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Introduction

Interstitial lung disease comprises an ill-defined group of pulmonary disorders that are chronic with insidious progression to pulmonary fibrosis [1]. These diseases are characterized morphologically by a derangement of alveolar structure and a loss of functional gas exchange units. It may lead to life threatening respiratory distress due to hypoxemia which results from a progressive limitation of oxygen transfer from air to blood [2-4]. The causes of interstitial lung disease are numerous and include infectious agents and toxins. There are probably two types of equine interstitial lung disease: One in foals and one in the adult horse. In foals, the disease appears as an acute respiratory distress syndrome in foals aged 1 to 8 months (Fig. 1). Adult horses with interstitial lung disease may have clinical signs resembling those of heaves. Most cases of interstitial lung disease in adult horses are of unknown causes. The diagnosis is based on history, clinical signs, thoracic radiographs, serology, and cytologic evaluation of tracheal bronchial fluid. A lung biopsy may provide a definitive diagnosis. Most often the cause of the interstitial lung disease is undetermined.

Etiology

A variety of agents can be responsible for causing interstitial lung disease in animals. Fewer than 20 agents have been implicated in horses, the most common of which are infectious agents and ingested toxins [1-3]. In horses, specific syndromes have not been identified and the suggested classification has been made to differentiate interstitial lung disease in foals from that of adult horses [5]. Viruses, immune complexes, infectious agents, and abnormalities of lung defense mechanisms have all been implicated in humans with pulmonary fibrosis [1]. The difficulty in determining the causative agent is due to the fact that the lung responds in a single manner to most injuries.

Infectious Agents - Infectious agents are the most common known causes of interstitial lung disease in domesticated animals [2]. The lung disease is acute and often progressive causing severe damage to the inter-alveolar space. Reported infectious causes of interstitial lung disease in horses include viral, bacterial, parasitic, protozoal, and fungal agents [1,6-8]. Viruses have been implicated as a cause of acute severe bronchointerstitial lung disease in many foals and adult horses [1,6-8]. In most of the reported cases of interstitial lung disease, despite the use of histology, serology, and viral isolation, a viral agent was rarely confirmed. Many have speculated that there are unknown equine respiratory viruses responsible for this interstitial damage [6]. The most commonly recognized respiratory viruses, including equine influenza virus, equine herpes virus Types I and IV, rhinovirus, equine viral arteritis, equine herpes virus Type II, and equine adenovirus, during natural infection can cause mild clinical signs and may well be responsible for contributing to the development of secondary bacterial infection of the lower respiratory tract, however, they have rarely been implicated in interstitial lung disease. While bacterial infections of the lung most often result in a bronchopneumonia, bacterial agents have been isolated in horses with interstitial lung disease. Most likely these are opportunistic infections rather than the primary cause of the interstitial lung disease. It is suggested that bacteria in conjunction with another insult may induce interstitial lung disease. The protozoan Pneumocystis carinii has been isolated sporadically from foals with acute interstitial lung disease [6,7,9,10]. Its role as a primary agent for interstitial lung disease is unknown and it may well be a secondary invader of some other infectious lung disease. Parasitic infestation of the lung can cause interstitial lung disease. This would include migration of ascarid larvae in foals and lungworms in adults.

Toxins - Toxins either ingested or inhaled can be responsible for diffuse lung injury in horses. Plants are the most commonly ingested pneumotoxic. Perilla ketone derived from the plant Perilla frutescens, is a potent pneumotoxic in many animals and has been demonstrated to cause acute restrictive lung disease in horses [2,11]. Toxicity requires further metabolism of the 3-substituted furans by a mixed-function oxidase system which probably occurs in the lungs.
Silicosis - A chronic granulomatous lung disease has been associated with inhalation of forms of silican dioxide crystals by horses from the Carmel valley region in California [17]. Silicic dioxides, which are inorganic dust, commonly found in the earth crust, are cytotoxic to macrophages as well as fibrogenic. Cristobalite is the most fibrogenic form of silican dioxide identified. Once inhaled the particles are ingested by macrophages causing lysis of the macrophage, persistent alveolitis, and subsequent fibrosis. Multiple granulomas are present with submicron intra-cyttoplasmic crystalline particles present in macrophages [17,18]. The disease in horses is similar to the chronic or accelerated form of silicosis in humans [18].

Hypersensitivity reactions - Hypersensitivity pneumonitis is a chronic, lymphocytic bronchointerstitial lung disease with granuloma formation and fibrosis [2,3]. It is caused by inhalation of organic antigens such as microorganisms or animal tissues to which the animal has become sensitized [2,3]. In humans, this disease includes farmer’s lung and chicken breeder’s syndrome. Hypersensitivity pneumonitis is rare in horses. Fungi in chicken dust were implicated in causing severe chronic bronchointerstitial lung disease in six horses [19-21].

Metabolic and toxic conditions have been associated with acute pulmonary damage in humans and animals. The pulmonary lesions are associated with endotoxemia [3,11].

Idiopathic - Most cases of interstitial lung disease in horses remain undiagnosed. There may be a different pathologic process for the interstitial lung disease in foals versus adult horses.

Pathogenesis
The pathogenesis of interstitial lung disease involves progression through four phases [3,4,6,22]. In phase I, an initial insult causes injury to parenchymal cells as well as to acute alveolitis. Phase II is a proliferative phase with cellular and connective tissue changes involving lung parenchyma. In cases of chronic infection, there is progression to phase III, which is a development of irreversible interstitial fibrosis. Phase IV is the end stage, irreparable fibrosis of the lung [1]. All of these structural changes in the lung that occur with interstitial lung disease reduce the number of functional alveoli, thus altering pulmonary function [1]. There is reduced lung compliance due to reduction in total volume of the lungs and increased transpulmonary pressure at total lung capacity [22]. Pulmonary gas exchange is impaired and this is primarily due to mal-distribution of ventilation and profusion [23]. Total and vital lung capacity is decreased due to a loss in gas exchange units and the change in the elastic properties of the lung [11]. Stiff fibrotic lungs increase the work of breathing, resulting in exercise intolerance and dyspnea. Pulmonary hypertension and cor pulmonale are occasional sequelae to interstitial lung disease in other species. It should be noted that these changes in the lung result in restrictive pulmonary disease in comparison to obstructive disease which occurs with primary airway pathology.

Diagnosis
Horses with interstitial lung disease may present with an acute to chronic history of weight loss, recurrent cough, nasal discharge, fever and respiratory distress. Foals and chronically affected adult horses may be bright and alert, despite dyspnea, and have a variable appetite [18,19,23,24]. The lung disease is generally unresponsive to antimicrobial and anti-inflammatory therapy in both adults and foals. Physical examination findings include tachypnea, tachycardia, and variable fever. Mucous membranes may be cyanotic in severe cases. There is a rapid, shallow respiratory pattern with occasional respiratory dyspnea. Diffuse crackles and wheezes may be heard on auscultation of the lung or there may be
an absence of lung sounds in the presence of severe pulmonary edema. Hematologic findings may include neutrophilic leukocytosis and hyperfibrinogenemia. Peripheral eosinophilia may accompany hypersensitivity or parasitic pneumonitis. Arterial blood gas analysis reveals a spectrum of disorders, but hypoxemia is usually present.

Thoracic radiographs are useful to determine the presence of pulmonary disease and to monitor its course. The most common radiographic finding is severe, diffuse, nodular interstitial disease [5,7,18,24] (Fig. 2). Pulmonary infiltrates are often present with fungal or parasitic pneumonia. Radiographs are not a specific or sensitive method to monitor alveolitis, because the extent to which the lung shows radiographic changes does not correlate well with the severity of the disease.

![Figure 2. Thoracic radiograph of a horse with chronic interstitial lung disease. Notice the typical diffuse, nodular interstitial pattern. - To view this image in full size go to the IVIS website at www.ivis.org. -](image)

Culture of tracheal wash or bronchoalveolar lavage fluid in horse with interstitial lung disease often yields no significant growth of bacteria or fungal pathogens [5,7]. Ultrasonographic findings of the thorax may demonstrate changes suggestive of severe fibrosis if a sub-pleural distribution exists [24]. A trans-thoracic lung biopsy is the definitive test for diagnosing chronic interstitial lung disease [1]. A representative sample can be obtained when the lung disease is diffuse or when a lesion can be identified ultrasonographically. Histopathological evaluation of the biopsy during the acute phase of the disease may demonstrate coagulation necrosis of alveolar walls, hyaline membrane formation and focal hemorrhage and edema [5,7,25]. In chronic cases the biopsy may show evidence of severe fibrosing alveolitis with minimal airway involvement [5,8,23]. The interlobular septa may be thickened, alveolar fibers replaced with collagen and reticulum fibers and there may be evidence of Type II cell hypoplasia. Multi-focal granulomas and bronchiolitis may also be seen. Except in cases of silicosis and pneumocystis infections, biopsy rarely defines the cause of the disease [17,18].

**Treatment**

Corticosteroids have been used to treat interstitial lung disease in horses [5,7-9,24]. The goal of therapy is to limit inflammation and to prevent further fibrosis. In the acute phase of interstitial lung disease antimicrobial drugs are also recommended to prevent secondary bacterial infections. While bronchodilating agents have been used in horses with interstitial lung disease their effectiveness is limited to the fact that this is a restrictive and not an obstructive condition. While corticosteroids have been recommended as a course for treatment there is no evidence to suggest that these drugs or any other anti-inflammatory agent effectively suppress the alveolitis which occurs. Preventive measures are difficult in as much as the inciting cause is rarely known.

In summary interstitial lung disease in horses is a recognized clinical entity. The condition has been recognized in Europe and in the United States and has evaded detection as to its cause(s) [26].

**References**


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