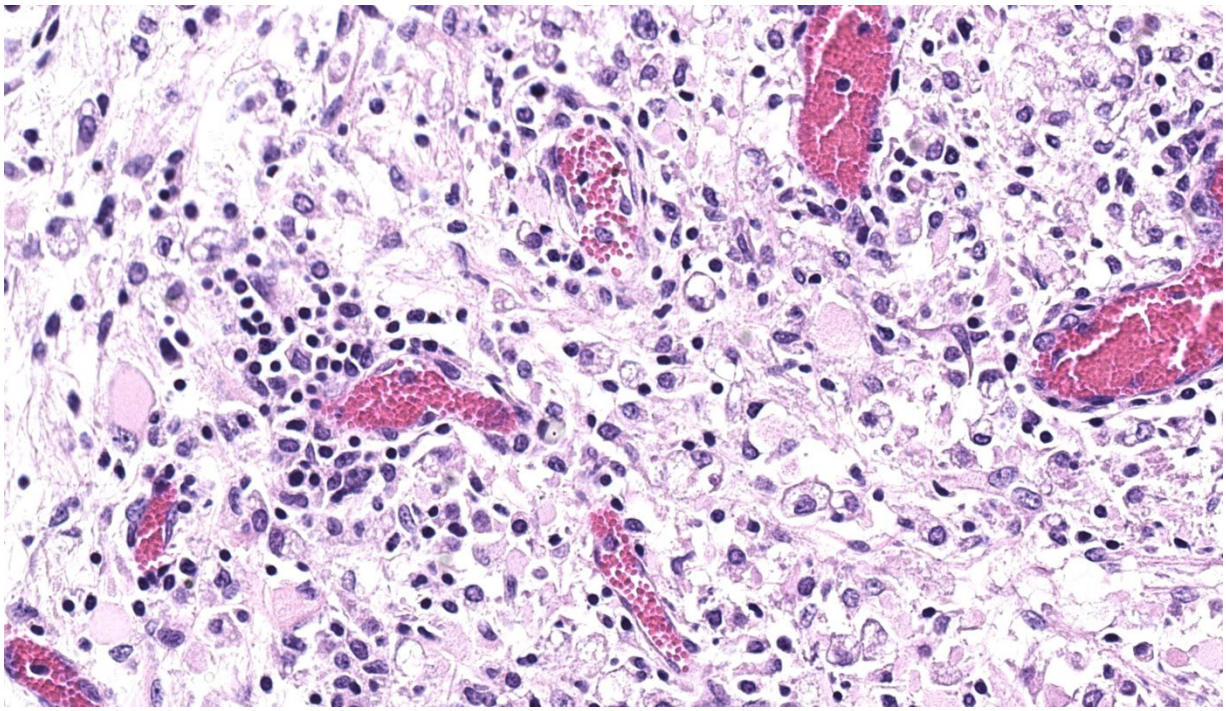
Contributor's Comment:
Brainstem lesions, interstitial pneumonia, and immunohistochemistry results in this case are consistent with small ruminant lentivirus infection (SRLV), or Caprine Arthritis and Encephalitis Virus (CAEV).

CAEV is a lentivirus within the Retrovirus family. CAEV and Maedi-Visna virus (MV), also called Ovine Progressive Pneumonia, are together referred to as the small ruminant lentiviruses (SRLV).[4] Previously CAE and MV were considered species-specific, with CAEV affecting goats and MV affecting sheep; however, several studies have documented cross-species and co-infections demonstrating both species are susceptible to each virus.[1, 7]

Other prominent lentiviruses include Equine Infectious Anemia Virus, Bovine Immunodeficiency Virus, and Feline Immunodeficiency Virus in domestic species and Human Immunodeficiency Virus in humans. In contrast to these other lentiviruses, SRLVs are unique in



Brainstem, goat: There are multifocal areas of profound inflammation and parenchymal necrosis within the brainstem along the midline subjacent to the 4th ventricle. Vessels in these areas are cuffed by lymphocytes and plasma cells. (HE, 131X)

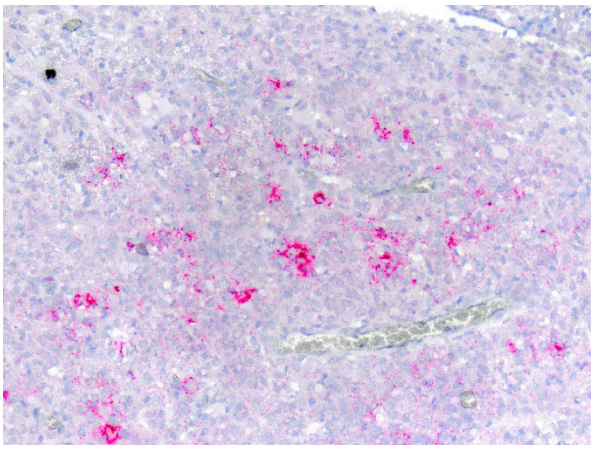


Brainstem, goat. Higher magnification of inflamed areas with chromatolytic swollen neurons, numerous Gitter cells and other glia, and cuffs of lymhocytes around vessels. (HE, 713X)

that they do not cause immunodeficiency in infected animals.[3, 6] The mechanism by which SRLVs are able to evade the host immune system despite an appropriate immune response is not fully understood. One proposed mechanism is that tropism of SRLVs for monocytes, macrophages, and dendritic cells allows the virus to evade the host immune system and disseminate systemically.[6] Once in target tissues, the virus can infect other cell types including microglia, endothelial cells, fibroblasts, and epithelial cells, though replication is restricted in these cells.[1, 3, 5] These additional tissue targets, particularly mammary epithelium, likely serve as important reservoirs of infection.[1, 5]

Transmission primarily occurs through ingestion of milk/colostrum or inhalation of nasal secretions.[3, 5] In utero transmission can occur infrequently in sheep and SRLVs have been detected in semen, though transmission via this route has not been documented.[2, 3] In the present case, the dam of the affected goat kid tested positive for CAEV prior to pregnancy and the kid likely became infected following ingestion of colostrum and milk. This is further supported by the reported similar clinical signs in the sibling of the present animal.

Infection with SRLVs leads to slowly progressing, often subclinical, inflammatory disease.[3] When clinical, four pathologic presentations, either alone or in combination, are recognized: encephalomyelitis, interstitial pneumonia, arthritis, indurative mastitis. Which form is present is variable and depends on various factors including species affected and age of the animal. Adult sheep typically present with pneumonia and/or encephalomyelitis while adult goats present with the arthritic form and goat kids present with the neurologic form.[4, 5, 8]



Brainstem, goat. Multifocally mononuclear cells demonstrate strong cytoplasmic immunolabeling for CAEV. (anti-CAEV, 400X) (Photo courtesy of The Ohio State University College of Veterinary Medicine, Department of Veterinary Biosciences, https://vet.osu.edu

As in the present case, the neurologic form in both sheep and goat kids is histologically characterized by lymphocytic and/or histiocytic demyelinating leukoencephalomyelitis frequently resulting clinically in progressive ataxia beginning in the hindlimbs.[3] The respiratory form is histologically characterized by lymphohistiocytic interstitial pneumonia, lymphoid follicle proliferation, and alveolar septa that are thickened by interstitial fibrosis and smooth muscle hypertrophy.[3, 8] In sheep, type II pneumocyte hyperplasia is uncommon, while in goats it is frequently present.[3] Additionally alveoli can be filled with abundant dense eosinophilic proteinaceous material.[3, 8] Electron micrographs of this fluid reveal numerous myelin figures consistent with surfactant.[9] In human medical literature, this accumulation of surfactant is termed alveolar proteinosis and is considered secondary to functional disruptions of alveolar macrophages.[10] There are a variety of documented causes of alveolar proteinosis in humans while in goats it has been described with CAEV as well as pulmonary adenomatosis.[9, 10] Therefore, alveolar proteinosis does not appear to be specific to CAEV but likely manifests secondary to alveolar macrophage dysfunction during infection.

The arthritic form, common in adult goats, is characterized by synovial villous hyperplasia with necrosis, mineralization, and fibrosis of the synovium with chronic infection.[3] Finally, the mastitis form is frequently subclinical and is a significant source of economic losses. It is frequently non-painful and involves infiltration of the mammary interstitium by lymphocytes, plasma cells, and macrophages that with time progresses to fibrosis.[3,5]

The concurrent suppurative bronchopneumonia in this case is not typical for reported SRLV respiratory lesions. We suspect that this may represents a separate bacterial infection; multiple bacterial agents were cultured from the lung to support this hypothesis, but the weak growth of mixed bacteria makes it difficult to interpret whether this reflect true infection or contaminants. *Mycoplasma* spp. infection was also considered as an additional contributor, but PCR for this agent was negative.

Contributing Institution:

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JPC Diagnosis:

1. Lung: Pneumonia, interstitial, lymphohistiocytic, chronic, diffuse, marked, with peribronchiolar and perivascular lymphoid

hyperplasia, type II pneumocyte hyperplasia, and alveolar proteinosis.
2. Lung: Bronchopneumonia, suppurative, subacute, multifocal, moderate.
3. Brainstem: Rhombencephalitis, necrotizing and lymphohistiocytic, subacute, focally extensive, severe, with gliosis.

JPC Comment:
The final case of this conference was descriptively rewarding for participants. The presence of brain and lung on the same slide from a young animal prompted many to immediately favor small ruminant lentiviruses, though there were several features of this case that were perplexing given the age of this animal. Foremost, the degree of alveolar proteinosis is marked, reflecting significant dysfunction of pulmonary macrophages. Given that these viruses utilize monocyte precursors both as a reservoir and means of trafficking virus to naïve tissue macrophages,[11] we considered whether this might reflect coinfection (CAEV and OPP) and/or a distinct viral subtype that is more virulent. In theory, only few monocyte precursors retain lentivirus (i.e. susceptible but not permissive to viral replication) and it should take time to develop histiocytic interstitial pneumonia.

As the contributor notes, pneumonia is a more common finding in older animals (reflecting this notion) and is rarer in goats. It is likely that the goat kids in this case were secondarily infected with another agent that augmented monocyte recruitment and subsequent tissue macrophage activation and cytokine production that hampered surfactant handling.[11] Notably, there is BALT hyperplasia present which is suggestive of *Mycoplasma* infection (or at least marked antigen presentation) which aligns with bacterial culture results and the airway-specific histological changes. For his reason, we separated this secondary bronchopneumonia out as a distinct morphologic diagnosis.

Dr. Highland concluded the conference discussion reminding participants about challenges in testing for small ruminant lentiviruses and emphasized that young animals with few infected monocytes may be seronegative or below detection limits of given assays. In larger goat herds and sheep flocks, the cost of serial testing presents a significant economic roadblock for controlling or eradicating these diseases.

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