Diffuse Fibrosing Alveolitis in Three Adult Cattle

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Introduction

Diffuse fibrosing alveolitis, also known as interstitial pneumonia or chronic interstitial fibrosis, is a descriptive histologic term used to classify a clinical presentation of pulmonary lesions characterized by cellular infiltration of interalveolar septa and diffuse fibrosis. While the syndrome is well-documented in Great Britain, it is not commonly recognized clinically in the United States. However, interstitial pneumonia does account for a significant proportion of the known respiratory diseases in veterinary medicine. Therefore, it is important that veterinarians be aware of and can recognize the syndrome, including it in the differential diagnosis for pulmonary disease.

Case Reports

During a four month period, three unusual bovine cases with similar histories and clinical signs were presented to the Boren Veterinary Medical Teaching Hospital, Oklahoma State University, Stillwater, Oklahoma. The beef cattle, two cows and a bull, ranged in age from six to eight years. Upon admission, the cows' presenting complaints included chronic weight loss (2 to 15 months duration), weakness, exercise intolerance and respiratory distress. The bull was presented for a preputial prolapse, however the history and physical exam revealed findings suggestive of more serious disease. These findings included poor body condition, tachycardia, hyperpnea and a 12 month history of lagging behind the herd and visible respiratory difficulty when forced to exert himself. All three were range cattle, the diet varying from native grass to improved pasture. In addition, supplemental nutrition was furnished during the winter months. The cattle were pastured in Oklahoma; the two cows were kept in the northern part of the state, while the bull was from central Oklahoma.

Upon physical examination, Cow 1 was hypothermic (98.8° F) while the other two cattle were normothermic (101° F). The bull was tachycardiac (80 bpm), while Cow 1 was bradycardiac (40 bpm) and Cow 2 was normal (60 bpm). The heart sounds were muffled in the three animals. All three were hyperpneic (35-40 rpm). Cow 1 had increased inspiratory lung sounds, extensive edema involving the mandible, brisket region, lower abdomen and all four limbs. A bilateral jugular pulse was present. Neither cow was pregnant.

Biochemically, all three cattle had elevated liver enzymes. Initial hematologic values for Cow 1 and the bull are summarized in Table 1. Both animals had a neutrophilia and reactive lymphocytes. In addition, the bull had a lymphopenia and an elevated fibrinogen level. Because Cow 2 was extremely debilitated and in light of a poor prognosis, the owners elected euthanasia shortly after examination.

TABLE 1. Data Base

Complete Blood Count	Reference Values	Cow 1	Cow* 2	Bull
Total WBC (no./ul)	4,000 - 12,000	8,700		10,500
Neutrophilis, segmented (no./ul)	600 - 4,000	4,872		7,455
Neutrophilis, bands (no./ul)	0 - 120	87		0
Lymphocytes (no./ul)	500 - 7,500	2,610**		2,100**
Monocytes (no./ul)	25 - 850	870		420
Eosinophils (no./ul)	0 - 2,400	261		525
Total RBC (X 10^6 /ul)	5.0 - 10.0	6.28		7.78
Hgb (gm/dl)	8.0 - 15.0	10.30		11.50
Hct (%)	24.0 - 46.0	30.60		32.40
MVC (femtoliters)	40.0 - 60.0	49.00		42.00
MCH (picograms)	11.0 - 17.0	17.40		15.20
MCHC (%)	30.0 - 36.0	34.60		35.60
Plasma Proteins (gm %)	6.0 - 8.0	7.20	5.7	8.00
Fibrinogen (mg/dl)	100.0 - 600.0	300.00		1,200.00

* Due to the animal's debilitated condition, she was euthanized within hours of presentation. Minimal laboratory work was performed in light of economic constraints.

** Some reactive lymphocytes were seen.

Note: Reference values listed are those determined by the Department of Pathology, Clincal Pathology Laboratory, College of Veterinary Medicine, Oklahoma State University, Stillwater, Oklahoma 74078.

The physical condition of both Cow 1 and the bull deteriorated during hospitalization and Cow 1 was euthanized on day two of hospitalization.

The bull developed markedly increased inspiratory respiratory sounds and a cough on day four of hospitalization. In addition, he was constipated. On day seven, hematologic and biochemical profiles were re-evaluated. The hemogram revealed a leukocytosis with a neutrophilia and monocytosis. The total protein had decreased from 8.0 to 7.4 and he was hypoalbuminemic (1.7). Biochemically, the bull was azotemic with an elevated blood urea nitrogen (BUN) of 60 and a creatinine of 2.9. The SGGT was elevated to 360 (normal 12.2-38.4) indicative

of cholestasis. Clinically, he developed a very liquid diarrhea and displayed extreme exercise intolerance.

On day eight, he was hypothermic (98.4° F), tachycardiac (64 bpm) and hyperpneic (48 rmp). The bull was unresponsive and sternally recumbant when examined at 7:30 a.m. and died within an hour.

Significant post-mortem findings of all three animals were lesions compatible with chronic fibrosing interstitial pneumonia. The elevated liver enzymes recorded in all three were probably due to chronic passive liver congestion. Alterations in hepatic blood flow such as those occurring with chronic passive congestion result primarily in hepatic centrilobular hypoxemia. Clinically, this is characterized by an elevation in liver enzymes. The development of diarrhea in the bull is also a sequela to hepatic congestion. With obstruction or stasis of the biliary system there is a deficiency or absence of bile salts from the digestive tract resulting in decreased digestion and absorption. Constipation followed by attacks of diarrhea often occurs.

The presence of inflammatory disease in the bull, as confirmed by the elevated fibrinogen levels and further supported by a mature neutrophilia, may be explained by evidence of traumatic reticuloperitonitis. A wire foreign body was present in the reticulum and a fibrous adhesion had formed between the reticulum and the diaphragm. In addition, multiple small abscesses were present on the diaphragm.

Discussion

Diffuse fibrosing alveolitis designates a form of lung disease in which fibrosis occurs throughout alveolar walls as a result of attempts to heal widespread acute or chronic damage to alveolar walls. The etiology of the condition in cattle is unknown. In human medicine approximately 130 defined forms of interstitial pulmonary disease have been identified. In about 35% of human cases an etiology can be established with the majority of cases due to the inhalation of toxic substances or organic antigens, or from adverse drug reactions.[1] In cattle, suspected etiologies include infectious or parasitic agents, ingested toxins or precursors (i.e. L-tryptophan, perilla mint ketones, pyrrolizidine alkaloids, moldy sweet potatoes), hypersensitivity pneumonitis *(Micropolyspora faeni)* and idiopathic causes.[1] It has been suggested that ingested precursors or toxins are the most significant cause of interstitial pneumonia in cattle.

Pathogenetically, interstitial pneumonia develops following an initiating injury to the alveolar capillary endothelial and epithelial cells. This causes a profuse exudate to accumulate within the alveolar walls and lumen. Simultaneously, an infiltration of mononuclear cells (initially lymphocytes and plasma cells) aggregate within the alveolar interstitium in response to inflammation. There is also an increase in the amount of interstitial reticulin and collagen. Alveolar cell proliferation marks the beginning of the proliferative stages of pneumonia in which fibroblasts appear and lay down thick collagen bundles. The onset of fibrosis is a critical feature of this phase in that if basement membrane degradation is present the changes of fibrosis are irreversible.[1,2,4] With time, the intra-alveolar cell accumulation becomes primarily a macrophage aggregation and the alveolar epithelium may become hyperplastic or metaplastic.[1,6] The interstitial inflammatory cells may decrease and the infiltration become more lymphoid in nature. An extensive collagen deposition may occur in the interalveolar septa.[1,6]

Functionally, increasing pulmonary fibrosis results in reduced lung distensibility. There is an increased alveolar-capillary barrier which causes gas transfer impairment. This decreased gas exchange is believed to be due primarily to a ventilation-perfusion mismatch.[4] In severe stages there may be retention of carbon dioxide and respiratory acidosis. In response to restricted ventilatory movements, hyperventilation and respiratory alkalosis may occur.[3] In addition, pulmonary arterial hypertension may initiate cor pulmonale late in the course of disease and progression to congestive heart failure may occur.[3,6]

Recently it has been recognized that interstitial pneumonia may develop secondary to an acute insult causing diffuse damage to the alveolar walls. This results in an early intra-alveolar exudative phase which may rapidly progress to the proliferative and fibrotic phases. If severe exudative lesions exist, fibrosis may be a striking feature as early as 14 days post-insult. However, few acute cases have been reported and interstitial pneumonia is generally regarded as a chronic, diffuse inflammatory condition in which there is a proliferative response involving the alveolar walls and and supporting stroma.

Diffuse fibrosing alveolitis is an individual animal disorder usually affecting those in the middle-age category. It is generally seen in both beef and dairy cattle over six years of age and in humans usually affects late middle-age adults.[2,7] While the disease appears to be slightly more predominant in human males,[3] there has been no sex predilection noted in cattle. There appears to be some familial predisposition in humans and it has been suggested that some cases may be transmitted by an autosomal dominant mode of inheritance.[3]

The history of affected cattle is that of insidious onset and chronic, progressive pulmonary disease with a duration of months to years. The cattle are usually "poor-doers" despite an availability of adequate nutrition and a normal appetite. As the syndrome progresses the affected cattle develop a non-productive cough, tachypnea, hypernea and progressive exercise intolerance. As previously mentioned, cor pulmonale and congestive heart failure may occur in the course of the disease.

Interstitial pneumonia is typically diagnosed upon post-mortem examination. Grossly the lungs appear very pale and are heavy. The syndrome may be differentiated from

common chronic suppurative conditions such as bronchopneumonia by the pattern of the lesion distribution.[1,2] Grossly the lesions of interstitial pneumonia, while generally distributed widely throughout the lungs, occur with greater involvement in the dorsocaudal regions. This is in marked contrast to the usual cranio-ventral pattern observed with bronchopneumonia. Histologically, the two may be differentiated by a lack of orientation of interstitial pneumonia lesions around small airways.

As noted earlier, diffuse fibrosing alveolitis manifests its most apoparent changes histologically. It is important to note that the acute lesions of extrinsic allergic alveolitis (i.e. bronchiolitis obliterans, epitheloid granulomata) are not present. The absence of these lesions in addition to the previously described post-mortem changes strongly supports a diagnosis of interstitial pneumonia.

Antemortem diagnosis is based mainly on clinical signs. If the disorder is recognized early, therapeutic management may be attempted. Corticosteroids are of benefit for their anti-inflammatory and anti-proliferative properties.[1,4] When high doses are given they arrest pulmonary fibrosis in vivo (human model) and fibroblast proliferation in vitro. The mechanism for these actions is not yet understood although there are several hypotheses.[4] It is important to realize that the use of corticosteroids for case management results in variable levels of efficacy. While multiple other agents have been experimentally used, there is no established therapeutic regime.

Summary

Interstitial pneumonia is an increasingly common disorder affecting individual middle age dairy and beef cattle. While the etiology is yet unknown, it has been suggested that the most common cause of the syndrome in cattle is due to the ingestion of toxins or precursors. The chronic development of pulmonary fibrosis is responsible for the clinical signs of a non-productive cough, tachycardia, hyperpnea and cor pulmonale. If the syndrome is recognized early treatment with high doses of corticosteroids may be attempted. Definitive diagnosis of the disease is made on post-mortem examination by the histologic presence of interalveolar septal fibrosis and cellular infiltrates, as well as those alveolar changes of hyperplasia and mononuclear cell exudate.

References

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Student Clinical Reports

The AABP Board of Directors meeting in Washington, D.C. on July 21, 1980 approved a recommendation from the Forward Planning Committee to encourage veterinary medicine students to write case reports for *The Bovine Practitioner.*

The first prize ($200) is awarded this year to **Wendy Lou Mohr,** Oklahoma State University (see page 156).

The second prize ($100) is awarded to **Amy Horn,** University of Wisconsin (see page 159).

The third prize ($50) is awarded to **Timothy J. Jones,** Kansas State University (see page 163).