Fibrotic Interstitial Pneumonia in 2 Thoroughbred Broodmares

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INTRODUCTION

Fibrotic interstitial pneumonia has been reported sporadically in horses. The disease is chronically progressive and involves an inflammatory response that predominantly affects the alveolar walls and interstitial tissue of the lung resulting in damage with loss of function of the alveolar capillary unit (Buergelt 1986). The most common presenting clinical sign is acute respiratory distress although cough, exercise intolerance, fever, weight loss and reduced appetite are also reported (O' Sullivan 1985, Winder 1988, Kelly 1995, Bruce1995). A presumptive diagnosis can be made on history, clinical examination, ultrasonography, radiography, serology and cytological examination of fluid obtained from transtracheal aspirate (TTA) or bronchoalveolar lavage (BAL) (Bruce 1995). Definitive diagnosis requires a lung biopsy (Bruce 1995). Although many causes have been implicated in human medicine, a causative agent is only identified in one third of patients (Buergelt 1986). This is reflected in the veterinary literature where the aetiology in the majority of cases remains unidentified (Derkson 1982, Buergelt 1986, Winder 1988, Kelly 1995, Donaldson 1998). The causes of fibrotic interstitial pneumonia in horses can be broadly divided into toxic or chemically induced, infectious, inflammatory and allergic (Buergelt 1986). In Australian, Crofton weed (Ageratina adenophora also known as Eupatorium adenophorum) is a documented cause of interstitial pneumonia (Offord 2006). The following is a report on 2 thoroughbred mares with end stage, chronic fibrotic interstitial pneumonia.

CASE 1

Case History. A 22-year-old Thoroughbred mare, with a 3.5 month old foal at foot, was examined after a routine reproductive examination and found to have tachypnoea, pyrexia and poor body condition. On haematology and serum biochemistry there was a leukocytosis (23.7 x 10^9/L; reference 6-12 x 10^9/L), hyperfibrinogenaemia (12 g/L; reference 2-4 g/L), hyperproteinaemia (67 g/L; reference 55 – 65 g/L), hypoalbuminaemia (25 g/L; reference 29-37 g/L) and hyperglobulinaemia (42 g/L; reference 13-37 g/L). The mare was treated with procaine penicillin (25 ml intramuscularly (IM) every 12 hours) and gentamicin (60 ml intravenously (IV) every 24 hours) without response and was referred to the Scone Veterinary Hospital Intensive Care Unit 2 days later with respiratory distress.

Clinical Examination. On physical examination the mare was in moderate to poor body condition. The mare had a moderate appetite and passed normal manure. She was afebrile, tachycardic (60 beats/minute) and tachypnoeic (60 breaths/minute). The mucous membranes were pink and moist with a capillary refill time less than 3 seconds. Borborygmi were quiet to absent on abdominal auscultation. There was an increased respiratory effort with an abdominal component to inspiration and nostril flaring. Thoracic auscultation revealed loud expiratory sounds and the occasional crackle over the left lung field. Breath sounds were quieter than expected given the increased respiratory effort. No cough or nasal discharge was noted.

Diagnosis. The mare's clinical signs were consistent with respiratory tract disease. Further diagnostic tests including TTA, thoracic and abdominal ultrasound, thoracic radiographs, arterial blood gas analysis, abdominocentesis, rectal examination, haematology and serum biochemistry were performed. A TTA was cloudy with particulate matter, and on cytological examination contained 96% neutrophils which were mainly intact, with the occasional degenerative, pyknotic cell. The remaining cells were macrophages with single nuclei and foamy cytoplasm. This was interpreted as inflammation. No bacteria or fungal elements were seen on smear. Mixed fungal species, interpreted as contaminants, were grown on culture. Ultrasonographic examination of the thorax showed there were numerous comet-tail artefacts over the left and right lung fields. The left lung showed an extensive area of consolidation over the mid to ventral thorax with multiple small areas of consolidation dorsally. This pattern was repeated in the right lung however the ventral area of consolidation was smaller. No increase in pleural fluid was seen.

Arterial blood gas analysis revealed mild hypoxia (PaO_2 75 mmHg). Radiographs of the dorsal caudal lung lobe showed an interstitial pattern with diffuse, multiple nodules. Rectal examination revealed no abnormalities. Abdominal ultrasonographic examination revealed there was an increased volume of peritoneal fluid. The fluid obtained by abdominocentesis was an exudate from which there was no significant growth on bacteriological culture.

Haematology and serum biochemistry obtained 3 days after admission showed ongoing leukocytosis (23.9 x 10^9/L), hyperfibrinogenaemia (10 g/L), hyperproteinaemia (70 g/L), hypoalbuminaemia (22 g/L) and hyperglobulinaemia (48 g/L). Serum protein electrophoresis showed a mild increase in α-2-globulins (15 g/L, reference 8-13g/L) and γ-globulins (17 g/L, reference 7-14g/L). The findings were indicative of inflammation.

Differential diagnoses after the initial tests included pulmonary neoplasia, granulomatous pneumonia and fibrotic interstitial pneumonia. A lung biopsy was performed to provide a more precise diagnosis and assist with prognosis. Ultrasound guided biopsy of the area of consolidation in the left and right lung was performed at the 8th intercostal space using a 14-gauge, 15cm Tru-cut biopsy instrument (Allegiance Healthcare Corporation, McGaw Park, IL, USA). Initial biopsy samples were not diagnostic therefore the procedure was repeated. The second biopsies obtained from the left lung were from separate areas perceived to be normal and abnormal on ultrasound examination. The samples were submitted for bacteriological culture and histology. Histopathologic examination of haematoxylin and eosin (H and E) stained sections revealed there was severe fibrosis and interstitial pneumonia resulting in adenomatosis amongst dense fibrous tissue trabeculae with a mixed inflammatory cell infiltrate. A second sample obtained from an area of more aerated lung contained less severe fibrosis and chronic inflammation. Both samples were consistent with severe chronic fibrosing inflammatory lung disease. There was no significant microbial growth from culture of the biopsies.

Treatment. Broad-spectrum antimicrobial therapy was instituted with trimethoprim sulfamethoxazole (30 mg/kg per os (PO) every 12 hours) for 11 days until the results of the biopsies were available. The mare was discharged on prednisolone (800mg PO every 24 hours) and housed in an air-conditioned stall during the day. She was euthanased 7 days later due to continued clinical deterioration including tachypnoea and poor appetite.

Post-mortem. Abnormal findings at post-mortem were limited to the thoracic cavity. The lungs were pale and firm, and did not deflate after opening the thoracic cavity. Histopathological examination of H and E stained sections of lung tissue reported adenomatosis amongst dense fibrous tissue with a mixed inflammatory cell infiltrate. More active areas were present with ongoing fibrosis, epithelial necrosis and neutrophilic infiltrates into affected alveoli. Post-mortem results confirmed severe fibrosis and chronic active interstitial pneumonia.

CASE 2

Case History. A 10-year-old Thoroughbred mare,

with a 3-month-old-foal at foot, presented for a routine 30 day pregnancy scan with an elevated respiratory rate and pyrexia. She was treated with procaine penicillin (25 ml IM every 12 hours), gentamicin (60 ml IV every 24 hours), phenylbutazone (1g PO every 24 hours) and altrenogest (12 ml PO every 24 hours) for 3 days without response. The mare was then referred to the Scone Veterinary Hospital Intensive Care Unit with tachypnoea and pyrexia.

Clinical Examination

On physical examination the mare was alert, with a moderate appetite, but in poor body condition. She had pink, moist, mucous membranes, was afebrile, tachypnoeic (52 breaths/minute) and tachycardic (56 beats/minute). The mare had flared nostrils and an abdominal component to expiration. On thoracic auscultation there were harsh inspiratory sounds with occasional quiet expiratory wheezes over both hemithoraces.

Diagnosis

The clinical signs were consistent with a respiratory tract disease. Haematology, serum biochemistry, TTA, thoracic and abdominal ultrasound, thoracic radiography, arterial blood gas analysis, thoracocentesis and rectal examination were performed to further characterise the disease process. Abnormalities on haematology and serum biochemistry were leukocytosis (14.6 x 10^9/L), hyperfibrinogenaemia (6 g/L), and hyperproteinaemia (73 g/L) with hyperglobulinaemia (41 g/L). The TTA was a white mucoid fluid with 70% neutrophils, 27% macrophages and 3% columnar epithelial cells on cytological examination. The fluid analysis was consistent with inflammation. No bacteria or fungal elements were seen on smear and there was no significant bacterial or fungal growth on culture. Thoracic ultrasonographic examination revealed scattered small areas of consolidation and pleural sprays over the majority of both the left and right lung surfaces. A small amount of pleural fluid was seen at the cranioventral aspect of the right hemithorax; however an attempt to sample this fluid was unsuccessful. Thoracic radiographs showed a diffuse nodular pattern associated with an interstitial pattern. Arterial blood gas analysis revealed mild hypoxia (PaO_2 73 mmHg).

The differential diagnoses included pulmonary neoplasia, granulomatous pneumonia or fibrotic interstitial pneumonia. A lung biopsy was performed to differentiate between these conditions. Ultrasound guided lung biopsies were performed at the left and right 8th intercostal space using a 14-gauge, 15cm Tru-cut instrument (Allegiance Healthcare Corporation, McGaw Park, IL, USA) and samples were submitted for histology and microbiology. Histologic examination of H and E stained sections revealed severe pulmonary fibrosis with cuboidal metaplasia of remaining epithelium. There was almost complete obliteration of airways and a patchy, focally severe, active inflammatory process with macrophages and neutrophilic infiltrates. No micro-organisms were obtained on culture of the biopsy specimen. An antemortem diagnosis of nodular pulmonary fibrosis most likely due to interstitial pneumonia was made.

Treatment

Initially the mare was placed on broad-spectrum antimicrobial therapy of benzyl penicillin (40,000 IU/kg IV every 6 hours), gentamicin (6.6 mg/kg IV every 24 hours), metronidazole (25 mg/kg PO every 8 hours), altrenogest (26.4 mg PO every 24 hours) and ranitidine (6.6 mg/kg PO every 8 hours). Over the ensuing four days recurrent fevers continued and therapy was changed to trimethoprim sulphamethoxazole (30 mg/kg PO every 12 hours) and metronidazole (25 mg/kg PO every 8 hours). Seven days after admission the tachypnoea increased (64 breaths/minute), no breath sounds were auscultated in the right and left caudodorsal lung fields and crackles were heard over the cranioventral half of both lung fields. A venous blood gas analysis confirmed mild tissue hypoxia (PvO_2 of 30 mmHg and oxygen saturation of 58%) (Divers 2003). Intranasal oxygen at 5 L/min and dexamethasone (0.01 mg/kg IV every 12 hours) were administered. Due to the continued clinical deterioration and hopeless prognosis associated with the biopsy results the

mare was euthanased.

Post-mortem

At post-mortem examination abnormal findings were confined to the thoracic cavity. The lungs did not collapse when the thorax was opened. The pleural surface was pale and thickened most severely over both left and right caudal lung lobes. The lungs had a nodular consistency and bulged outward on cut section. There were diffuse, poorly demarcated, irregular areas of pale cream consolidation replacing greater than 50% of normal aerated lung. The cranial mediastinal lymph nodes were enlarged. Histopathologic examination of H and E sections revealed severe pulmonary fibrosis, pulmonary epithelialisation, moderate to severe alveolar exudate of neutrophils and macrophages, and lymphoplasmacytic interstitial infiltrates. There was almost complete obliteration of the lung tissue with only small residual air pockets and a chronic pleuritis. Special stains for acid fast bacteria, fungi and routine bacteria did not show any infectious agents. Histopathology revealed the lymph node enlargement was due to both cortical and paracortical lymphoid hyperplasia with plasma cell hyperplasia in the medullary cords indicative of reactive lymphoid hyperplasia. The aetiology could not be identified and the disease was classified as a severe chronic interstitial pneumonia with pulmonary fibrosis.

Discussion

Interstitial pneumonia is an uncommonly reported condition in horses. There are two different presentations of interstitial pneumonia reported in horses, one seen in foals from 6 days to 6 months and the other seen in adults as with the two mares reported in this case study (Burgelt 1995). The adult type affects horses aged 2 years and older, and is characterised by chronic insidious progression where acute alveolitis results in morphological changes to the lung parenchyma causing fibrosis and irreversible interstitial pneumonia (Bruce 1995).

In human medicine there are over 100 reported causes of interstitial pneumonia yet over two thirds of cases are classified as idiopathic pulmonary fibrosis (Burgelt 1986). In most equine cases the aetiology remains unknown but the suspected aetiologies are chemical/toxin induced, infectious, allergic and inflammatory (Buergelt 1986).

Toxins implicated in the disease include pyrolizidine alkaloids (from plants including Crotalaria, Trichodesma spp and Senecio spp), paraquat, silicosis and perilla ketone derived from the plant Perilla frutescens (Buergelt 1986, Bruce 1995, Wilkins 2003). Exposure of the mares to paraquat, silicosis, perilla keton was highly unlikely. The post-mortems of both mares excluded pyrolizidine alkaloids as a cause because significant abnormalities were restricted to the thoracic cavity and did not reveal the pathognomonic hepatic histological changes of megalocytosis, bilary hyperplasia or fibrosis (Barton 2004). Infectious causes are rarely confirmed however Pneumocystis carinii infection has been documented in a 5 year old horse (Franklin 2002). Viral causes have not been confirmed although one study inferred a viral cause on the basis of a single elevated equine influenza serum titre (Turk 1981). No infectious agents were identified in these mares and equine influenza virus was an exotic disease to Australia at the time of the mare's presentation. Crofton weed toxicity could not be excluded as a potential cause of the interstitial pneumonia in these mares.

Crofton weed toxicity (Numinbah horse sickness in NSW or Tallebudgera horse disease in QLD) causes severe pulmonary disease characterised by pulmonary fibrosis in horses (O'Sullivan 1979). Horses will preferentially graze this weed or consume as dried feed or as a contaminant of hay or other feed. The specific toxin and exact mechanism by which it causes pulmonary disease remains unknown but ultimately toxicity results in extensive pulmonary fibrosis (Offord 2006). The severity of lesions appears to be directly related to the length of exposure and amount of weed consumed. (O'Sullivan 1985). Pulmonary changes are irreversible and can be detected after 50 days of Crofton weed ingestion (O'Sullivan 1985). Feeding studies have shown the closely related Mistflower (Ageratina riparia) will also produce

similar symptoms in horses. (Offord 2006). Both mares had multiple owners in their lifetime and it was not possible to accurately document potential exposure to Crofton weed or Mistflower. However both mares' reproductive history (Case 1: 13 years, Case 2: 7 years) involved breeding to stallions in the Upper Hunter Valley and Victoria. Crofton weed and Mistflower have not been reported in the thoroughbred breeding regions of the Upper Hunter Valley or Victoria, although Crofton weed has been documented in other areas of the Upper Hunter Valley. It is possible that the mares spent time between breeding seasons in regions that contained Crofton weed or Mistflower. As the effects of toxicity are additive and irreversible, exposure to the weeds may have occurred in these regions or prior to the start of the mares' breeding career.

The clinical presentation of both mares in respiratory distress is not unusual where a chronic end stage disease presents as an acute identity (Kelly 1995). The history available from both mares did not document any previous respiratory disease. Interestingly both mares were admitted at a similar time of year in summer. The acute onset of clinical signs may be explained by the high ambient temperature exacerbating a chronic condition, and thus overwhelming the ability of the lungs to compensate for the pulmonary pathology. Both mares were admitted with an increased respiratory rate and mild hypoxia. The interstitial pneumonia and subsequent pulmonary fibrosis results in a reduced number of functioning alveoli as well as decreased elasticity of the lung. Therefore impaired pulmonary gas exchange, due to ventilation and perfusion mismatching, results in clinical signs of dyspnoea, exercise intolerance and hypoxia (Bruce 1995).

Ultrasonographic examination of the thorax is a non-invasive diagnostic technique that can be used in a dyspnoeic horse without causing respiratory distress. It is sensitive for diagnosis of pathology at the pleura and outer surface of the lung. In man the subpleural regions of the lung bases are the primary site for idiopathic pulmonary fibrosis, making ultrasonography a valuable tool in the diagnosis and monitoring of the disease (Donaldson 1998). Although there are no reports of the subpleural distribution occurring in horses, ultrasound should be employed as an aid to diagnosis and was useful in these mares. Ultrasound examination showed an extensive area of consolidation in the lung parenchyma of Case 1. Case 2 had small scattered areas of consolidation in the lung parenchyma. Both horses had sheets of comet-tail artefacts over the majority of both hemithoraces; an ultrasound finding characteristic of interstitial pneumonia (Lichtenstein 1997). Such ultrasonographic changes are similar to those found in foals with interstitial pneumonia. Neither mare exhibited pleural effusion, a finding which may be seen in association with acute pneumonia and neoplasia of the thoracic cavity.

Lung biopsy is the definitive test for diagnosing chronic interstitial pneumonia (Bruce 1995) and in both cases reported it provided the antemortem diagnosis. The findings differentiated neoplastic or granulomatous disorders from fibrotic interstitial pneumonia. Reported complications during the procedure include haemorrhage, epistaxis, respiratory distress, pneumothorax, peritonitis from penetration of the large colon or death (Savage 1988, Bruce 1995). None of the reported complications occurred in these cases. Failure to obtain a representative sample is a complication with all biopsy procedures. Ultrasound guidance should increase the likelihood of obtaining a representative sample and reduce the risk of some reported complications. Thoracoscopically guided pulmonary wedge resection is a newly described technique for obtaining pulmonary biopsy samples that could be considered to reduce the risk of serious complications of the transthoracic biopsy method (Lugo 2002). The technique allows visualisation of the area to be sampled however there are still potential complications such as pneumothorax and bleeding. Except in the case of silicosis and Pneumocystis spp infection a biopsy will rarely define the cause of the fibrotic interstitial pneumonia due to the chronicity of disease at diagnosis (Bruce 1995).

Both mares had a high neutrophil count (70 and

96% respectively) indicative of an inflammatory or infectious process, but no significant bacterial growth on TTA. This is a common finding in other reported cases of fibrotic interstitial pneumonia (Donaldson 1998). The interpretation of the proportion of neutrophils in a TTA sample is difficult and studies have shown a poor correlation with pulmonary histopathology (Hodgson 2004) particularly in the evaluation of horses with chronic lung disease (Derksen 1989). Acute pneumonia will commonly result in high numbers of toxic and degenerative neutrophils often associated with the presence of bacteria. The large number of aged neutrophils in these two cases was supportive of a chronic disease and, coupled with the absence of intracellular bacteria, was indicative of a non-infectious process. A BAL is a valuable technique for obtaining specimens from the lower respiratory tract for cytology. It is especially useful in diffuse airway disease as was seen in both mares. The combined results of BAL and TTA are superior in identifying lower airway disease. Although important information may have been obtained, without the risks involved in performing a lung biopsy, a BAL was not performed as the extensive ultrasound and radiograph findings combined with physical and laboratory data indicative of chronic disease indicated the importance of a lung biopsy to obtain a definitive diagnosis.

Radiology was important in both horses to document the extensive nature of the pathology and for identification of lesions consistent with neoplasia or granulomatous fibrosis. In both mares radiographs indicated a diffuse disease process thus the biopsy sample would be representative of the disease process. It is important to note however that radiographic changes in the pulmonary parenchyma do not correlate well with the severity of the disease (Bruce 1995).The underlying aetiology is rarely diagnosed in reported cases of fibrotic interstitial pneumonia because fibrosis is the end stage of the disease process and the original insult is no longer present.

The mainstay of treatment of fibrotic interstitial pneumonia is corticosteroid therapy to reduce inflammation and prevent further fibrosis (Wilkins 2003). Other supportive treatments include treatment of secondary infection, maintaining normal oxygen tension and treatment of other complications. (Bruce 1995). In both reported cases the mares' condition was so advanced that supportive treatment was not successful and euthanasia remained the only option. Of the reported cases of interstitial pneumonia in adult horses, all except one were euthanased (O'Sullivan 1979, Turk 1981, Derksen 1982, Burgelt 1986, Winder 1988, Kelly 1995, Donaldson 1998, Franklin 2002). The survivor was treated with corticosteroids orally for 1 year, and 2 years after discharge the gelding returned to competition as a jumper (Donaldson 1998). The severity of the clinical signs was not as marked in this horse which may explain the favourable outcome and return to work of the gelding.

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