Joint Pathology Center
Veterinary Pathology Services

WEDNESDAY SLIDE CONFERENCE 2025-2026

Conference #22 16 April 2026

CASE I:

Signalment:

A 2.5 year old primiparous Holstein Friesian cow *(bos taurus).*

History:

This dairy cow was from a herd of 360 animals, and had been exhibiting clinical signs consistent with toxic mastitis within the previous three weeks. Initially, this cow was treated with broad spectrum antibiotics, non-steroidal anti-inflammatories, and oral fluids, but failed to improve and was euthanized on welfare grounds.

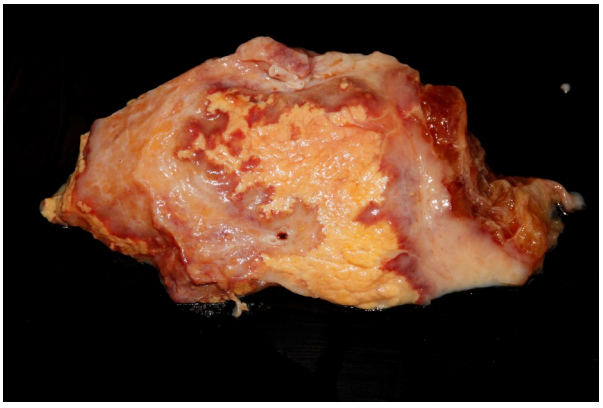

Figure 1-1. Mammary gland, ox: The mammary gland is enlarged and fibrotic, and on cut surface there is a distinct area of pallor (sequestrum) surrounded by a hyperemic halo.. (*Photo courtesy of*: University of Nottingham, https://www.nottingham.ac.uk/vet/service-for-business/veterinary-pathology-service/index.aspx)

Gross Pathology:

The right cranial mammary gland is enlarged and firm, and on the cut surface there is locally extensive fibrosis, with a distinct area of pallor (sequestrum) surrounded by a hyperemic halo. Within the teat cistern there is pale yellow, watery, fibrinosuppurative content. There is a focal, ~1-2cm diameter, capsulated abscess within the parenchyma as well. There is marked subcutaneous oedema surrounding the affected quarter.

Diagnostic Testing:

The aerobic bacteriology of the affected mammary gland identified *Klebsiella pneumoniae*, which was resistant to Ampicillin and sensitive to Neomycin, Streptomycin, Amoxicillin/Clavulanic acid, Cefpodoxime, Trimethoprim/Sulphamethoxazole, Enrofloxacin, Tetracycline. The culture and PCR-denaturing gradient gel electrophoresis (DGGE) testing for *Mycoplasma* was unrewarding.

Microscopic Description:

Mammary Gland - Right cranial quarter
The mammary gland is effaced in a focally extensive manner by moderately well demarcated palely eosinophilic parenchyma with partial loss of differential staining and cellular detail whilst retaining preservation of the overall architecture (coagulative necrosis - sequestrum). Within the necrotic ar-

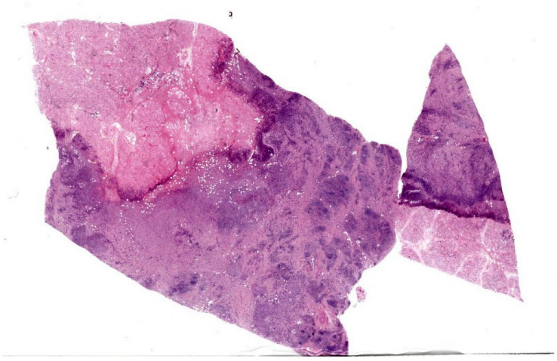

Figure 1-2. Mammary gland, ox: Two sections of mammary gland are submitted for examination. Both sections contain extensive areas of coagulative necrosis (infarcts, sequestra) which are bounded by a dense area of cellular debris. There is loss of architecture and hypercellularity of the remnant mammary gland. (HE, 0.7X).

ea, there are scattered pale basophilic, 2-3 micron in length, coccobacilli. The necrosed area is bordered by a thick rim of granulation tissue and nascent fibrosis. Throughout the remaining parenchyma, the mammary gland is multifocally effaced by extensive areas of abundant lytic and karyorrhectic leucocytes and debris (lytic necrosis) with abundant fibrin, alongside abundant granulation tissue, and a marked inflammatory infiltrate comprising of lymphocytes and plasma cells, often forming small clusters. Multifocally, there are small numbers of compressed and distorted interlobular ducts, remnants of compressed and atrophic mammary alveoli or basophilic mineral concretions of proteins and salts, that are sometimes accompanied by macrophages or very rare multinucleated giant cells (foreign body type). Within the inflamed granulation tissue, a small number of ducts are dysplastic, and scattered throughout the parenchyma are a moderate number of round optically empty spaces (lipid). Within some ducts, there are accumulations of lytic leucocytes and necrotic debris. A small number of mammary alveoli multifocally contain viable, degenerated and lytic neutrophils as well as necrotic debris that is bordered, dissected, and compressed by collars of fibrosis.

Morphological Diagnosis:

Mammary Gland: Severe, chronic-active, multifocal to coalescing neutrophilic, necrotizing and lymphoplasmacytic mastitis with intralesional bacteria, granulation tissue and sequestrum formation

Disease: Coliform mastitis

Aetiology: *Klebsiella pneumoniae*

Contributor's Comment:

The post-mortem findings are compatible with the history of mastitis. Based on the gross post-mortem appearance of the mammary glands, a coliform mastitis was considered most likely, with *E. coli, Klebsiella spp.,* and *Enterobacter spp.* considered as the top differentials. Furthermore, the macroscopic and histopathological findings of necrosis and inflammation within the mammary parenchyma were compatible with coliform mastitis.

Bovine mastitis is one of the most prevalent and consequential diseases of dairy cows globally, carrying significant detrimental welfare and financial implications (1). Mastitis in dairy cows is caused by a wide varie-

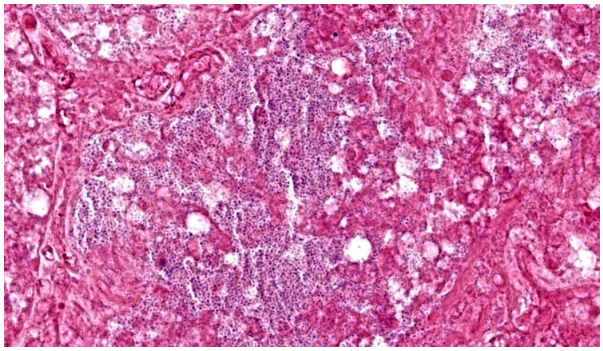

Figure 1-3. Mammary gland, ox: High magnification of tissue within the sequestrum. There is a diffuse loss of staining affinity. Scattered throughout this area, there are numerous individualized 2um bacilli. (HE, 915X).

ty of pathogens, including Gram-positive cocci, Gram-negative bacilli, *Mycoplasma bovis*, and the *Prototheca* species. Among these, Gram-positive cocci and Gram-negative bacilli are the main agents and the pathogenesis encompasses ascending infection. *Streptococcus agalactiae* and some types of *Staphylococcus aureus* are obligate parasites of the gland and inevitable pathogens, but the great majority of infections are opportunistic and environmental (see JPC 1210466).

Coliform bacteria such as *Escherichia coli* (the most common), and other Enterobacteriaceae *(Enterobacter, Klebsiella, Citrobacter, Serratia, and Proteus).* are ubiquitous in the environment and have the capacity to cause severe environmental mastitis via ascending infection from the teat.[1] Coliforms produce endotoxins causing hemorrhage, oedema, thrombosis, and vascular damage, subsequently damaging tissues and potentially leading to death. Lactating cows are more likely to succumb to the effects of the endotoxins, as their response is determined by their reproductive cycle.[5] The typical coliform mastitis in cows presents clinically with a sudden drop in milk production, watery or bloody milk, and a swollen, hot, and painful udder. Affected cows often show systemic signs such as fever, depression, dehydration, and, in severe cases, may become recumbent or die rapidly due to endotoxemia. As seen in this case, if the cow survives this acute and toxic stage, the affected mammary gland is then likely to sequester and slough off due to necrosis of the glandular tissue secondary to chronic coliform mastitis.[12]

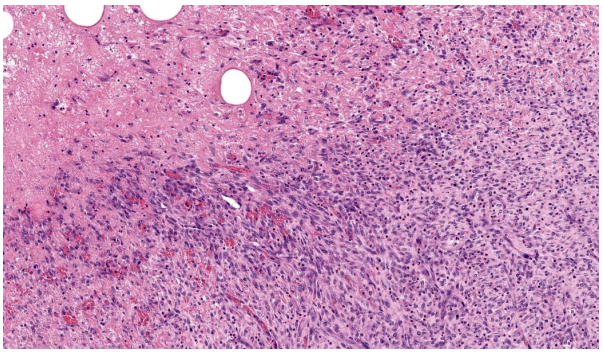

Figure 1-4 Mammary gland, ox: Areas of infarction are also bounded by maturing granulation tissue, which forms dense bands of fibrous connective tissue effacing the adjacent alveolar tissue. ERE. (HE, 468X).

Extensive investigations on the virulence profile of the *E coli* associated mastitis did not identify a clear set of virulence genes, and some authors prefer the use of mastitis associated *E. coli* (MAEC), with MAEC being more an "ecotype" rather than a "pathotype" .[6, 16]

Klebsiella pneumoniae is one of the most common coliforms causing clinical bovine mastitis, but has been found to be one of the most damaging when considering milk production, treatment costs, and mortality rate. *K. pneumoniae* mastitis has a poor cure rate after antimicrobial treatment, and although it is commonly an environmental opportunist, lateral spread from diseased to healthy cattle is possible.[11, 12]

The pathogenicity of *K. pneumoniae* is related to its virulence factors, with the primary factors being capsular polysaccharide (CPs), lipopolysaccharides, siderophores, and fimbriae. Furthermore, *Klebsiella* species are a known reservoir for antibiotic resistance genes, which can spread to other Gram-negative bacteria.[12, 16, 17] In vitro infection of bovine mammary epithelial cells with *K. pneumoniae* resulted in, showing rapid adherence to, and invasion of, mammary epithelial (milk-producing) cells by *K. pneumoniae* leading to cellular damage and apoptosis. *K. pneumoniae* was shown to promote the production of the following cytokines:

IL8, IL-1β, and Tumor Necrosis Factor-α (TNF-α), as well as promoting the transcriptional expression of the pro-inflammatory genes for IL-6, IL-8, IL-1β, and TNF-α.[10]

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JPC Morphologic Diagnosis:

Mammary gland: Mastitis, necrosuppurative, chronic-active, multifocal to coalescing, severe, with infarction and innumerable coccobacilli.

JPC Comment:

The one and only Dr. Corrie Brown, livestock infectious disease expert extraordinaire from the University of Georgia, moderated the JPC's 22nd conference this year before presenting the keynote lectures at the Northeastern Veterinary Pathology Conference in Washington, D.C. She put WSC participants through their paces with a quartet of excellent ruminant cases, starting off with this classic, but deceptively nuanced, case of coliform mastitis. This served as a springboard to review the anatomy, immunology, and epidemiology of mastitis in dairy cattle. One participant astutely reminded everyone that, in the lactating mammary gland, the term "acinus" should be substituted in favor of the term "alveolus" to help differentiate between the stages. This is a small but important distinction when describing the functional unit of milk production.

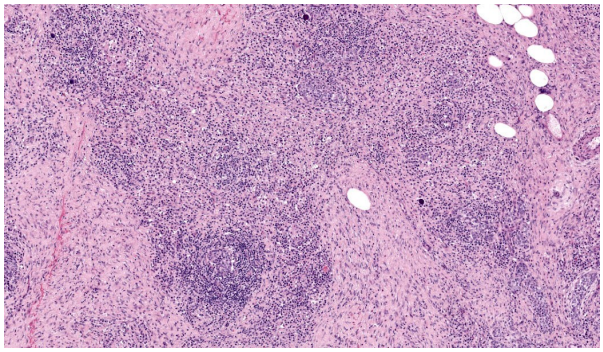

Figure 1-5. Mammary gland, ox. Within the remaining mammary gland, there is effacement of alveolar tissue by fibrous connective tissue and a diffuse infiltrate of macrophages, fewer neutrophils, and aggregates of lymphocytes and plasma cells. Remnant alveoli and ducts are shrunken and infiltrated by inflammatory cells and occasionally contain corpora amylaceae and few neutrophils. (HE, 121X)

Participants initially considered *Staphylococcus aureus* as a potential cause in this case. However, the absence of Splendore–Hoeppli material and the overwhelming necrosuppurative characteristic of the lesion made this etiology less likely. *Trueperella pyogenes* was also suggested as a differential, but its hallmark abscess formation was not present. Instead, presentation of overwhelming necrosis pointed towards coliforms, which, as the contributor mentioned in their comment, include *E. coli, Enterobacter, Klebsiella, Citrobacter, Serratia,* and *Proteus*.[1,2]

Dr. Brown emphasized that mastitis is primarily a disease of dairy cattle, not because other animals don't get mastitis, but because dairy cows experience far more teat trauma through repeated hand- or machine-milking. The teat canal and cistern normally provide excellent immune protection, but chronic mechanical stress compromises this barrier. This is why pre- and post-milking teat dipping remains one of the most effective mas-

titis prevention strategies in modern dairy management.

A key teaching point was that effectively all mastitis pathogens enter the mammary gland through the teat with one important exception: highly pathogenic avian influenza.[14,15] This virus is currently the only virus known to infect the bovine mammary gland. HPAI was recently seen in the WSC this year during Conference 17, Case 2.

Dr. Brown contrasted the clinical behavior of the major mastitis pathogens as important clues to assist the pathologist in narrowing down differentials. *Staphylococcus aureus* and *Streptococcus spp.* typically cause subclinical or mild clinical mastitis — the cow feels fine, but the milk looks and smells abnormal. Dry cow therapy has nearly eradicated *Streptococcus* mastitis in the United States, although *Staphylococcus* continues to be one of the most common mastitis pathogens affecting dairy cattle.[7] Coliform mastitis, however, is entirely different. Cows become acutely, profoundly ill, often immediately postpartum, with systemic endotoxemia driving the severity of disease.[2] Recovery rates are poor even with aggressive therapy.[2,11,12]

Participants differed in opinion regarding the use of the term "sequestrum." While the contributor provides a cogent explanation for why this term may be used in cases of mastitis - due to the body walling off the affected quarter and eventually sloughing it - some participants opined that the sharply demarcated, devitalized region of mammary tissue was better described as an infarct given the endotoxin-induced thrombosis that is characteristic of coliform mastitis. This distinction mattered, they argued, because the pathogenesis is vascular, not traumatic.

Discussion then turned to *Klebsiella pneumoniae*, the major pathogen in this case. *Klebsiella* thrives in wood products such as sawdust and shavings, making bedding a common source of exposure.[8] While sometimes described as "contagious," Dr. Brown clarified that transmission is environmental, not cow to cow.[11] Participants debated whether *Klebsiella* can enter mammary epithelial cells; while *Salmonella* and *Shigella* are well-established as intracellular pathogens, the evidence for *Klebsiella* is less clear.[4] There are, however, some in-vitro studies that suggest possible invasion, although whether this translates in-vivo has yet to be fully elucidated.[4]

One participant noted that the bacterial morphology in this case did not match their mental image of *Klebsiella*, which is typically produces a capsule. The capsule of *Klebsiella* is one of its most important virulence factors.[10,17] The organisms here appear to lack a capsule on H&E, which contributed to diagnostic hesitation. Others wondered whether a *Staphylococcus aureus* co-infection might be present, which is certainly possible given that there were several gram-positive bacteria present on a Gram stain. However, capsule production by *Klebsiella* may be downregulated secondary to certain host factors, such as increased extracellular iron as occurs with severe tissue damage, so reliance on capsule presence may be deceptive.[10]

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lecular characterization of Klebsiella pneumoniae in clinical bovine mastitis in 14 provinces in China. *Vet Res Commun*. 2025;49(18).

CASE II:

Signalment:

Four-year-old Holstein cow (*Bos taurus taurus*).

History:

A 5-year-old Holstein cow was presented with a history of breathing difficulty, and progressive weight loss before calving. The cow was treated with tetracycline, dipyrone, and flunixin meglumine for approximately two weeks; however, the doses were not recorded by the farmer. After calving, weight loss worsened and muffled heart sounds were noticed 3 days before the animal died.

Gross Pathology:

A five-year-old Holstein cow was submitted for necropsy examination presenting a poor body condition and markedly pale mucous membranes. Grossly, extensive areas of hemorrhage were observed in the pericardium, epicardium, extending to the pulmonary artery. Examination of the heart cavities demonstrated a friable, irregular, mottled white, brown and red vegetative mass of approximately 5.0 x 3.0 x 2.0 cm firmly adhered to all cusps of the pulmonary valve (Figure 1). In the lungs, multifocal to coalescent areas of consolidation were observed in all pulmonary lobes, and these were characterized by firm consistency, reddish color, and were associated with interlobular edema. Additionally, multiple yellowish, firm structures were observed occluding blood vessels (thrombi) (Figure 2). The abomasum was markedly distended and filled with free non coagulated blood, associated with severe multifocal mucosal ulcerations. Hemorrhagic content was seen throughout the intestinal tract. No other lesions were observed in the remaining organs.

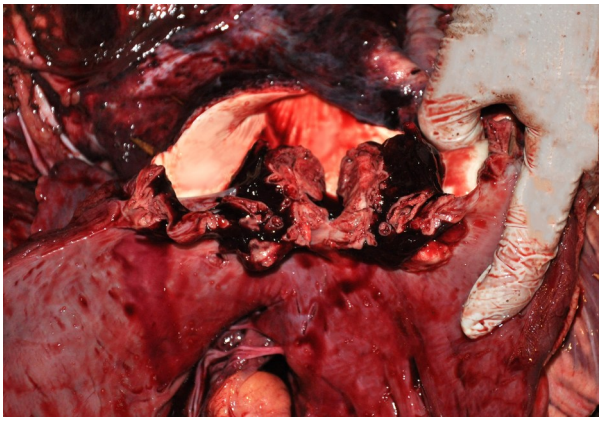

Figure 2-1. Pulmonary valve, ox: A friable vegetative mass of approximately 5.0 x 3.0 x 2.0 cm firmly adhered to all cusps of the pulmonary valve (*Photo courtesy of:* Faculdade de Veterinária, Universidade Federal do Rio Grande do Sul, Setor de Patologia Veterinária, http://www.ufrgs.br/

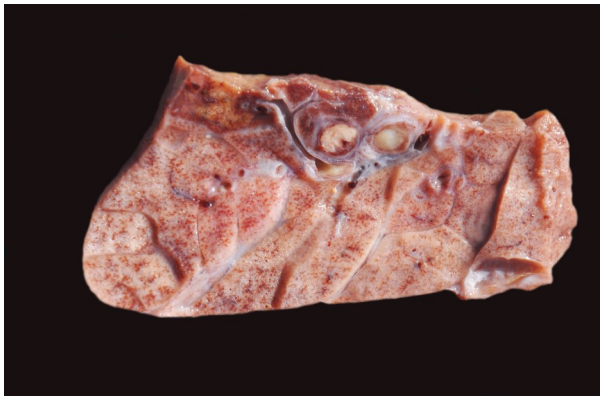

Figure 2-2. Pulmonary valve, ox: The lungs are multifocally consolidated firm, and were associated with interlobular edema. Yellow thrombi are present within vessels. (*Photo courtesy of:* Faculdade de Veterinária, Universidade Federal do Rio Grande do Sul, Setor de Patologia Veterinária, http://www.ufrgs.br/patologia)

Laboratory Results:

Refrigerated samples of the lungs and valve were cultured and submitted to the 16S

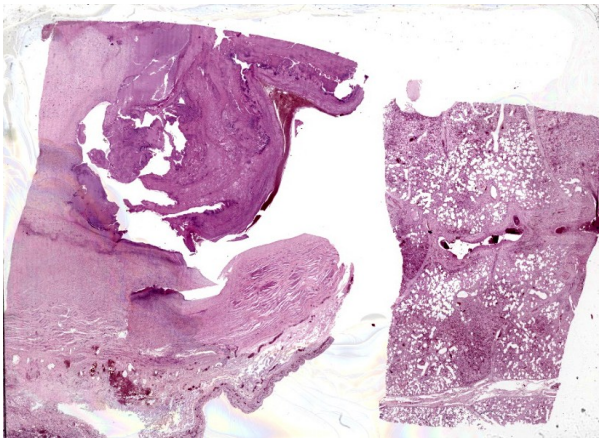

Figure 2-3. Pulmonary valve and lung. ox: A markedly remodeled section of the pulmonary valve with a large thrombus on the dorsal surface is submitted as well as a section of markedly consolidated lung.

rRNA gene sequencing that revealed *Helcococcus ovis* in the valve sample. No bacterial growth was obtained from the lung sample. Gram stain was performed in the lungs and valve showing abundant Gram-positive coccoid bacterial aggregates inside arterioles in the lungs and in the vegetative structures in the heart.

Microscopic Description:

The submitted slides present one section of heart and one section of lung (Figure 3). In the heart, severe thickening of the pulmonary valve endocardium is observed, characterized by marked proliferation of fibrovascular tissue, inflammatory infiltrate of non-degenerate and degenerate neutrophils, as well as macrophages, deposition of eosinophilic material (fibrin), cellular debris, and an abundant number of coccoid basophilic bacterial colonies. The lung exhibits multifocal severe thrombosis characterized by large amounts of fibrin deposition inside large and small arterioles, associated with Gram-positive bacterial colonies (Figure 4), similar to those seen in the pulmonary valve (not all slides contain bacterial colonies in the lungs). Adjacent to these areas, in the alveolar space, a moderate inflammatory infiltrate of neutrophils, areas of necrosis, edema, and fibrosis, as well as free erythrocytes (hemorrhage), and a moderate number of macrophages are observed. Interlobular septa are thickened by fibrous connective tissue and inflammatory infiltrate of non-degenerate and degenerate neutrophils, as well as fibrin deposition. There is also a moderate thickening of the visceral pleura, characterized by the proliferation of fibrous connective tissue.

Contributor's Morphologic Diagnosis:

Heart: Valvulitis and Endocarditis, fibrinosuppurative, diffuse, severe, with intralesional coccoid bacterial aggregates.
Lung: Pneumonia, suppurative, thromboembolic, multifocal to coalescent, severe, with intralesional coccoid bacterial aggregates.

Contributor's Comment:

The gross and microscopic findings observed in this case were compatible with vegetative valvular endocarditis and thromboembolic pneumonia caused by a bacterial agent, that was confirmed through culture and molecular analysis as *Helcococcus ovis*. This bacterium is a gram-positive coccus

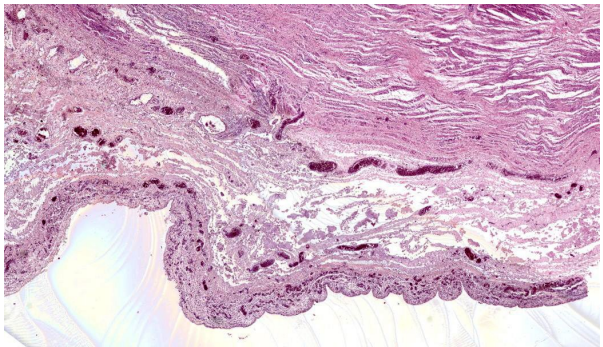

Figure 2-4. Pulmonary valve, ox: The valve is markedly remodeled by abundant edema, moderate suppurative inflammation, granulation tissue and fibrosis. (HE, 32X)

that has been associated with multiple clinical presentations, such as mastitis in sheep, endocarditis and abortion in cattle, and pulmonary abscesses in horses.[2,6] Reports in Germany suggest that *H. ovis* is an emerging pathogen that can lead to valvular endocarditis.[5] Differential diagnoses must include other bacterial agents, such as *Streptococcus* sp. and *Trueperella pyogenes*, which are the most common agents associated to endocarditis in cattle.[1] Besides bacteria, occasionally mycotic or parasitic infection can lead to endocarditis, as a result of systemic mycotic disease caused by zygomycetes or *Aspergillus* sp., or larvae of *Strongylus vulgaris*.[7]
Endocarditis is the inflammation of endocardium, and even though any part of this tissue layer may be affected, lesions usually affect primarily the valves.[7] In cattle, the tricuspid valve, followed by the mitral valve are more commonly involved in endocarditis, and the pulmonary valve is considered to be an uncommon presentation.[1,5] Usually, endocarditis in cattle is associated with traumatic lesions, followed by bacterial infection, with sustained or recurrent bacteremia, such as in cases of peritoneal abscesses, hepatic abscesses, mastitis and metritis.[7] It is not well understood how *H. ovis* enters the bloodstream or its original habitat; however, Rothschild suggested that the possible source of

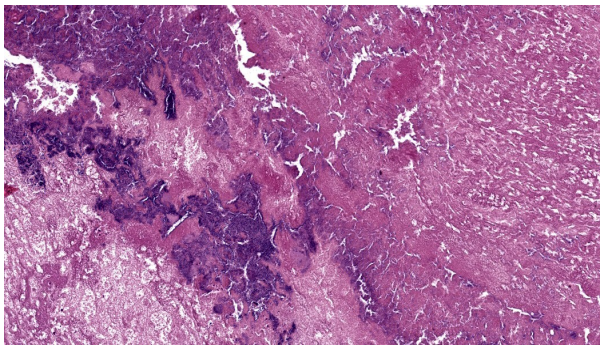

Figure 2-5. Pulmonary valve, ox: Adherent to the valve is a large fibrin thrombus with entrapped colonies of cocci. (HE, 387X)

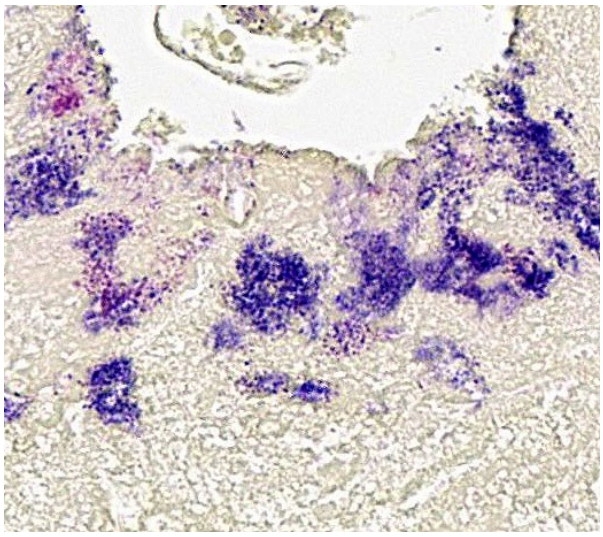

Figure 2-6. Pulmonary valve, ox: Numerous colonies of gram positive cocci are embedded within the fibrin thrombus. (Brown-Brenn, 1350X)

infection could be the skin.[8] Bacteria from the skin can enter into the systemic circulation due to lesions that break the skin barrier, leading to bacteremia, and may adhere to heart valves.[7] In the present case, no surgical procedure was done, nor open wound or history of previous diseases, including mastitis or metritis, were observed or reported. Even though the cow presented abomasal ulcers at the time of necropsy, those were considered to be acute as a result of anti-inflammatory treatment and not related to the endocarditis.

Post reported a case of valvular endocarditis by *H. ovis* in the right atrioventricular valve of a bull in the state of North Carolina (USA), and the microscopic findings, such as severe inflammatory infiltrate and areas of necrosis, were similar to those observed in this case.[6] Similar patterns of chronic endocarditis caused by *H. ovis* were described by Kutzer, which consisted of valvular emboli characterized by a luminal zone showing unorganized fibrinous exudate.[5]

Common clinical signs of endocarditis in cows are reported as progressive weight loss,

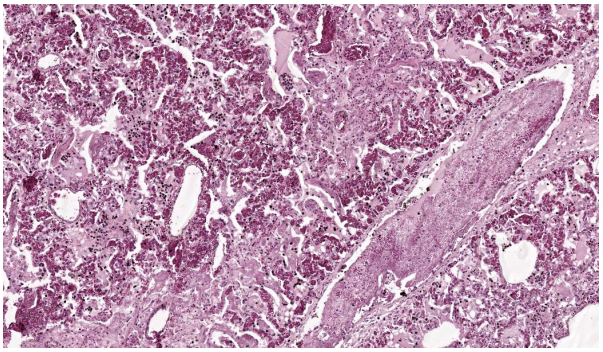

Figure 2-7. Lung, ox: In areas of consolidation, septa are markedly congested, and alveoli contain abundant edema, hemorrhage, and polymerized fibrin. Intralobular septa are markedly expanded by edema and lymphatics contain occlusive fibrin thrombi. (HE, 220X)

drop in milk production, lameness, tachycardia with auscultation of heart murmur, fever, and consequent respiratory distress.[1,7] In the case here described, the owners noticed weight loss, milk drop and fever, however, these clinical signs were thought to be associated with other infectious diseases, including tick fever. Valvular endocarditis is usually fatal, and valvular damage and embolism are common sequelae.[4,7] Some portions of the vegetative lesion can detach and be carried through the blood circulation as emboli and, in some cases such as the one described here, those emboli are also septic, carrying the bacterial agent involved in the endocarditis. Emboli that arise from the right heart usually produce pulmonary abscessation or pulmonary thrombosis, as observed in this case.[7] The lung lesions were consistent with pulmonary thromboembolism due to the right heart endocarditis. Surrounding the thrombi areas in the lungs, areas of coagulative necrosis with inflammatory cells and hemorrhage could be observed.

In the case here described, it was only possible to culture the bacteria from the heart sample (affected valve), and not from the lungs. This difference may be caused by several features related to the location of bacterial aggregates, bacteria behavior, selection of sampling area and previous antibiotic treatment. One of the main characteristics of *H.ovis* is that it shows growth in satellites, and the lack of inoculation with other bacteria (e.g. Staphylococcus aureus) may have disadvantaged the isolation of the agent.[5] The methods used in classical bacteriology are unable to reach the definitive diagnosis of infection by *H.ovis,* and molecular analysis is necessary to identify this bacterium.

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JPC Morphologic Diagnosis:

Pulmonary valve: Valvulitis, fibrinosuppurative, chronic-active, focally extensive, severe, with remodeling and colonies of cocci.

Lung: Pneumonia, embolic, fibrinosuppurative, chronic-active, diffuse, severe with marked edema and septic thrombi.

JPC Comment:

This case challenged participants right from the start with tissue identification. Several attendees initially thought they were looking at the aorta or another large elastic artery. Only after it was revealed in conference to be heart valve did many realize the tissue in question was pulmonic valve. This tissue ID, which very few participants managed to get to before conference, could be aided by a small region of cardiac muscle (likely at the valve root, with central nuclei and fibrosis,

a subtle but critical clue. This set the tone for a case that required attention to anatomic context and lesion distribution.

Once oriented, participants quickly recognized the hallmarks of valvular endocarditis with septic thromboembolic pneumonia, a classic pairing when emboli originate from the right heart. A separate case in a non-human primate was seen in this year's Conference 5, Case 2. Dr. Brown emphasized this point: right-sided endocarditis causes pulmonary emboli, whereas left-sided endocarditis produces systemic infarcts (especially in the kidneys). The lung lesions in this cow (fibrinosuppurative embolic pneumonia with septic thrombi) were textbook examples of this pathogenesis.

Differentials for bovine endocarditis were reviewed, with *Streptococcus bovis* and *Trueperella pyogenes* topping the differential list for many participants. These two bacteria remain the most common etiologies for this disease in cattle.[1] However, the contributor identified the culprit as *Helcococcus ovis*. There is also a recently described related species that is able to cause human disease called *Helcococcus bovis,* which is closely related to *H. ovis*.[3] This organism is becoming recognized as an emerging pathogen in ruminants, though it is still unfamiliar to many diagnosticians.[3,4,5] Dr. Brown noted that *Helcococcus ovis* and *H. bovis* are believed to be part of the skin microbiome, gaining access to the bloodstream through minor breaches in the integument.[5] *H. ovis* has also demonstrated widespread resistance to tetracyclines.[3]

A particularly interesting point mentioned in conference was the organism's growth behavior. *Helcococcus bovis* demonstrates satellite growth, requiring the presence of *Staphylococcus* spp. on blood agar to grow robustly.[5] This helps to explain why the organism was isolated from the valve, where bacterial load was highest, but not from the lungs, despite clear histologic evidence of septic emboli. Dr. Brown reminded participants that failure to culture an organism does not exclude its presence, especially when dealing with fastidious bacteria.

This cow also had abomasal ulcers, which prompted a brief review of NSAID-associated ulceration. Dr. Brown walked participants through the mechanism: NSAIDs inhibit prostaglandin synthesis, which among other deleterious processes, leads to decreased bicarbonate secretion. A lack of bicarbonate results in increased abomasal acidity, leading to mucosal injury and ulcer formation. These lesions were considered acute and unrelated to the endocarditis by the contributor.

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CASE III:

Signalment:

Angus feeder calf (*Bos Taurus)* less than one year of age. Unknown gender.

History:

Acute onset of severe respiratory distress with cough and expiratory noise. The calf was afrebrile (102.6 °F). When the calf was removed from its pen to administer treatment, it died in the chute.

Gross Pathology:

No gross lesions were reported.

Laboratory Results:

PCR on lung tissue was negative for *Pasteurella multocida, Histophilus somni, Mannheimia haemolytica, Mycoplasma bovis,* Bovine herpesvirus 1, Bovine viral diarrhea virus, Bovine coronavirus, and Bovine respiratory syncytial virus.

Aerobic culture of lung yielded no bacterial pathogens.

Microscopic Description:

Lung: Sections of lung display a severe diffuse proliferative and exudative inflammatory process. Alveolar spaces contain variable amounts of homogenous eosinophilic fluid (edema fluid) mixed with fibrin and leukocytes. There is diffuse type II pneumocyte hyperplasia. Alveoli are lined by hyaline membranes (variability in the severity of hyaline membranes is observed among the sections submitted). Bronchi and bronchioles in some locations appear within normal limits whereas in other regions they are lined by attenuated epithelial cells and contain edema mixed with macrophages and sloughed epithelial cells within their lumina. There is pleural, peribronchiolar, and interlobular edema. Alveolar septa are thickened and severely congested.

Contributor Morphologic Diagnosis:

Lung; pneumonia, interstitial, histiocytic, subacute, diffuse, severe, with hyaline membrane formation, type II pneumocyte hyperplasia, and edema

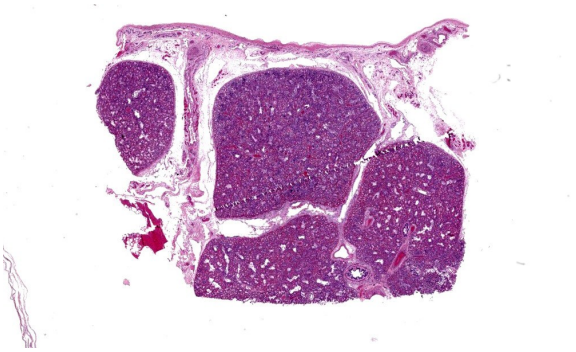

Figure 3-1. Lung, ox: A section of lung is submitted for examination. A subgross magnification, the interlobular septa and pleura is markedly expanded by clear space, and the pulmonary parenchyma is consolidated. (HE, 10X)

Contributor Comment:

Atypical interstitial pneumonia (AIP) represents a sporadic disease of cattle that has traditionally been known by a number of names including "fog fever", "dust pneumonia", and "acute bovine pulmonary emphysema and edema", among others.[5,7] A number of causes have been proposed in the literature including ingestion of compounds toxic to pneumocytes, poor air quality, inhalation of foreign material, as well as parasites and viruses, most notably BRSV.[4]

The metabolic activation and accumulation of 3-methyl indole (3-MI), a metabolite of tryptophan is the most widely accepted cause and is traditionally seen in cattle moved to lush green pastures in the early fall. Animals affected with AIP have been shown to have significantly higher plasma levels of 3-MI compared to unaffected animals.[1] Additionally, a syndrome mimicking AIP was experimentally reproduced in cattle and goats after the administration of 3-MI.[3]

Within the rumen, L-tryptophan is converted first to indoleacetic acid and subsequently to 3-MI by *Lactobacillus* spp. of bacteria.[2] Within the lung, nonciliated epithelial cells called Club cells (formerly called Clara cells) further metabolize 3-MI resulting in a compound that is toxic to pneumocytes and

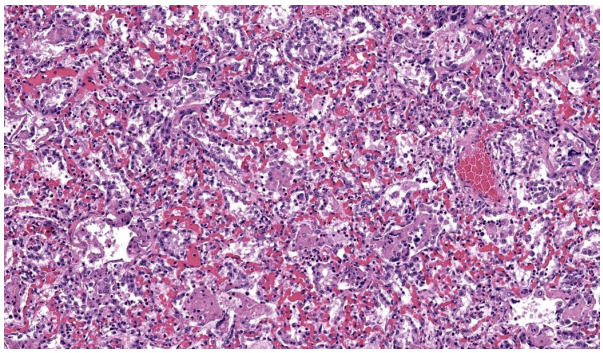

Figure 3-2. Lung, ox: Diffusely, alveolar spaces contain abundant edema fluid, polymerized fibrin, and moderate numbers of alveolar macrophages and fewer neutrophils. HE, 256X)

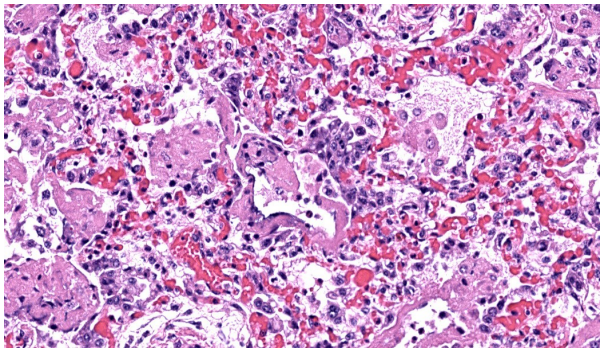

Figure 3-3. Lung, ox: Multifocally, polymerized fibrin occasionally compacts at the periphery of alveoli to form hyaline membranes (center). (HE, 556X)

endothelial cells.[4] The resulting vascular and epithelial cell damage results in large amounts of high protein content edema fluid that polymerizes forming the hallmark histologic feature of hyaline membranes. The lining of alveolar walls with hyaline membranes decreases oxygen exchange efficiency leading to the severe respiratory distress and ultimately death in these animals.

Further complicating the etiologic component behind AIP is the fact that the disease also occurs in feedlot animals who are not fed lush grasses but instead a more concentrated ration. Potential AIP causes or inciting factors unique to feedlot environments that have been proposed are discussed in a recent review and include melengestrol acetate (MGA), BRSV infection, bacterial respiratory disease, heat, and dusty conditions.[9]

Response to treatment for AIP is traditionally very poor.[4] In the contributor's experience, feedlot cases of AIP tend to happen in fat cattle (most often heifers) at the end of the feeding period during the late summer months with high daytime temperatures. Experiencing sudden deaths due to AIP the week, or even the day of shipment to slaughter is not uncommon, making the economic losses even greater on a per case basis. The contributor has observed numerous cases

with a history like this case where the stress of movement in these respiratory compromised animals proves too much and they often die on the way to, or within the chute when treatment is attempted.

Contributing Institution:

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JPC Morphologic Diagnosis:

Lung: Pneumonia, interstitial, necrotizing, subacute, diffuse, severe, with hyaline membranes, type II pneumocyte hyperplasia, and interlobular and pleural emphysema and edema.

JPC Comment:

This case illustrates a classic picture of acute interstitial pneumonia (AIP) in cattle. This condition has been historically known by a few different names, including "atypical interstitial pneumonia," "acute bovine pulmonary emphysema and edema" (ABPEE) or "fog fever." The names "fog fever" and ABPEE are still widely used clinically. Participants were reminded that this syndrome fits under the clinical umbrella of acute respiratory distress syndrome (ARDS), whereas pathologically it is best described as diffuse alveolar damage (DAD). It is important to note that DAD is a pattern rather than a single disease entity. Dr. Brown discussed with participants the five major causes of DAD in cattle that are worth having as a mental list: Lush pasture/L tryptophan (3 MI ("fog fever")), moldy sweet potatoes (4-ipomeanol), perilla mint toxicity, high oxygen exposure ("oxygen toxicity"), and radiation/certain chemotherapeutics.

On histology, the lung showed the expected constellation of hyaline membranes, type II pneumocyte hyperplasia, and interlobular and subpleural emphysema that are consistent with DAD. The group focused temporarily on the interlobular septa, where the clear spaces were debated as edema versus emphysema. Several participants emphasized that, in this context, the expansion of the interstitium and septa are far more likely to be emphysema from ruptured alveoli rather than just edema, especially when accompanied by the clear space dissecting along septa and into the pleura. This correlates well with the most reported gross findings for AIP in cattle, which include interlobular emphysema, a "checkerboard" appearance to the lungs of alternating firm, dark red areas and fluffy, pink areas, and overinflated lobes. [8]

The pathogenesis discussion centered on the classic pasture-associated form of AIP, which is covered by the contributor in their comment. The resulting vascular and epithelial injury leads to protein-rich edema, hyaline membrane formation, and interstitial emphysema, all of which were seen in this case. The feedlot form of AIP received special attention because, as noted by the contributor, its pathogenesis differs. Unlike the well-characterized pasture-associated 3-MI form, the etiology of AIP in feedlot cattle remains unclear. While 3-MI toxicity is central to the disease in pastured cattle, evidence for the same mechanism in feedlot animals is lacking.[6] Other factors mentioned by the contributor, including dietary composition, ruminal microbiome, concurrent respiratory disease, heat, dust, MGA administration in heifers, and management stressors, are all under consideration in the literature and were discussed in conference.[6,8]

Finally, conference goers addressed the chronicity (or lack thereof) of this case, which puzzled many participants. One participant remarked that, in subacute DAD, one expects fibrin and hyaline membranes whereas, in more chronic stages, type II pneumocyte hyperplasia predominates as the lung attempts repair. It is unusual, but not impossible, to see prominent hyaline membranes and marked type II pneumocyte hyperplasia together. When they do coexist, it likely reflects a lesion in transition, with ongoing injury superimposed on early repair.[8] Both lesions together have been reported in cases of AIP in cattle.[8] In fact, in a recent review, the most consistent histologic features in cases of AIP included hyaline membranes, type II pneumocyte hyperplasia, obliterative bronchiolitis, and interlobular emphysema.[8] This nuance helped reconcile the features seen histologically with the clinical history of acute, severe respiratory distress.

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CASE IV:

Signalment:

Four-year-old Texel ewe, sheep (*Ovis aries*)

History:

In January 2018, a farm owner reported clinical signs of blindness and stumbling gait in three sheep. These sheep were part of a flock of 96 Texel sheep, ranging from 5 months to 7 years old. The sheep were raised in a semi-intensive grazing system. Sheep from different origins were purchased and introduced into the flock without any testing for infectious agents. The clinical course lasted approximately 2 months, and other clinical signs included anorexia and progressive

weight loss. Due to poor prognosis, these three sheep were humanely euthanized and submitted for postmortem examination. One of the sheep is represented in this conference.

Gross Pathology:

At the gross examination, the ewe was in poor body condition. Sections of the cerebrum revealed multifocal to coalescing, irregular, yellow to brown, soft areas delimiting the periventricular region. The lungs were heavy and non-collapsed, with rib impressions, with a pale gray to pink color, and a diffusely rubbery texture. On the cut surface, multiple white and firm foci, measuring 0.1 to 0.5 cm in diameter were observed, mainly around bronchi. The mammary gland was mildly hardened. No significant lesions were observed in other organs, including multiple joints (stifle, carpi, and tarsi).

Laboratory Results:

The macerated brain and lungs of each animal were pooled, proviral DNA was isolated using a standard phenol-chloroform protocol (Sambrook and Russel, 2001), and the nested PCR was performed using a protocol that amplifies a 460 bp of 5'LTR region of proviral SRLV DNA (Ryan et al., 2000). The nested PCR for VMV was positive on the sheep's tissue pool (brain and lung).

Microscopic Description:

Cerebrum: In the white matter of the cerebrum, adjacent to the lateral ventricles, there is a well-demarcated, focally extensive area of marked neuropil rarefaction and liquefactive necrosis with numerous gitter cells and reactive astrocytes, including gemistocytes. Amidst this area, multifocal, marked inflammatory infiltrate of foamy macrophages and lymphocytes is observed, predominantly surrounding perivascular spaces, sometimes forming nodule-like structures. A similar inflammatory component is observed infiltrating, expanding, and partially effacing the adjacent ependymal epithelium. Additionally, cholesterol clefts, multifocal hemorrhage, multifocal white matter vacuolation, and mineral deposits are observed amidst this periventricular area of necrosis. The choroid plexus of the lateral ventricles (present in some slides) is expanded by abundant fibrin deposition, a small number of macrophages, and moderate to marked infiltrate composed mainly of lymphocytic aggregates forming lymphoid follicle-like structures. In the brainstem, the leptomeninges is moderately expanded by similar areas of perivascular infiltrate (not shown in the slides).

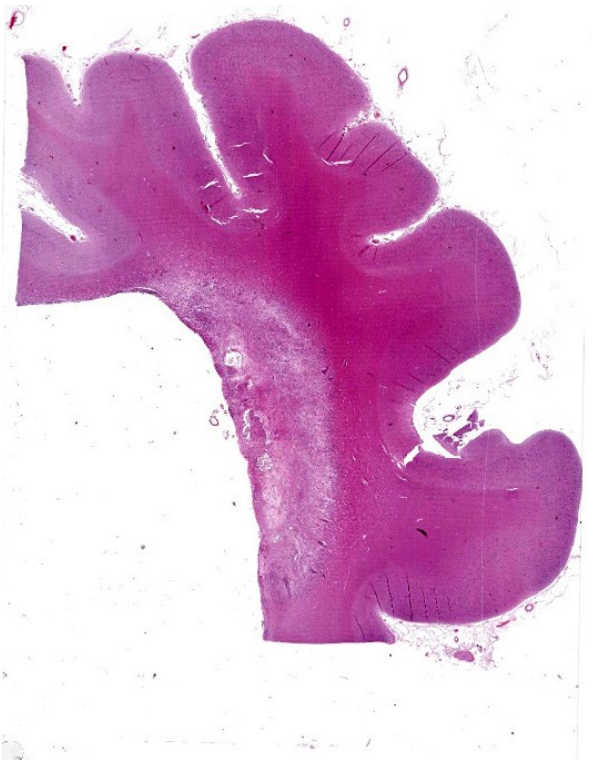

Figure 4-1. Cerebrum, sheep: At subgross magnification, the lateral ventricle is dilated and the cerebral gyri are flattened. There is profound pallor of the periventricular white matter. (HE, 7X)

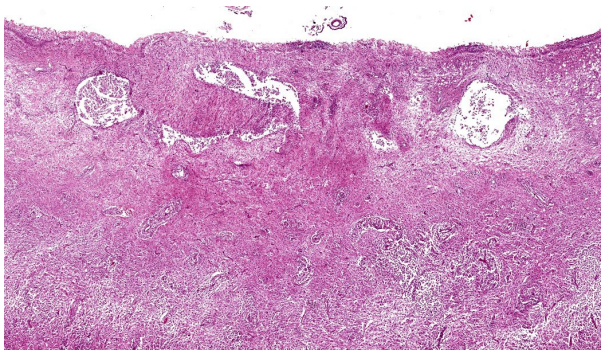

Figure 4-2. Cerebrum, sheep: There is segmental loss of the ependyma. The periventricular white matter is markedly rarefied with foci of liquefactive necrosis and extensive infiltration with inflammatory cells. (HE, 42X)

Contributor's Morphologic Diagnosis:

Cerebrum: Leukoencephalitis and ependymitis, necrotizing, lymphohistiocytic, focally extensive, marked, with demyelination, Texel, ovine.

Choroid plexus: Choroid plexitis, lymphohistiocytic, multifocal, marked, Texel, ovine.

Contributor's Comment:

Small ruminant lentiviruses (SRLV) are non-oncogenic retroviruses that infect sheep and goats, leading to diseases known as visna-maedi (VM; also known as ovine progressive pneumonia) and caprine arthritis and encephalitis (CAE).[2] The etiological agents of VM and CAE are Visna-maedi virus (VMV) and caprine arthritis encephalitis virus (family *Retroviridae*, genus *Lentivirus*). The major tropism of SRLVs is for monocyte/macrophages and dendritic cells.[2,9] Both diseases (VM and CAE) are multisystemic, progressive, and degenerative, with the establishment of persistent viral infection via viral genomic integration into the host's genome.[1,9]

Sheep infected with VMV develop a chronic wasting syndrome characterized by persistent infection in several organs, including lungs, central nervous system, mammary gland, and joints.[1,10] The respiratory form (maedi) is characterized by lymphocytic interstitial pneumonia, smooth muscle hyperplasia and is the most common form of the disease.[2] Clinical signs consist of progressive weight loss and dyspnea.[1,2,10] Chronic progressive arthritis of the carpus or tarsus is seen in SRLV-infected animal, with a higher incidence in goats.[2] A large proportion of sheep and goats infected by this virus present a non-suppurative, indurative mastitis.[2] The neurologic form of the disease (visna) is sporadic and was first described in Iceland as non-suppurative demyelinating encephalitis clinically characterized by a chronic progressive paralytic disease of adult sheep.[10] Different from other studies that describe that the lesions of the nervous form are mainly located in the white matter of the cerebellar peduncles, pons, and the medulla oblongata[1]. In our study the lesions were commonly observed extending from the periventricular areas, and choroid plexus. The occurrence of visna can be related to the involvement of neurotropic strains of VMV, and the severity of the lesions suggests that highly pathogenic strains of the virus are a probability.[1]

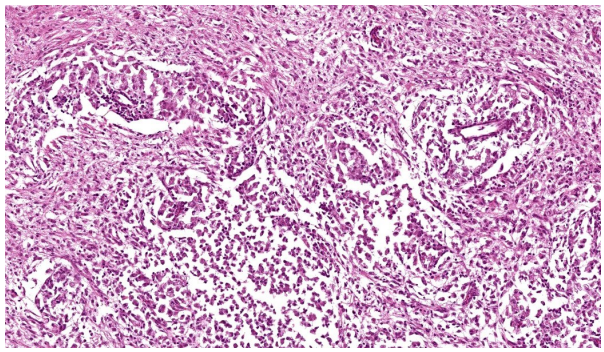

Figure 4-3. Cerebrum, sheep: The rarified periventricular white matter is infiltrated by large numbers of gitter cells which also form thick cuffs around vessels. (HE, 221X)

Clinical signs of visna are not pathognomonic; therefore, pathological and ancillary laboratory testing is necessary to differentiate this condition from those caused by other pathogens. Differential diagnoses for neurological disease in sheep include listeriosis, Border disease, rabies, louping-ill, polioencephalomalacia, coenurosis, and scrapie.[4,7,8] The clinical features of rabies can be mistaken with the neurologic form of SRLV, as described in our cases, in which the sheep demonstrated similar neurologic signs. Nonetheless, the time lapse between the onset of clinical signs and death significantly differs between the two diseases. Rabies has acute clinical progression (approximately 5 days); visna is instead a chronic and progressive disease that can last for weeks or months.[1,7]

Contributing Institution:

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

JPC Morphologic Diagnosis:

Cerebrum: Periventricular demyelination, diffuse, severe, with liquefactive necrosis, hydrocephalus ex vacuo, and histiocytic leukoencephalitis and ependymitis.

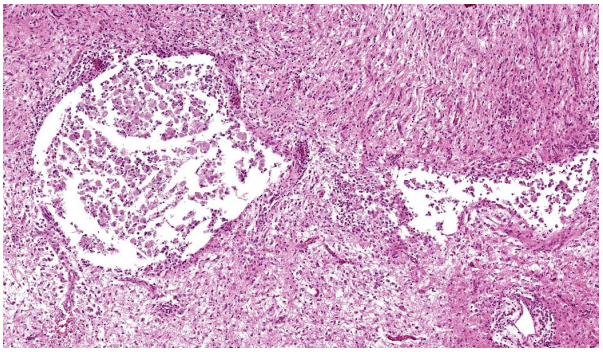

Figure 4-4. Cerebrum, sheep: Gitter cells also fill areas of liquefactive (cavitary) necrosis. (HE, 164X)

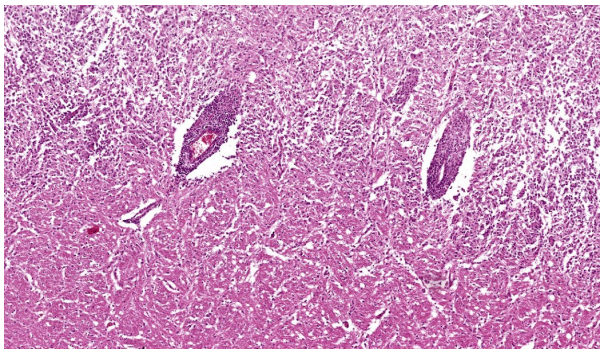

Figure 4-5. Cerebrum, sheep: Vichow-Robins' spaces at the interface of the gray (bottom) and white matter (top) are expanded by numerous macrophages, lymphocytes, and plasma cells. (HE, 125X)

JPC Comment:

This last case highlighted the classic neuropathologic presentation of the "visna" form of small ruminant lentivirus (SRLV) infection, and it prompted a rich discussion on lesion distribution, viral tropism, and breed susceptibility. "Maedi" is Icelandic for "dyspnea", referring to the respiratory form of SRLV infection, while "visna" means "shrinkage", describing the progressive neurologic wasting syndrome first recognized in Icelandic sheep. In the United States, the pulmonary form is more commonly known as ovine progressive pneumonia (OPP). Regardless of the clinical manifestation, the underlying agent is still SRLV, a non-oncogenic retrovirus with a major tropism for monocytes, macrophages, and dendritic cells.[5,9]

The histologic features in this case were striking. The dominant lesion was massive demyelination of the periventricular white matter, with relative sparing of the internal capsule. The presence of choroid plexus epithelium and lateral ventricle placed this section in the posterior telencephalon, consistent with the known predilection of small SRLV lesions for periventricular regions. Participants noted the flattened gyri and

marked ventricular dilation, which are consistent with hydrocephalus *ex vacuo*. This is a form of hydrocephalus seen secondary to a loss of significant amounts of neuroparenchyma, which expands the ventricular system.

Dr. Brown emphasized that SRLV exemplifies a lifelong infection. Viral integration into the host genome allows the virus to persist silently for years before clinical disease emerges.[5] Transmission patterns differ somewhat between syndromes: caprine arthritis encephalitis virus (CAE) is classically associated with ingestion of colostrum and milk transmission from infected ewes, whereas MVV is associated with spread via respiratory secretions among adult sheep.[2] However, both viruses can use either route, and both establish chronic infection of macrophages.[5] This macrophage tropism correlates well with the prominent histiocytic infiltrates in the CNS in this case.

The group briefly reviewed the clinical and epidemiologic implications of SRLV infection. Because infected animals remain lifelong carriers, seropositive sheep should be culled in control programs, and flock management must focus on preventing both respiratory spread and milk-borne transmission. The interplay between viral strain and host genetics determines whether an infected animal develops pulmonary "maedi", neurologic "visna", indurative mastitis, or chronic arthritis, and this Texel ewe exemplified the severe neurotropic form of the disease.

Texel sheep, as in this case, are among the breeds reported to be more susceptible to SRLV-associated disease. The reasons are not fully understood, but host genetics are thought to influence both viral replication and lesion severity.[3] Texels have repeatedly been implicated in flocks with high disease burdens.[3] Corriedales and Valais blacknose sheep are also reported to be more susceptible.[3,6]

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