Joint Pathology Center
Veterinary Pathology Services

WEDNESDAY SLIDE CONFERENCE 2019-2020

C o n f e r e n c e 1

22 August 2019

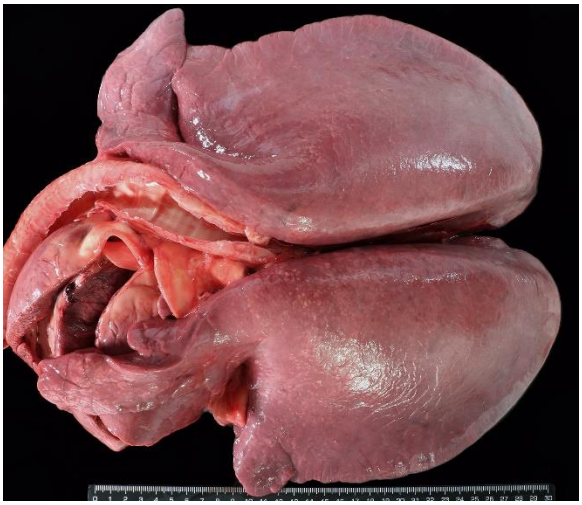
CASE I: NT-556 (JPC 4119798).

Signalment: 4-day-old male Arabian foal (*Equus caballus).*

History: Foal was weak but ambulatory with expiratory dyspnea and tachypnea since birth and showed an elevated respiratory and cardiac rate and fever. Mucous membranes were hyperemic with multifocal petechiation of the oral mucous membranes and in the skin's ear inner side. The capillary refill time was less than 2 seconds. Pulmonary auscultation revealed snoring, wheezing, and crepitation with a diffuse and moderate alveolar pattern on thoracic radiographs. Supportive care and treatment, including positive pressure ventilation, were pursued without success and the foal was eventually euthanized.

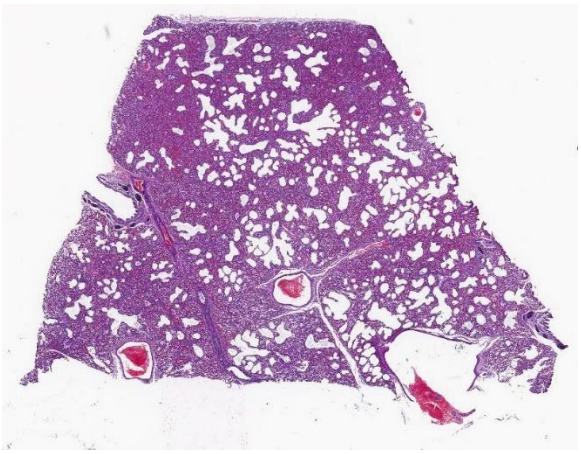
Gross Pathology: Records indicate the horse to be in good body condition with multifocal petechiae of the oral mucous membranes and in the inner side of the pinna. Bilaterally, the lungs appeared markedly collapsed, were diffusely firm and heavy with an edematous consistency, and a reddish to gray discoloration.

Laboratory results: No clinically significant alterations detected in the blood, including an adequate level of immunoglobulins.



Lung, foal. There is diffuse pulmonary atelectasis with a firm, heavy and edematous consistency and reddish to gray coloration. (Photo courtesy of: Servie de Diagnostic de Patologia Veterinaria, Facultat de Veterinaria UAB, Bellaterra (Barcelona).

Microscopic Description:
Lung: Affecting all evaluated section there is a severe and diffuse thickening of alveolar septa as a result of moderate to intense hyperplasia of type II pneumocytes and mild septal inflammatory cells mostly lymphocytes, macrophages and neutrophils. In addition, the totality of alveolar, bronchial and bronchiolar lumens are markedly reduced (pulmonary atelectasis) with



Lung, foal. A single section of lung is submitted. The lack of open alveoli suggests atelectasis. (HE, 4X)

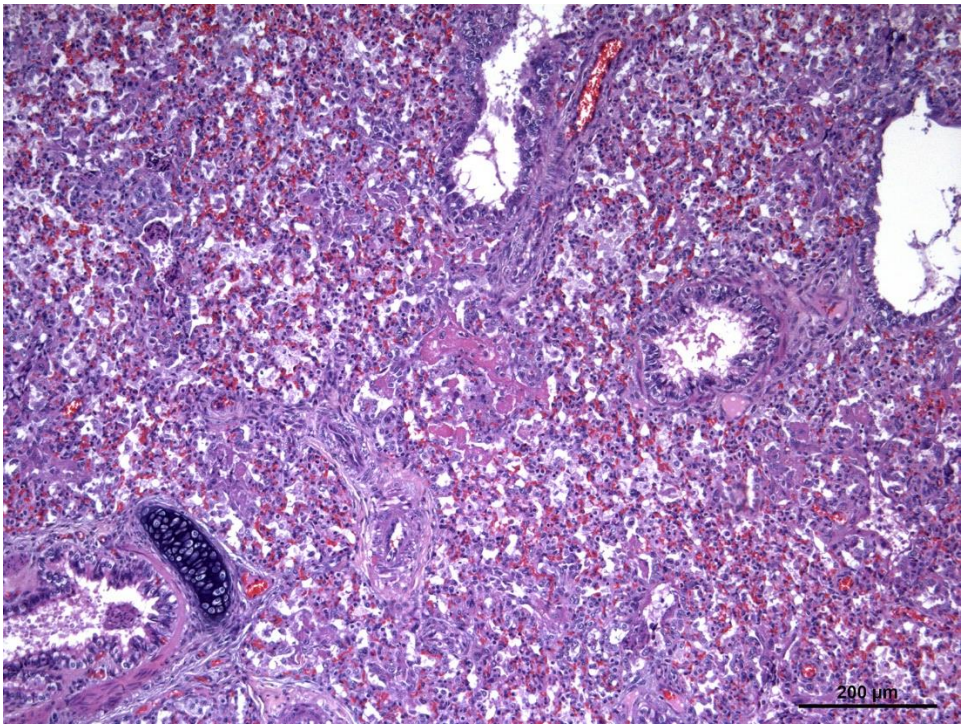
multifocal aggregates of hypereosinophilic, homogeneous and amorphous material (fibrin) covering the alveolar walls or partially filling the alveolar lumens, and occasionally, bronchial lumens (hyaline membranes). Abundant foamy macrophages with occasional multinucleated cells, neutrophils, cellular and nuclear debris and mild edematous fluid are seen within alveolar lumens admixed with aforementioned hyaline membranes.

Contributor's Morphologic Diagnoses: Lung: Diffuse severe, subacute interstitial pneumonia with intra-alveolar and intra-bronchiolar hyaline membranes and diffuse severe pulmonary atelectasis.

Contributor's Comment: The histologic findings observed in this case such as the presence of hyaline membranes in alveolar and occasionally in bronchioles, as well as the severe and diffuse pulmonary atelectasis and the widespread presence of hyperplastic type II pneumocytes are compatible with the disease known as **Neonatal hyaline membrane disease** also known as Respiratory Distress Syndrome (RDS).

This syndrome is well recognized in premature or full-term foals but has not been further investigated in this species. Affected foals have respiratory distress from the time of birth, an expiratory grunt or "bark," hypoxemia, heart failure and/or convulsions and opisthotonos.[1] The lungs are diffusely atelectatic, plum-red, rubbery, and sink or become partially submerged in formalin.[1] Histologically, in addition to the thickened hypercellular alveolar septa expected in immature lung, hyaline membranes line collapsed alveoli and sometimes the small bronchioles. Alveoli are edematous, and cellular debris is occasionally noted.[1] Also the pathogenesis is not well established, is assumed that is occurs because of failure of the immature type II pneumocytes to secrete functional surfactant or surfactant dysfunction resulting in increased alveolar surface tension and alveolar and small bronchioles collapse at the end of expiration.[1] The tension and shear stress imparted on the lung during reinflation of these collapsed airspaces injures type I pneumocytes and club cells. [1]

This condition has been investigated primarily in humans, piglets and calves, but it also has been documented in premature puppies, lambs and primates. A familial form of neonatal respiratory distress is described in piglets with congenital fetal hypothyroidism and possibly hypoadrenocorticism, as thyroid hormone is necessary for maturation of type II pneumocytes. Affected piglets have diffuse alveolar damage with hyaline membranes and bronchiolar necrosis, as well as features suggesting hypothyroidism, including mildly prolonged gestation, fine hair coat, generalized edema, and thyroid follicular hyperplasia with lack of colloid. Other contributing factors in all species are fetal asphyxia, aspiration of meconium in amniotic fluid, reduction in pulmonary arteriolar blood flow, and inhibition of surfactant by fibrinogen, other serum constituents in edema fluid, or by



Lung, foal: There is diffuse and severe collapse of alveolar and bronchial lumina with multifocal aggregates of hypereosinophilic, fibrillar acellular material (fibrin) admixed with erythrocytes and inflammatory cells partially filling the alveoli extending along alveolar septa. (Photo courtesy of: Servie de Diagnostic de Patologia Veterinaria, Facultat de Veterinaria UAB, Bellaterra (Barcelona). (HE, 100X)

components in aspirated amniotic fluid. A similar condition is prevalent in cloned calves. In this case, the condition has also been associated with abnormalities of surfactant, but have not been adequately investigated in other species of domestic animals.

In humans, RDS is one of the main cause of respiratory distress in the newborn[9] and occurs soon after birth, and worsens during the first few hours of life.[9,11] Pulmonary edema plays a central role in the pathogenesis of RDS because of the excess lung fluid is attributed to epithelial injury in the airways, decreased concentration of sodium-absorbing channels in the lung epithelium, and a relative oliguria in the first 2 days after birth in premature infants. [9] Symptoms are similar than in domestic animals and include tachypnea, grunting, retractions and cyanosis.[7,10] The disease progresses rapidly,[5] with increased respiratory effort, intrapulmonary shunting, ventilation perfusion mismatch, and hypoxia with eventual respiratory failure.[9,11] The risk of RDS is inversely proportional to gestational age; RDS occurs in approximately 5% of near-term infants, 30% of infants less than 30 weeks gestational age, and 60% of premature infants less than 28 weeks gestational age.[9,11] Additional factors associated with development of RDS are male sex in Caucasians, infants born to mothers with diabetes, perinatal asphyxia, hypothermia, multiple gestations, cesarean delivery without labor, prematurity and presence of RDS in a previous sibling.[6,9,10,11]

The differential diagnosis of interstitial pneumonia in 1- to 4-month-old foals are bacterial or viral infections or treatment with erythromycin or other xenobiotics including 3-methylindole pyrrolizidine alkaloids and pentachlorophenol. *Rhodococcus equi*, or an aberrant response to that infection, is the main bacterial cause. Respiratory syncytial virus and equid herpesvirus 2 (EHV-2) are documented as the principal viruses for interstitial pneumonias. Other but less frequent causes are endotoxemia and *Pneumocystis carinii* infection. Because of the presence of severe and diffuse

hyperplasia of type II pneumocytes and the multinucleated cells in the lumen of alveolus, we performed immunohistochemistry to eliminate equine herpesvirus infection. No immunopositive cells were seen in any of the sections evaluated.

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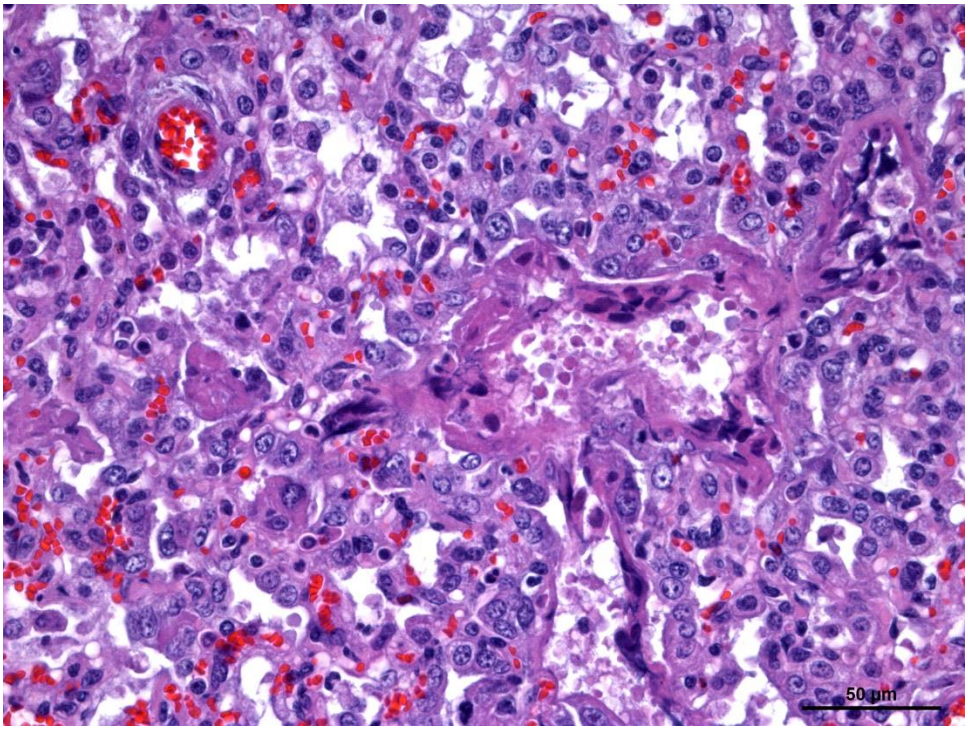
JPC Diagnosis: Lung: Pneumonia, interstitial, lymphohistiocytic, diffuse, marked, with type II pneumocyte hyperplasia, hyaline membrane formation and marked atelectasis.

JPC Comment: The contributor provides an excellent review of a disease in foals that replicates a very important and tragic disease in per-term human neonates.

Pulmonary surfactant is not only important for initial inflation of the lung, but for reinflation of the lung after end expiration as well. It is 80-90% by weight composed of lipid with approximately 70% of this in the form of dipalmitoylphosphtidylcholine.[5] Surfactant lipids are produced by Type II alveolar cells. This product, combined with surfactant proteins (SP) A-D, (produced by club cells) provide the reduction in surface tension required, but surfactant actually performs more functions in the lung.[5] Surfactant proteins are also known as collectins, and are part of the innate immune system.[5] Bacteria, viruses and some fungi have surface receptors for the lectin domains on the hydrophobic SPs A and D, allowing these proteins to participate in clearance activities for the pathogens. In addition, SP A and D also acts as immunomudulators, inhibiting allergen-induced lymphoproliferation, dendridic cell matureation, and eosinophil release of IL-8.[5]



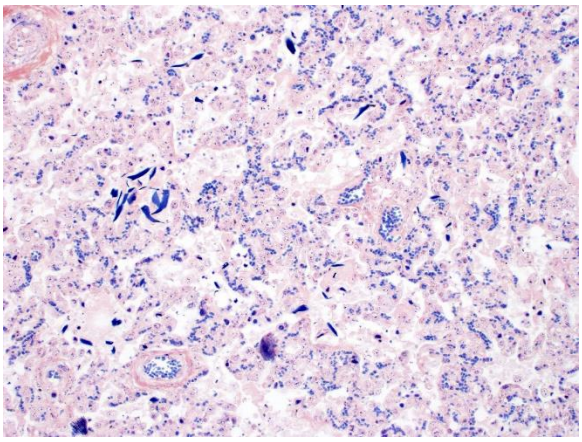
Lung, foal. There is diffuse type II pneumocytes hyperplasia as well as multifocal aggregates of fibrin covering the alveolar walls or partially filling the alveoli (hyaline membranes) admixed with foamy macrophages and occasional multinucleated cells. (Photo courtesy of: Servie de Diagnostic de Patologia Veterinaria, Facultat de Veterinaria UAB, Bellaterra (Barcelona). (HE, 400X).

In 1929, German scientist Kurt von Neergaard performed the first investigations on surface tension in atelectatic porcine lungs, noting the intense pressures required to inflate the lungs for the first time, similar to a baby's first breath.[3] Fifteen years later,

Dr. Peter Gruenwald, a New York pathologist, unaware of von Neergaard's experiments, repeated them on the lungs of stillborn infants, noting that the resistance to inflation appeared to be the result in increased surface tension. In the early 1950s, three independent researchers in different countries (one of whom, John Clements, worked at the US Army Chemical Center in Edgewood, Maryland) independently identified surfactant while studying the effects of nerve gas on the lungs.[3]

A research fellow, at the Harvard School of Medicine, Dr. Mary Avery, hearing of Clement's research, visited him to learn about this new "surface film" in the lung and devised a way to measure it in lung extracts from babies dying soon after birth. Her publication, "*Surface properties in relation to atelectasis and hyaline membrane disease*" in 1959, noted that it took 30 dynes of pressure to inflate the lungs of babies with hyaline membrane disease versus only 8 dynes in babies dying of other causes. One of the most high-profile infant deaths attributable to respiratory distress syndrome was Patrick Bouvier Kennedy, last child of John F. Kennedy and Jacqueline Kennedy, who died 39 hours after birth. [3]

1972 proved to be a banner year for treatment of neonatal hyaline membrane disease the discovery by Howie et al. that the administration of corticosteroids to mothers at risk for preterm birth reduced preterm rates of RDS by stimulating surfactant synthesis.[4] Finally, in the early 1980's , independent testing with modified bovine and porcine surfactants showed great promise, with five different formulations being put into clinical trials: 1) old synthetic or protein free, 2) natural minced lung extracts, 3) natural lung lavage extracts, 4) natural amniotic fluid extracts, and 5) synthetic protein analogues.[4] Today, prophylactic treatment with natural



Lung, foal. A PTAH stain highlights the presence of squames within alveoli, which are often difficult to ascertain against a background of polymerized fibrin. (PTAH, 400X)

surfactants has been considered to decrease RDS by up to 50% and overall, neonatal mortality in the US by 6%.[4]

The moderator started off the conference with an admonition to residents to review pulmonary slides (of which today's conference has four) on a consistent basis, as well as reviewing the important segments of the lung that bear review on each slide. He then reviewed five basic categories of pneumonia – bronchopneumonia, interstitial, bronchointerstitial, embolic, and granulomatous, and defined his rare usage of the simple term "pneumonia" as a morphologic diagnosis (when the precise location of the inflammation cannot be localized to a particular segment).

This case generated spirited debate, and at the end of the discussion, we could not definitely identify equine respiratory disease as the cause of the histologic changes in this slide. While there was polymerized fibrin within alveoli, participants did not appreciate hyaline membrane formation. In addition, the distributed sections contained significant necrosis within terminal bronchioles, which was not described by the contributor. While these are non-specific findings, they are also

reminiscent of the well-known entity of interstitial and bronchointerstitial pneumonia seen in foals from 1 week to 9 months, for which a single definitive cause has not been established.[1] As mentioned by the contributor, possible causes for this syndrome includes viruses (RSV and EHV-2, aberrant responses to *Rhodococcus equi* or other common bacterial pathogens, surfactant dysfunction secondary to production of phospholipase A2 by alveolar macrophages, hyperthermia, or a variety of xenobiotics or toxins.

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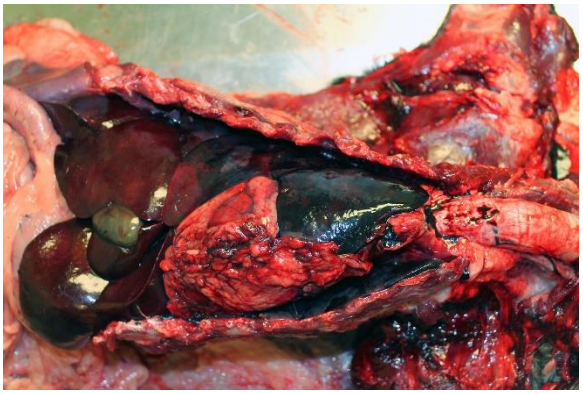
CASE II: 17-0282 (JPC 4117511).

Signalment: 11-year-old, female spayed, dachshund canine (*Canis familiaris)*

History: After two weeks of boarding at the referring veterinarian, the dog became acutely lethargic, tachypneic, and had two episodes of vomiting. Evaluation at the veterinary clinic that day revealed pyrexia (temperature: 106.9 ^{o}F), mild coughing, and mucoid nasal discharge. Thoracic radiographs were unremarkable. The dog was administered a fluid bolus and then later received Lasix and supplemental oxygen. Although the temperature decreased to 101.8 ^{o}F, clinical signs of dyspnea and tachypnea progressed, and the dog developed epistaxis, hemorrhagic discharge from the mouth, as well as bloody diarrhea/melena. The



Lung, dog. The lungs are dark red and firm. (Photo courtesy of: Department of Pathobiology, University of Pennsylvania, School of Veterinary Medicine, Philadelphia, PA 19104 (http://www.vet.upenn.edu/diagnosticlabs)

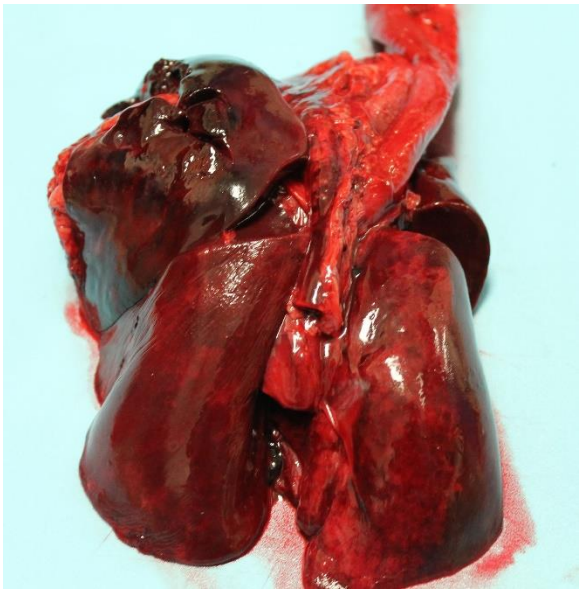
temperature dropped to 95.4 ^{o}F the next morning and the dog died.

Gross Pathology: The pleural cavity contained approximately 125 mL of dark red slightly turbid fluid. The lungs were diffusely dark red, heavy, and firm with failure to collapse and generalized consolidation/"hepatization". Scattered throughout all lobes were pinpoint to 0.1 cm diameter hard white bony spicules. The pulmonary parenchyma exuded copious serosanguinous to hemorrhagic fluid on cut surface and sections from all lobes sank 10% formalin.

There was generalized venous congestion of the splanchnic vasculature. Few "paintbrush" hemorrhages were multifocally dispersed along the serosa of the descending colon. The mucosa of the stomach, duodenum, and orad jejunum were mottled tan-red and the luminal contents consisted of abundant partially digested blood and mucus.

Laboratory results: Aerobic culture of the lung postmortem yielded heavy growth of *Escherichia coli (E. coli*) and a second isolate of *Streptococcus* minor. Antimicrobial susceptibility testing results indicated that the E. coli isolate was sensitive to amikacin, cephalexin, enrofloxacin, imipenum, marbofloxacin, tetracycline, tobramycin, and trimethoprim/sulfamethoxazole.

Microscopic Description:
Lung: Multiple sections of lung are examined and similarly affected. Approximately 25-60% of the pulmonary parenchyma is disrupted by coagulative to lytic necrosis characterized by loss of tissue architecture with replacement by coalescing lakes of hemorrhage admixed with a dense inflammatory exudate. Airways are often occupied by high numbers of erythrocytes, toxic neutrophils, and foamy macrophages enmeshed in eosinophilic proteinaceous edema fluid and fibrillar fibrin. Scattered extracellular and intrahistiocytic short basophilic bacilli are occasionally observed within alveolar spaces, bronchioles, and bronchial lumina. The respiratory epithelium is often attenuated with cellular swelling, rounding, and loss of cilia (degeneration) or



Lung, dog. The lungs fail to collapse and exuded copious amounts of a hemorrhagic fluid. (Photo courtesy of: Department of Pathobiology, University of Pennsylvania, School of Veterinary Medicine, Philadelphia, PA 19104 (www.vet.upenn.edu/diagnosticlabs)

hypereosinophilia and pyknosis with luminal sloughing and exposure of a denuded basement membrane (necrosis). There is a paucity of bronchial associated lymphoid tissue. Pulmonary capillaries are occasionally distorted by luminal fibrin thrombi, and larger vasculature is multifocally variably obscured by deposition of hyalinized fibrin within the vessel wall (fibrinoid vascular necrosis). Other vessels are congested, lined by plump reactive endothelium, and surrounded by perivascular edema.

Alveolar septa multifocally contain low numbers of hematopoietic precursor cells (extramedullary hematopoiesis). Few small trabeculae of bone are randomly dispersed throughout the parenchyma. Rarely adjacent to larger airways are small clusters of histiocytes that contain finely granular black intracytoplasmic pigment. Histiocytes are intermingled with lymphocytes and fewer plasma cells.

Sections of the stomach, small intestine, and colon (slides not submitted) are diffusely hyperemic with marked transmural vascular congestion. Increased numbers of lymphocytes and plasma cells expand the gastrointestinal mucosa and there is occasional leukocyte exocytosis. Low numbers of neutrophils are intermingled within the superficial gastric mucosa.

Special staining of the lung reveals gram-negative bacilli within airways.

Clinical Signs– acute onset of dyspnea, tachypnea, pyrexia, and vomiting with rapid progression to epistaxis, hemoptysis, and melena

Contributor's Morphologic Diagnoses: Lung:

1. Severe diffuse acute necrohemorrhagic and fibrinosuppurative pneumonia with numerous gram-negative bacilli
2. Multifocal heterotopic bone
3. Minimal multifocal pneumoconiosis

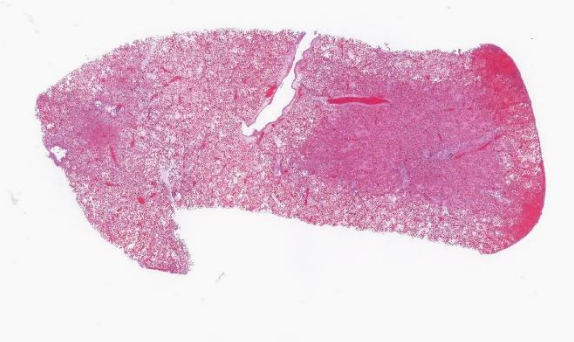
Stomach (not submitted):

1. Mild multifocal chronic neutrophilic and lymphoplasmacytic gastritis
2. Marked mural congestion

Small intestine, colon (not submitted):

1. Mild to moderate diffuse chronic lymphoplasmacytic enterocolitis
2. Marked mural congestion

Contributor's Comment: In dogs, bacterial pneumonia is most often attributed to opportunistic pathogens that occur as commensals of the normal microflora. Diagnosis therefore warrants an investigation for a predisposing cause that resulted in impairment of the pulmonary defense mechanism. Possible primary causes include viral infection (distemper, adenovirus-2, parainfluenza) or immunosuppression.[5,6,8,12] Aside from *Bordetella bronchiseptica*, which can be a primary pathogen, common opportunistic bacterial isolates include *Streptococcus* spp, *E coli*, *Pasteurella multocida*, and *Klebsiella pneumonia*e.



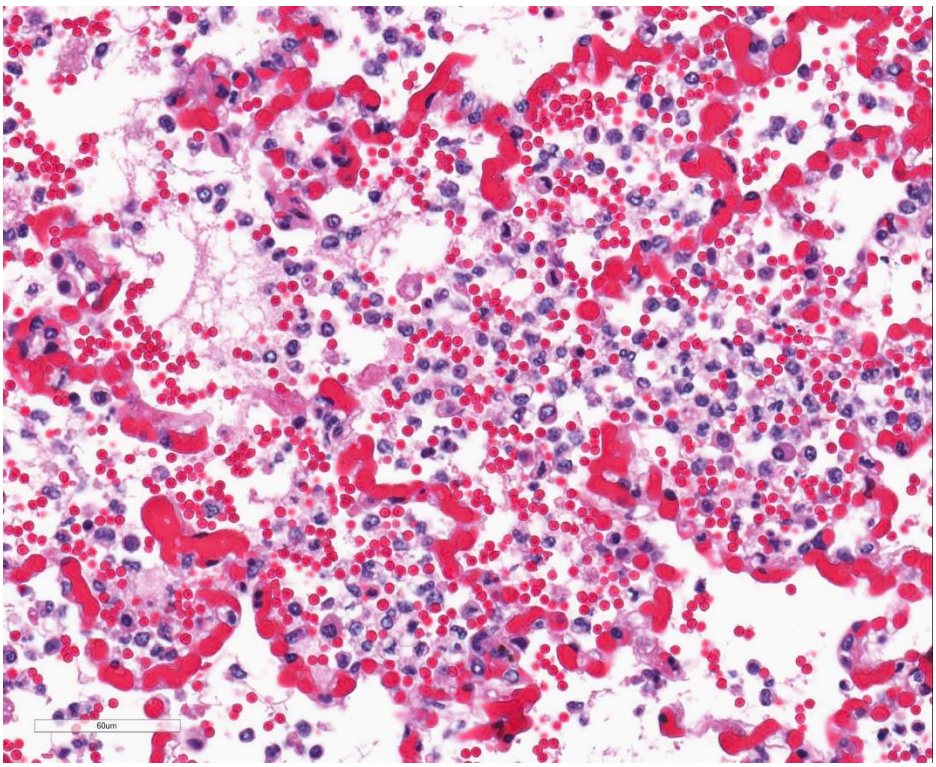
Lung, dog. A single section of lung is submitted for examination. At subgross magnification, diffuse severe congestion, edema, and subpleural hemorrhage is evident. (HE, 4X)

Mixed bacterial infections are not infrequent.[5,6,8,12]

E. coli is often isolated in cases of aspiration pneumonia, and lesions are typically unilateral, necrotizing, and sometimes reveal the presence of foreign material within airways.[5] A predisposing factor to either aspiration pneumonia (i.e. dysphagia, regurgitation, megaesophagus) or bacterial pneumonia was not identified in this dog. Affected animals with either bacterial and/or aspiration pneumonia are susceptible to subsequent bacteremia, disseminated intravascular coagulation, and diffuse alveolar damage, which manifests clinically as acute respiratory distress syndrome (ARDS).[5]

Alternatively, mucosal barrier dysfunction in the gut can lead to bacterial translocation and hematogenous spread of the organism to the lungs.[5,7] Evaluation of the gastrointestinal tract in the present case revealed changes compatible with chronic inflammatory bowel disease. No definitive foci of ulcers/erosions were identified, however the presence of neutrophils identified within the gastric mucosa could suggest mucosal barrier disruption.

Characterization and virulence typing of the *E. coli* isolate was unfortunately not pursued in this case. Previous reports of *E. coli*-associated hemorrhagic pneumonia in dogs have yielded isolates with an O serotype (specifically O4 and O6).[2,7,11] In a case series describing the disease in four dogs, Handt *et al*. identified the presence of the following virulence factors in all *E. coli* isolates: cytotoxic necrotizing factor 1 (CNF1), alpha hemolysin, and the adhesin factor papG allele III.[6] Both CNF1 and alpha hemolysin cause hemorrhage, necrosis, and edema [11,12] and are commonly produced by extraintestinal strains of pathogenic *E. coli*. [4,7,12] In another case report, the bacterial isolate was found to lack alpha hemolysin and instead possess fimbrial antigen K88.[2]



Lung, dog. There is extensive congestion and necrosis (discontinuity) of alveolar septa, with hemorrhage, fibrin polymerization, and numerous viable and degenerative neutrophils admixed with cellular debris. (HE, 389X)

Extraintestinal pathogenic *E. coli* (ExPEC) harbor virulence factors not present in strains of commensal *E. coli*.[11] ExPEC are implicated in several human and animal disease conditions, including urinary tract infections, meningitis, septicemia, and pneumonia.[4,7,10]

Review of the literature sometimes refers to these strains as necrotoxic or necrotoxogenic *E. coli*.[2,7] The pathogenesis of ExPEC involves bacterial adherence to the mucosal surface of the host epithelial cell, which is mediated by their adhesin encoded by papG. Colonization ensues, and there is initiation of the immune response via molecular triggers (i.e. TLR4) and subsequent production of proinflammatory cytokines.[11,12] While mechanisms of infection are uncertain, it has been hypothesized that animal affected by ExPEC may be immunocompromised secondary to stress, possibly induced by shipping or shelter overcrowding. These animals could be then be infected through inhalation following exposure to their own microflora or fecal contamination from a subclinical animal or human.[7,11]

It is worth noting that in both of these studies,[2,7] all dogs had a recent history of travel and were reportedly healthy prior to the development of peracute, fulminant, respiratory disease. Sudden death occurred in two dogs, while the remaining animals (including the current case) died within 24 hours following the onset of clinical signs. Clinical findings frequently included tachypnea, dyspnea, lethargy, and inappetance; when available, clinicopathologic abnormalities typically showed neutropenia with left shift. [2,7] A retrospective study specifically investigating hemoptysis determined that bacterial pneumonia was the most common underlying cause.[1] Consumption of expectorated blood from the respiratory tract was considered the most likely cause for melena in the present cause, however unidentified gastrointestinal ulcers cannot be ruled out.

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JPC Diagnosis: Lung: Pneumonia, interstitial, fibrinosuppurative, necrotizing, and hemorrhagic, diffuse, severe with multifocal necrotizing vasculitis

JPC Comment: The contributor has given an outstanding review of extraintestinal *E. coli* infection in the dog. A second pathogen was isolated from the lung in this animal, a minor population of non-speciated streptococci was also identified.

Within the last decade, several outbreaks of necrohemorrhagic pneumonia have been reported in confined dogs as a result of infection with *Streptococcus equi* var. *zooepidemicus*, a common commensal bacterium and opportunistic pathogen of horses.[3,9,10] One of these outbreaks affected over 1000 shelter dogs in less than one year.[9] Other smaller outbreaks affected animals within shelters and in one case, a university research colony.[10] Prior to this, it had been identified as a sporadic pathogen in dogs.[10]

In these outbreaks, infected dogs presented with respiratory signs of coughing, mucoid or hemorrhagic nasal discharge, and dyspnea, with some dying within 24-48 hours of clinical signs. At autopsy, pleural cavities often contained hemorrhage, and the predominant clinical signs were a necrotizing and fibrinous bronchopneumonia affecting all lobes and extending to the pleura. Numerous cocci are present within the cytoplasm of neutrophils, macrophages, or free within alveoli.[10]

While the pathogenesis of this disease is yet unknown, the potential for exotoxins of *S. equi* var. *zooepidemicus* has been postulated to cause an exuberant inflammatory response, such as may be seen in *S. equi* var.

equi infection in horses and *S. pyogenes*, incriminated in toxic shock in humans. During the rapid clinical course of this condition, there is a marked elevation in a number of proinflammatory cytokines including IL-6, tumor necrosis factor, and interleukin-8 in the blood of infected animals. In these cases, *S. zooepidemicus* is routinely cultured from nasopharyngeal swabs or as a pure culture from affected lung tissue, and other common respiratory pathogens are seldom present. However, efforts to infect healthy dogs with cultures of *S. zooepidemicus* alone have not borne fruit, suggested as yet unexplained factors or co-pathogens in full-blown infection.

The moderator discussed the concept of diffuse alveolar phase, as well as the three phases of septal injury – exudative, proliferative (2-3 days later with type II pneumocyte hyperplasia) and repair (in which fibrosis may be seen in severe cases). Participants discussed the difficulty in this slide in differentiating hyaline membranes from necrotic alveolar walls or smooth muscle, as well as the remarkable amount of necrosis in the lung that apparently occurred within 24 hours in this animal.

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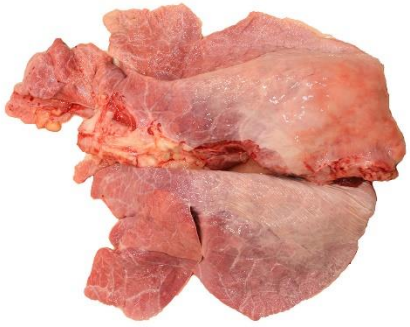
CASE III: P17-747 (JPC 4118594).

Signalment: 14 month old, female, Holstein-Friesian (*Bos Taurus*).



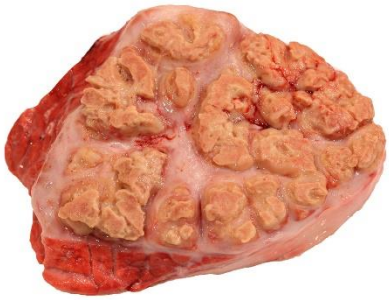
Lung, ox: There is marked fibrosis of the pleura overlying the caudal lobes, and a 25cm area of consolidation in the right pulmonary lobe. (Photo courtesy of: Friedrich-Loeffler-Institut, Department of Experimental Animal Facilities and Biorisk Management, Südufer 10, 17493 Greifswald-Insel Riems, https://www.fli.de/en/institutes/department-of-experimental-animal-facilities-and-biorisk-management-atb/)

History: This heifer was part of an experimental setting and inoculated by the intranasal and intratracheal route with 10^9 CFU of *Mycoplasma mycoides* subsp. *mycoides* (Mmm). The animal was humanely destroyed 4 weeks later and submitted for necropsy.

Gross Pathology: Lung: Multifocally, the pulmonary pleura was thickened and fibrotic with multiple adhesions to the thoracic wall. Only the right pulmonary caudal lobe was markedly enlarged and consolidated (25 cm in diameter). On cut section, there were variably sized bulging yellowish-grey to pale red and dry areas (necrosis) with marked interlobular fibrosis and distension of thrombosed lymph vessels. The left cranial lobe was diffusely atelectatic.

Laboratory results: PCR specific for Mmm in lung tissue - positive

Microscopic Description:
Lung: There are multifocal to coalescing areas of coagulative necrosis effacing 60% to 90% of the parenchyma (depending on location). Multifocally, there is mineralization in the central core of necrosis. Preexisting alveolar and bronchiolar lumina are replaced and expanded by an exudate composed of eosinophilic beaded fibrillar material (fibrin) admixed with large numbers of degenerate and few viable neutrophils, karyorrhectic debris and fewer alveolar macrophages, lymphocytes, and plasma cells. Adjacent and surrounding the necrotic foci the interlobular septa are markedly expanded up to 20 times by fibrovascular tissue

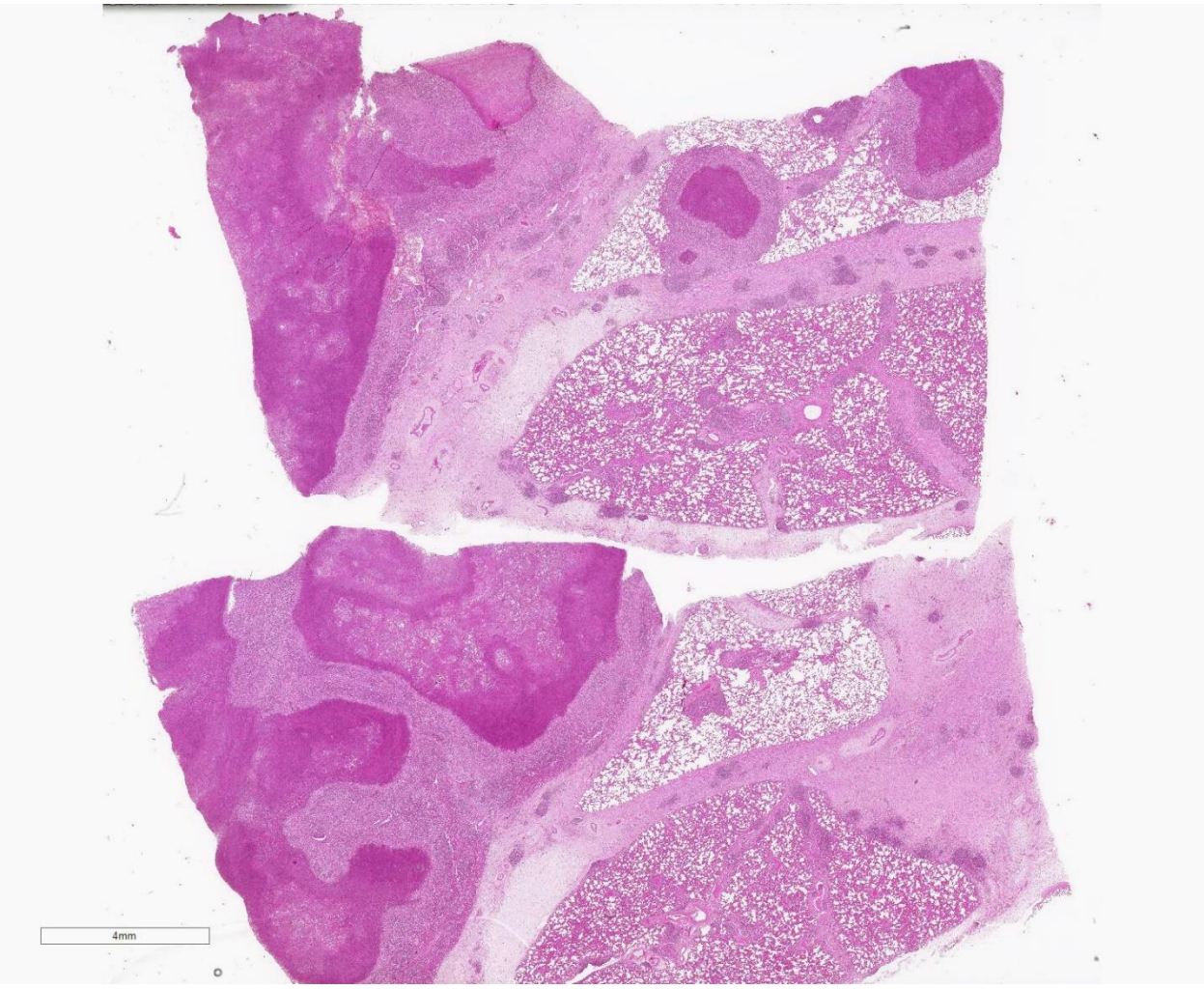


Lung, ox: On cut section, areas of necrosis bulge from the surface, and the interlobular septa are markedly expanded. (Photo courtesy of: Friedrich-Loeffler-Institut, Department of Experimental Animal Facilities and Biorisk Management, Südufer 10, 17493 Greifswald-Insel Riems, https://www.fli.de/en/institutes/department-of-experimental-animal-facilities-and-biorisk-management-atb/)

(fibrosis) with numerous aggregated lymphocytes (lymphoid hyperplasia), scattered plasma cells and histiocytes (sequestration). Necrotic debris and homogenous eosinophilic material is present in various lymphatic vessels (thrombosis). Medium sized bronchi are surrounded by thick layers of connective tissue. In less consolidated areas alveoli coalesce and are expanded by clear space (emphysema) or partially contain eosinophilic fluid (edema).

Contributor's Morphologic Diagnoses: Lung: Pleuropneumonia, fibrinonecrotizing, chronic, multifocal to coalescing, severe, with sequestrum formation, lymphoid hyperplasia, and interlobular fibrosis

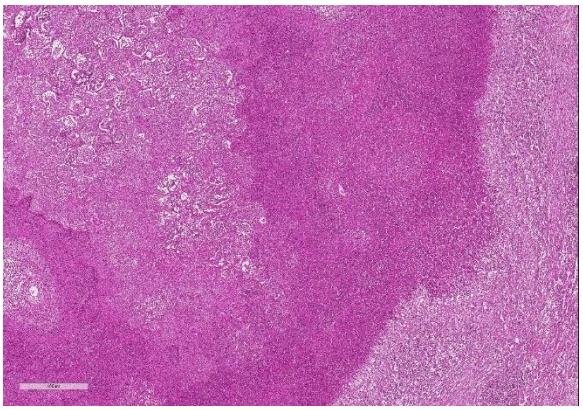
Contributor's Comment: Contagious bovine pleuropneumonia (CBPP) is a notifiable highly contagious disease caused by *Mycoplasma mycoides* subsp. *mycoides* (Mmm). Mycoplasma are pleomorphic, non-motile and the smallest (0.3-0.8 µm) self-replicating bacteria which lack a true cell wall. There are over 200 Mycoplasma species, which are usually host-specific.[8] Since small ruminants are not susceptible to the infection, Mmm is highly contagious for domestic cattle (*Bos taurus* and *Bos indicus*)



Lung, ox. At subgross magnification, lobules are separated by markedly edematous septa. Lobules exhibit large areas of necrosis, as well as variable degrees of atelectasis. (HE, 5X)

of all ages. CBPP is also reported in bison, yak, and domestic buffalo.[1] Usually, CBPP has an incubation period of 3-6 weeks, but it can be longer up to 6 months. CBPP is mainly spread by inhalation of droplets from infected animals, but transmission can also occur via urine. Transplacental infection may occur as well. Currently the disease is endemic in Africa, especially in the Sahel Zone with neighboring countries where sporadic outbreaks are very common. Western Europe and Australia are considered free of CBPP.[1,8]

Cattle exhibit a pronounced age-dependent course of the disease, with calves up to 6 months showing arthritis mainly affecting the carpal and tarsal joints. In contrast, older animals primarily present with respiratory disease/distress caused by Mmm induced fibrinous pleuropneumonia. After infection of the respiratory tract, bacteremia develops secondarily. Whereas sudden death may occur in peracute cases, acutely ill animals commonly show fever, anorexia, and depression, followed by typical respiratory signs as dyspnea, mucoid nasal discharge, and coughing.[1,3] Commonly, affected animals show reduced milk production. Clinical signs may be absent in the chronic phase of the disease or affected animals show intermittent cough and fever, respectively, while shedding the organism intermittently.[1]



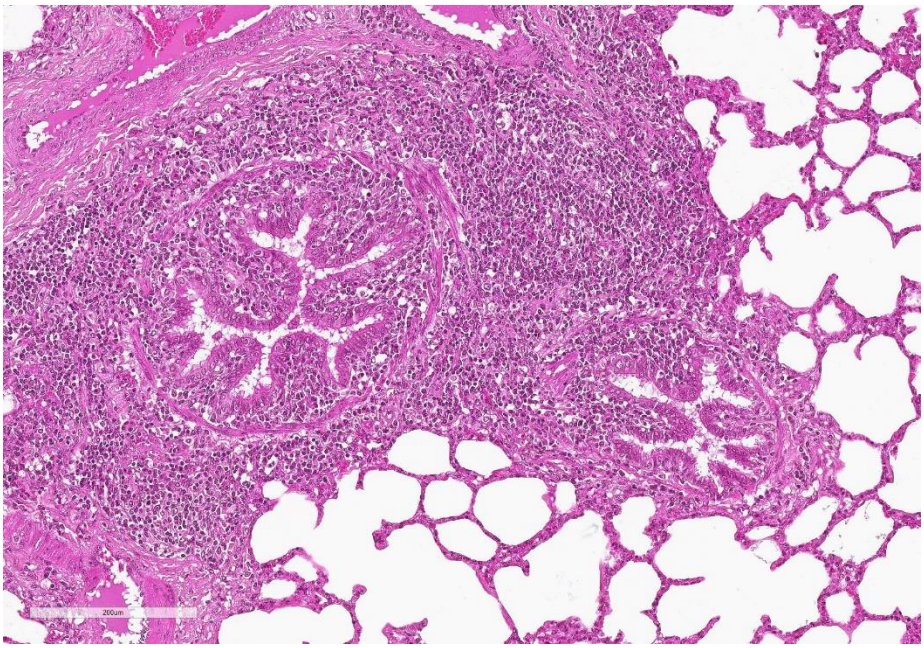
Lung ox. Large areas of central coagulative and more peripheral lytic necrosis are surrounded by a band of granulation tissue (right), forming a sequestrum. (HE, 100X)

Specific gross lesions in CBPP depend on the course of disease. Severe congestion and hemorrhage are characteristic in the acute phase of fibrinous pleuropneumonia leading to red discoloration of lung tissue. The term 'pleuropneumonia' derives from early deposition of fibrinous exudate on the pleural surface resulting in accumulation of abundant yellow material in the pleural cavity. There is marked thickening and inflammation of the pleura leading to fibrinous pleurisy. On cut surface, dilatation and thrombosis of lymph vessels accompanied with interstitial edema lead to distension of interlobular septa giving the lung a marbled appearance. In chronic cases, areas of coagulative necrosis eventually develop into 'sequestra' by which necrotic lung parenchyma is encapsulated by connective tissue.[2]

Due to the fact that the animal in this case was part of a challenge model targeting the immune response, necropsy was performed only in the chronic phase of disease. Thus, histological lesions of the early stages of CBPP-=like hyperemia, interstitial edema and marked lymphangiectasia with lymphatic thrombosis and obstruction as well as diffuse fibrinous exudation were not present in the slides. Later on, neutrophils invade diffusely within the parenchyma and the fibrin deposits.[2,3,4] Since the branches of the bronchioles within the necrotic foci remain unchanged, the demarcation starts in an angiocentric way. From here and in broad layers with peripheral leukocyte accumulation and demarcation, a fresh granulation tissue extends towards the surrounding necrosis and yields the sequestrum.[4]

The pathogenicity of CBPP is not completely understood. Virulence factors of

Mycoplasma species seem to be determined by intrinsic metabolic or catabolic pathway functions or by proper constituents of the mycoplasmal outer surface. It is unclear by which mechanisms Mmm can evade the killing by phagosome-lysosome fusion, which toxic molecules are produced that are responsible for cellular damage, and how vasculitis and thrombosis are induced. It is assumed that the bacterial membrane lipoprotein LppQ, is involved in the pathogenesis. The virulence of some Mmm strains seems to be related to the release of H_2O_2 which is cytotoxic.[5] Toxic galactan production, ciliary dysfunction, TNF-alpha dysregulation and immune-mediated vasculitis are also discussed to be involved in the pathogenic process of CBPP. Vasculitis and thrombosis of arteries, small caliber blood and lymphatic vessels are known to be crucial for the development of coagulative necrosis of lung tissue.[3] Little is known why CBPP is mainly restricted to the caudal pulmonary lobes and often occurs unilaterally.



Lung, ox. In less affected lobules, bronchioles are surrounded by marked BALT hyperplasia and the submucosa and mucosa is infiltrated by numerous neutrophils and lymphocytes). (HE, 159X)

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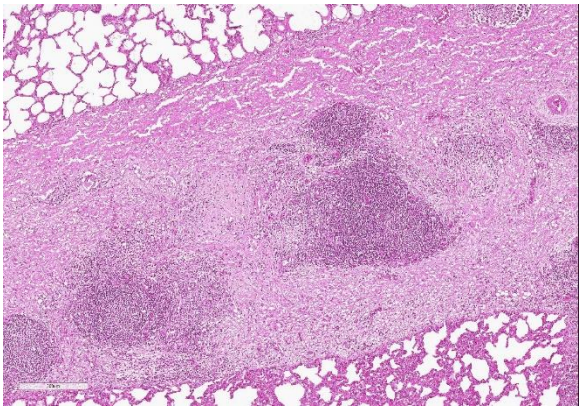
JPC Diagnosis: Lung: Bronchopneumonia, fibrinosuppurative and necrotizing, multifocal, severe, with marked interlobular edema.

JPC Comment: The contributor has done an outstanding job in reviewing this pathogen, which, with the eradication of rinderpest, is considered to be the most important pathogen in affected countries.[7] It is the only bacterial disease currently on the OIE's "A" list of severe infectious animal disease,[7] Eradicated from much of the world, it has never been reported in South America and several Saharan and Middle Easter countries. It is considered eradicated in North America, much of Asia, Australia, and countries comprising the southern part of Africa. In the remaining part of sub-Saharan Africa, the disease is present and yet causes marked livestock losses. Current information on outbreaks of this disease may be found at the World Animal Health Information Service

athttp://www.oie.int/wahis_2/public/wahid.php/Wahidhome/Home .

In the United States, the federal veterinary service, the US Bureau of Animal Industry, was founded in 1884, largely to eradicate the disease of contagious bovine pleuropneumonia. Its first director, Dr. Daniel Salmon had begun his years-long crusade to stamp out the disease in 1879, and was given the task of organizing the BAI in 1884, and established the Pathological Division in 1891. In addition to work on contagious bovine pleuropneumonia (which was eradicated from the United States in 1892, the BAI Pathological division did yeomans work in eradicating and developing vaccines for many other diseases, including foot-and –mouth disease, blackleg, tuberculosis, glanders, dourine, and Texas cattle fever (bovine babesiosis). Their groundbreaking research as a division of the USDA came to a halt in 1953 when their duties were transferred to the Agricultural Research Service, a newly created organization under the Eisenhower administration.[6]

MMM belongs to the so-called "*M. mycoides* cluster", containing MMM, *M. mycoides* susbsp *capri* (MMc), *M. capricolum* subsp *capricolum* (Mcc), *M. capricolum* susbsp. *capripneumoniae* (Mccp) and *M. leachii*, containing a number of closely related previous unclassified mycoplasmas. MMM's most closely related member of this cluster is *Mycoplasma mycoides* susbsp. *capri*, a bacterium which causes a syndrome called "MAKePS" in small ruminants, primarily goats, composed of mastitis, arthritis, keratitis, pneumonia, and septicemia. It can also be identified in the ears of normal goats.[7]



Lung, ox. Interlobular septa are markedly expanded by fibrous connective tissue, edema, and numerous lymphoid nodules (tertiary lymphoid centers) (HE, 69X)

The moderator reviewed several other severe fibrinosuppurative pleuropneumonias in cattle, and the subtle gross and histologic lesions that might help differentiate them, to include *Mannhemia hemolytic*a, *Histophilus somni*, *Pasturella multocida*, and *Mycoplasma bovis*, in addition to MMM.

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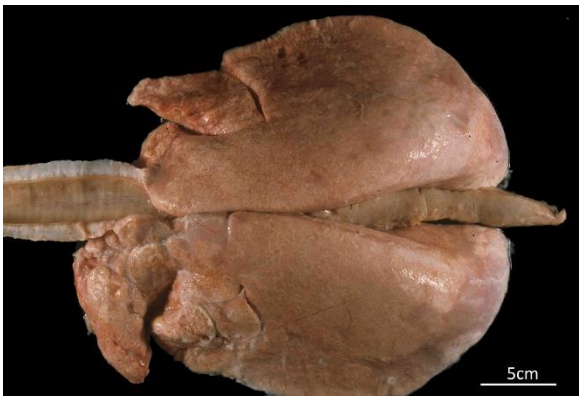
CASE IV: N198/18 (JPC 4120174).

Signalment: 3 year-old, female, Rasa Aragonesa sheep (*Ovis aries*)

History: The animal presented with signs of emaciation to the clinical service for ruminants (*Servicio Clínico de Ruminantes* – SCRUM) at the University of Zaragoza. Clinical examination of the animal showed respiratory dyspnea and increased respiratory sounds.

Gross Pathology: Prior to post-mortem examination, educational computed tomography (CT) scans were performed of the thorax and evinced a diffuse bronchointerstitial pattern and increased thickness of the bronchiolar walls. At necropsy, the sheep showed cachexia (1/5). The lungs were diffusely enlarged, grey, and had a rubbery-like firmness. Lung weight was also increased. Over the pulmonary surface there were multifocal 1-2 mm grey dots. Mediastinal and tracheobronchial lymph nodes were enlarged.

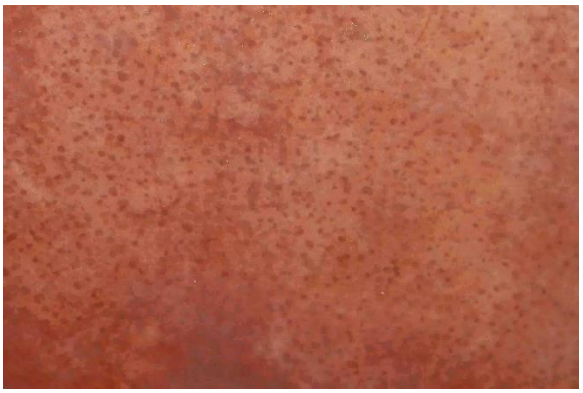


Lung, sheep: At autopsy, the lungs were expanded, grey and firm with a rubbery texture. (Photo courtesy of: Universidad de Zaragoza. Departamento de Patología Animal, Web: (https://patologiaanimal.unizar.es/)

Laboratory results: The blood count showed moderate normochromic, normocytic anemia.

Quantitative PCR, considered positive when quantitation cycle (Cq value) was lower than 38, was performed in a lung sample. It was positive for *Visna-Maedi/Caprine Arthritis Encephalitis* virus (Cq value: 27,7) and for *Mycoplasma ovipneumoniae* (Cq value: 35,5) and negative for *Pasteurella multocida* and *Mannheimia haemolytica*.

Microscopic Description:
Lung: There is a diffuse inflammatory process that expands the alveolar septa of around the 100% of the section and there is multifocal prominent hyperplasia of bronchial/bronchiolar associated lymphoid tissue (BALT). Diffusely, alveolar septa are



Lung, sheep: Numerous grey dots over the surface of the lung correspond to lymphoid nodules within the pulmonary parenchyma. (Photo courtesy of: Universidad de Zaragoza. Departamento de Patología Animal, Web: (https://patologiaanimal.unizar.es/)

thickened up to 5 times by lymphocytes, histiocytes, plasma cells and rare neutrophils. BALT follicles show an enlarged diameter by increased numbers of centrocytes/centroblast (BALT hyperplasia). These follicles tend to coalesce and multifocally bulge towards the pleura. Multifocally, interstitial and bronchial/bronchiolar smooth muscle is enlarged and there is an increased number of myocytes/myofibroblasts (smooth muscle hypertrophy-hyperplasia).

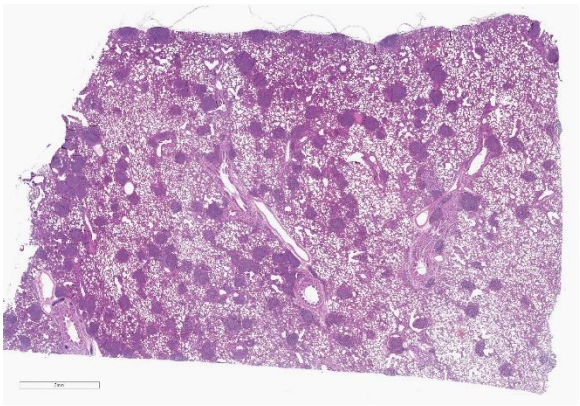
Contributor's Morphologic Diagnoses: Lung: Pneumonia, interstitial, diffuse, severe, chronic with prominent BALT hyperplasia and smooth muscle hypertrophy-hyperplasia.

Condition: Maedi. Ovine Progressive pneumonia
Cause: Small ruminant lentivirus (Visna/maedi virus)

Contributor's Comment: This is the respiratory form of small ruminant lentiviruses. This respiratory disease is caused by a group of non-oncogenic exogenous retroviruses of the genus lentivirus that target immune cells, mainly macrophages.

The Small Ruminant Lentiviruses are a group of highly related single stranded RNA viruses with high mutational potential that affect mainly sheep but also goats.[1] These viruses induce chronic inflammation that usually remains subclinical. When it becomes clinical, the disease can express mainly in four different locations: lung, joints (mainly carpus), central nervous system and mammary gland.[3] The expression of each form as well as the gravity of the lesion depends on host immune response and the viral factors.[2,5]

The respiratory form, termed maedi or ovine progressive pneumonia, is the most common presentation of the disease in sheep.[1] The process consists of an afebrile chronic progressive pneumonia that leads to weight loss and marked dyspnea. Grossly, the lungs show a rubbery firm appearance and do not collapse when the thoracic cavity is opened. Microscopically, is characterized by an inflammatory interstitial pattern and formation of lymphoid nodules with germinal centers around bronchioles and vessels. Mild interstitial fibrosis and smooth muscle hypertrophy are usually present. Unlike goats, type II pneumocytes hyperplasia is rarely seen in sheep.



Lung, sheep: At subgross magnification, numerous lymphoid nodules are dispersed throughout the section. (HE, 8X)

Neurologic form is characterized by leuokencephalomyelitis and demyelination that leads to ataxia and profound weight loss.[6] This form progresses faster than the respiratory one and usually occurs in adult sheep and goat kids (2-4 months). Articular form curse with arthritis affecting mainly the carpal joints.[4] The mammary form implies interstitial mastitis and is associated with agalactia.

The main route of transmission is aerosol, particularly under intensive housing. Colostrum transmission plays also an important role.[3] The virus infects a variety of cell types (mammary epithelium, fibroblast, endothelial cells, monocytes, choroid plexus) but its replication just occur in mature macrophages.[1] Lentiviral-infected macrophages produce cytokines that recruit and activate other leukocytes but also hence lentiviral replication. Indeed, clinical signs and histopathological lesions are the result of the inflammatory process instead of the direct viral damage to the organ. There is neither treatment nor commercial vaccines for the disease, which is what makes immunization of the ovine population against the virus challenging.[8]

The main differential diagnosis of maedi is the classical form of ovine pulmonary adenocarcinoma (OPA). This disease is also presented as chronic progressive respiratory problems. However, there is abundant fluid production that leads to nasal exudate and the gross appearance of the lung shows consolidation of the apical lobes and ventral areas of the organ. The contribution of *Mycoplasma ovipneumoniae* should be taken into consideration in our case either as possible enhancer of the lentiviral infection or as secondary opportunistic pathogen.

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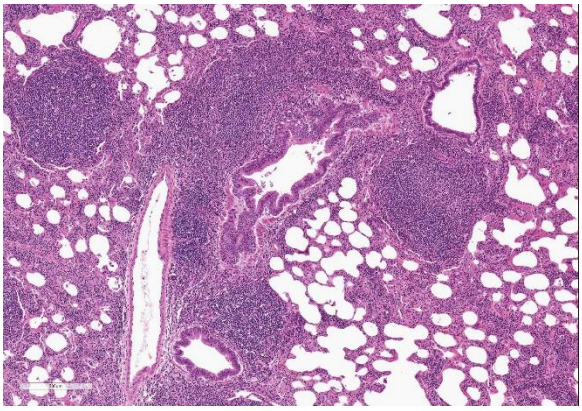


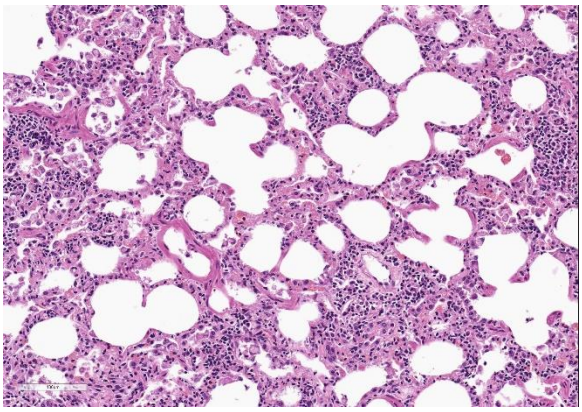
Lung, sheep: Lymphoid nodules are primarily adjacent to airways, but also extend along pulmonary vessels. Alveolar septa are markedly expanded and often atelectatic. (HE, 73X)

JPC Diagnosis: Lung: Pneumonia, interstitial, lymphohistiocytic, diffuse, moderate with peribronchiolar and perivascular lymphoid hyperplasia, and smooth muscle hyperplasia.

JPC Comment: The contributor provides a concise review of one of the most important respiratory diseases of small ruminants. The disease was first reported in South Africa in the eastern town of Graff-Rinet (hence the name "Graff-Rinet disease"). In 1923, it was identified in the United States by Dr. H.W. W Marsh (with various appellations such as "ovine progressive pneumonia" (OPP), "Montana progressive pneumonia", and "Marsh's progressive pneumonia"), and an errant combined paper by Dr. Marsh and Dr. E.V. Cowdry, determined that morphologically, the diseases of jaagsiekte (or ovine pulmonary carcinoma, OPA) and "Montana progressive pneumonia" were one and the same.[2]

The introduction of 20 infected Karakul sheep into Iceland in the early 1930's from Uzbehkistan introduced both OPA and ovine progressive pneumonia (OPP) to Iceland. [10] In 1935, cases of both were identified in Iceland, and cases of OPP (named "maedi" for "shortness of breath" in Icelandic) were identified in farms across the country and were traced back to the imported sheep. Maedi was not fully recognized as a disease different from OPA (jaagsiekte) until 1939 by Dr. G. Gislason, who further epidemiologically delineated the disease as a chronic progressive disease with a 2-3 year incubation period. He discovered that close housing of sheep spread the agent, and faced with a 20-30% mortality annually of older sheep, the Icelandic government slaughtered and replaced all sheep in affected areas and within 10 years, became the first country to eradicate OPP.[10] The disease still remains in all major sheep producing countries of the world, except for Australia and New Zealand, where it has never been seen.

Research in Iceland continued on maedi and a related virus, visna with numerous transmission tests, and the viruses were finally isolated in 1957 (visna) and 1958 (maedi). Following the discovery of reverse transcriptase in these viruses, they became the prototype for the non-oncogenic retroviruses the lentiviruses (lenti="slow"), of which additional viruses, were have isolated, including the disease agents of equine infectious anemia (EIAV – 1976) and caprine arthritis-encephalitis (CAEV-1980.) After experimental cross infection of sheep by CAEV and goats by MVV, the three viruses were grouped together under the name small ruminant lentiviruses (SRLV).[10] The grouping is further reinforced by the ability of SRLVs to cause disease syndromes in sheep that have been previously identified in only in goats, such as viral arthritis.[5]



Lung, sheep: Alveolar septa are expanded by a combination of lymphocytes (often in aggregates), and macrophages, as well as patchy type II pneumocyte hyperplasia. There is moderate scattered interstitial smooth muscle hyperplasia. (HE, 202X)

One of the other peculiarities of the SRLVs, like other lentiviruses, is its predilection for mutation, which may not only help it cross between small ruminant species, but also generate new quasi species, further confounding vaccinologists. Reproduction via reverse transcriptase is not a precise science, as insertional and deletion mutations occur with some frequency. While core genes of *gag* and *pol* are largely conserved, mutations are occasionally found in certain parts of *env* which result in variability, particularly in antibody-binding regions. [1]

As mentioned above, small ruminant lentiviruses may infected a range of cells, but like other lentivirus, they show a particular tropism for cells of macrophage/monocyte lineages to include dendritic cells, mammary gland epithelium (helpful for transmission in colostrum to neonates) and the endothelia and microglia of the CNS (which may help in causation of visna in young lambs and kids.) The maedi-visna virus (MVV) is also unique among lentiviruses as it is the only one in which respiratory transmission is significant (although whether free viruses or exhaled infected cells is the culprit remains to be seen.)[1]

This entity has made a number of appearances in the WSC over the years (see WSC 1995-96, Conference 21, Case 3; WSC 2005-2006, Conference 23, Case 1; WSC 2009, Conference 10, Case 1).

In the conference, the participants reviewed and compared the different manifestation of small ruminant lentiviruses. One of the points of discussion was the difference in pneumonia seen in the goat versus the lamb; the pneumonia in goats is characterized by less prominent lymphoid follicles formation and marked type II pneumocyte hyperplasia and filling of alveoli with surfactant.

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