History

A 3-year-old Hereford cow was submitted for necropsy. The cow had a 24-hour history of recumbency and vocalization with labored breathing and nystagmus prior to death. Another cow on the farm reportedly had similar clinical signs and died within 48 hours after initial evaluation. Both cows had been obtained from a sale barn 7 days prior to death. The vaccination history of these cows was unknown.

Clinical and Gross Findings

On gross examination, the cow was in good body condition (body condition score, 4/9). Approximately 2 L of yellow serous fluid with strands of fibrin was present in the thoracic cavity. The lungs failed to collapse after the thoracic cavity was opened, and several fibrinous adhesions connected the visceral pleura to the parietal pleura. Bilaterally, the ventral portions of cranial lung lobes were firm and dark red and 2 necrotic loci were grossly visible. On cut surface, the consolidated lung parenchyma had a red and gray marbled appearance with widening of the interlobular septa (Figure 1) and the bronchial and bronchiolar lumens contained an exudate. The tracheal lumen contained moderate amounts of straw-colored foam, and there were disseminated petechiae throughout the tracheal mucosa. Multifocal petechiae were visible on the epicardium near the coronary groove. The bronchial lymph nodes were large, wet, and red on cut surface. Fresh lung tissue was submitted for bacterial culture and antimicrobial susceptibility testing, and fresh brain tissue was submitted for rabies virus fluorescent antibody testing.

Formulate differential diagnoses from the history, clinical and gross findings, and Figure 1—then turn the page →
Histopathologic Findings

Samples of the lungs were sectioned and examined histologically. The architecture of the cranioventral areas of the lungs was obliterated by large areas of necrosis and inflammatory infiltrate centered on airways. Diffusely, the interlobular septa and pleura were markedly expanded by abundant fibrin and moderate numbers of degenerate and nondegenerate neutrophils (Figure 2). Bronchioles and alveoli were filled with eosinophilic cellular and karyorrhectic debris, abundant fibrin, edema, numerous necrotic leukocytes with streaming nuclei (oat cells), and macrophages (Figure 3). These areas contained colonies of gram-negative rods and intrabronchial gram-positive cocci. Multifocally, the blood and lymphatic vessels were distended and occluded by fibrin thrombi, and some of the vessels contained numerous colonies of gram-negative bacteria.

Aerobic bacterial culture of lung tissue samples yielded heavy growth of *Mannheimia haemolytica* (consistent with the gram-negative rods detected histologically). The intrabronchial gram-positive cocci were considered likely secondary invaders. Results of antimicrobial susceptibility testing indicated that the *M haemolytica* was susceptible to amikacin, ceftiofur, florfenicol, gentamicin, trimethoprim-sulfamethoxazole, and tulathromycin but resistant to ampicillin and tetracycline. The fluorescent antibody testing of fresh brain tissue for rabies virus yielded negative results.

Morphologic Diagnosis

Severe, acute, multifocal, fibrinonecrotic, cranioventral lobar bronchopneumonia and pleuritis with gram-negative rods consistent with *M haemolytica* (bovine pneumatic mannheimiosis [ie, shipping fever]).

Comments

The gross and histopathologic changes in the cow of this report were consistent with respiratory tract infection with *M haemolytica*. Respiratory tract disease in cattle is extremely common and is reported to cause 30% of all cattle deaths in the United States. Risk factors include crowding, mixing of naïve animals, shipping, change in diet, castration, dehorning, and concurrent viral or bacterial infection. The most commonly proposed scenario for respiratory tract disease development in cattle involves exposure to a predisposing stress factor, which is followed by development of a primary respiratory viral infection that allows secondary infective bacteria to thrive. Primary viral agents include infectious bovine rhinotracheitis virus, bovine respiratory syncytial virus, and parainfluenza 3 virus. In addition to *M hemolytica*, potential secondary infective bacteria include *Pasteurella multocida*, *Histophilus somnii*, and *Mycoplasma bovis*.

*Mannheimia haemolytica* is the most commonly cultured bacterium associated with severe respiratory tract disease in feedlot cattle and has an important role in enzootic pneumonia in neonatal calves. Pneumonic mannheimiosis is characterized by fever, tachypnea, labored breathing, signs of depression, and anorexia. In animals with severe disease, signs of endotoxic shock, such as pale or dark mucous membranes, prolonged capillary refill time, and extremities that are cool to the touch, may be evident. Because infection with *Mannheimia* organisms devel-
ops via inhalation, lung lesions have a cranioventral distribution. This is primarily due to gravitational influences that lead to an increased deposition of inhaled particles within the ventral portions of the cranial lung lobes as well as an increased incidence of pooling of respiratory secretions that can trap bacteria. Grossly, infection with M. haemolytica is characterized by fibrinopurulent pleuropneumonia and marbling of the lung tissue, with lobules that can be normal in color, gray, or red. Whole lobes can be hemorrhagic or undergo coagulation necrosis; interlobular septa are usually distended with fibrin-rich edema fluid, and interlobular lymphatic vessels may contain fibrin thrombi. Histologically, alveoli and interlobular septa are filled with large numbers of neutrophils and macrophages admixed with fibrin. The alveoli are often filled with necrotic leukocytes, termed oat cells, which have a streaming pattern of pale basophilic chromatin.

The differential diagnoses for fibrinous pleuropneumonia in cattle include infection with H. somni, P. multocida, and Mycoplasma mycoides small colony type; the latter is the etiologic agent of bovine contagious pleuropneumonia and an extremely important foreign animal disease of cattle. As in M. haemolytica infection, oat cells are a characteristic feature of H. somni pulmonary infections because both organisms produce a leukotoxin that causes pore formation within the leukocyte membrane, leading to lysis and necrosis. In cattle with P. multocida infection, the cranioventral lobes are firm and dark red to purple and there is purulent exudate in the airways; fibrin on the pleura is not expected. Bovine contagious pleuropneumonia and pneumonic Mannheimiosis are extremely difficult to distinguish grossly as well as histologically. However, grossly, Mycoplasma infections are associated with fibrinopneumonitis that is often unilateral and restricted to the caudal lung lobes. The effects of M. haemolytica infection can be chronic; thus, such infections can substantially increase morbidity in a cattle population. Common sequelae of animals that survive fulminant pneumonic mannheimiosis include chronic suppressive bronchopneumonia (which often allows colonization by secondary bacteria [eg, Arachnobacterium pyogenes]), pleural adhesions, pulmonary fibrosis, bronchiectasis, abscess formation, and pulmonary parenchymal sequestration. Sequestration is particularly debilitating because it is a permanent, nonfunctional nidus for infection.

Mannheimia haemolytica is a gram-negative aerobic bacterium of the family Pasteurellaceae, formerly known as Pasteurella haemolytica biotype A, that normally resides in low numbers in the nasopharynx of cattle. As a commensal and opportunistic microorganism, M. haemolytica can only cause disease when the innate defense mechanisms in the lungs are diminished by high circulating concentrations of cortisol or concurrent infection. When these conditions are present, the function of the mucociliary apparatus and pulmonary alveolar macrophages is diminished and production of secreted antimicrobial proteins decreases; this allows for reduced clearance of M. haemolytica from the lower airways and survival and overgrowth of the bacterium, leading to pneumonia. Mannheimia haemolytica has many important virulence factors that contribute to its ability to induce acute respiratory tract disease. These virulence factors include leukotoxin (exotoxin), lipopolysaccharide, superoxide dismutase, iron-regulated outer membrane proteins, O-sialoglycoprotease, capsular polysaccharide, and neuraminidase. Leukotoxin, considered one of the most important virulence factors, binds specifically to CD18 on ruminant leukocytes and causes pore formation, thereby leading to cytolysis. As a result of neutrophil and macrophage lysis, the cell contents are released, which causes even more extensive pulmonary damage. To induce protective immunity against M. haemolytica, vaccines must include several factors, such as leukotoxin, outer membrane proteins, capsular polysaccharide, and lipopolysaccharide. Lipopolysaccharides are an important virulence factor for any gram-negative bacterium and result in neutrophil and macrophage activation, production of proinflammatory cytokines (eg, tumor necrosis factor-α, interleukin-1β, and interleukin-8), endothelial activation as well as widespread activation of the coagulation cascade, and eventual hypotensive shock. Lastly, iron-regulated outer membrane proteins are produced in response to iron depletion and allow for iron acquisition, which is necessary for the survival of Mannheimia organisms in vivo. It is important to note that clinical disease is primarily caused by the hosts response to the infection rather than secondarily caused by the release of toxins into the tissues. The host responds to Mannheimia infections via overwhelming infiltration of inflammatory cells and fibrin into the alveoli, which results in severe respiratory distress. Many antimicrobials, such as oxytetracycline, ceftiofur, spectinomycin, tilmicosin, and tulathromycin, are approved for treatment of pneumonic mannheimiosis in cattle.

A common herd practice is to treat antimicrobials prophylactically (treatment of some animals in a herd at high risk for active disease as others are being treated prophylactically) because > 60% of calves in US calf-cow operations are not vaccinated against bovine respiratory diseases prior to weaning. However, the best way to avoid M. haemolytica infection is to precondition and properly vaccinate calves prior to feedlot sale. Appropriate management practices including preconditioning programs can be extremely beneficial to overall herd health by decreasing the incidence of bovine respiratory tract disease and its negative economic impact.

References