Chronic Idiopathic Pulmonary Fibrosis in Five Dogs

Five dogs presented with chronic and progressive pulmonary illness characterized by progressive dyspnea, exercise intolerance, and significant inspiratory crackles on auscultation. Radiographically, there was a widespread and diffuse interstitial lung pattern with varying degrees of bronchial involvement. Histopathological changes included thickened alveolar septa, interstitial fibrosis, and pneumocyte hyperplasia. Based on the clinical, radiographic, and histopathological changes, a diagnosis of idiopathic pulmonary fibrosis was made. Idiopathic pulmonary fibrosis is a chronic disease characterized by inflammation and fibrosis of the pulmonary interstitium and peripheral airspaces, which has been poorly characterized in the dog. J Am Anim Hosp Assoc 2001;37:119–127.

Introduction

Interstitial lung disease is a heterogeneous group of disorders of the lower respiratory tract characterized by derangements of the alveolar walls and loss of functional alveolar capillary units. Many forms of pulmonary injury can cause interstitial pneumonia, and in humans over 130 different causes are known to induce interstitial lung disease. However, in over 50% of cases, no cause can be identified. Commonly recognized causes include inhalation of toxic substances or organic antigens, adverse drug reactions, and diseases such as sarcoidosis, collagen-vascular disorders, and unusual granulomatous diseases such as Wegener’s granulomatosis or eosinophilic granuloma. In animals, most of the recognized causes of spontaneous interstitial pneumonia are infectious diseases, parasitic agents, or toxins. Potential known causes in the dog are infectious diseases (e.g., distemper, toxoplasmosis, lungworms or migrating ascarid larvae, pneumocystosis, fungi, or bacteria), pneumoconiosis, hypersensitivity reactions, neoplasia, inhaled gases or toxins, irradiation, and systemic lupus erythematosus. Since the clinicopathological picture of interstitial pneumonia is often nonspecific, many cases are not identified by a specific cause and likely go unreported. In the dog, the interstitial lung diseases are a poorly characterized group of respiratory conditions, and little is known of their prevalence, incidence, or etiopathogenesis.

Acute and chronic interstitial pneumonia of unknown cause, termed idiopathic pulmonary fibrosis (IPF), is encountered in all species. Idiopathic pulmonary fibrosis is characterized by inflammation and fibrosis of the pulmonary interstitium and peripheral airspaces. Idiopathic pulmonary fibrosis should, however, not be considered a specific disease as it may have varying etiologies, including underlying connective-tissue diseases, organic dust or other exposures, and prior acute lung injury. Less often, IPF may reflect a nonrepresentative biopsy of another process. The lack of a completely satisfactory morphological designation embracing the variants of interstitial pulmonary disease has resulted in a confusing array of terms. Two terms commonly used are interstitial pneumonia and diffuse fibrosing alveolitis. The former term is preferred, as it covers the broad range of morphological, etiological, and pathogenic...
aspects. Other terms used are chronic diffuse infiltrative lung disease and diffuse interstitial pulmonary fibrosis. In humans, IPF is a specific syndrome characterized by a combination of clinical, physiological, morphological, lavage, and scintigraphic features. Diagnosis of IPF in humans depends on histopathological analysis of open-chest lung biopsy samples. The findings are consistent with an active inflammatory disease resulting in progressive fibrosis and end-stage honeycombing of the lung. The alveolitis involves accumulation of monocytes (particularly macrophages), thickening of the alveolar septa with edema, fibrinous exudate, fibroblast proliferation, and deposition of excess quantities of collagen (fibrosing alveolitis).

Although IPF is a distinct clinical entity, the literature dealing with IPF is confusing, as it is referred to by different names (e.g., lone cryptogenic fibrosing alveolitis, desquamative interstitial pneumonia, usual interstitial pneumonia, and giant-cell interstitial pneumonia). In the dog, this disease entity is poorly characterized, and the lack of data is partly due to the difficulty of accurate diagnosis and the lack of biopsy or postmortem material from these cases. There are widespread anecdotal accounts of a chronic respiratory condition in dogs characterized by severe radiographic changes consistent with lung fibrosis and inspiratory crackles, with some resemblance to IPF in humans. The condition has been described primarily in middle- to old-aged terrier breeds, most notably the West Highland white. These dogs present with a chronic and progressive illness characterized by coughing, dyspnea, exercise intolerance, and significant inspiratory crackles on auscultation, and an interstitial pattern is shown on radiography. Histopathological changes are consistent with a chronic proliferative epithelial response, which has a similarity to the clinical entity of IPF in humans.

Case Reports

Case No. 1

A six-year-old, fully vaccinated, female schipperke was referred to the Onderstepoort Veterinary Academic Hospital (OVAH) with a two-month history of progressive dyspnea, exercise intolerance, and syncope. There was no history of coughing. On clinical examination, polypnea and inspiratory and expiratory dyspnea were evident. On thoracic auscultation, crackles were audible throughout the lung fields. Complete blood count (CBC) and urine and fecal analyses all were within reference ranges. Survey thoracic radiographs showed an advanced interstitial lung pattern tending to be bronchial to nodular and involving all lung fields [Figure 1]. Right heart enlargement was also evident and was attributed to cor pulmonale. The only abnormality on transtracheal aspirate (TTA) cytopathology was an increased amount of mucus. Transtracheal aspirate culture was negative for both bacterial and fungal growth. Fine-needle aspiration (FNA) cytopathology of the lung yielded no respiratory epithelial cells. Antinuclear antibody (ANA) titer was negative.

During the open-chest lung biopsy procedure, the lungs appeared fibrosed, showed poor compliance, and had two areas of bullous emphysema. Histopathology of a biopsy section showed severe, focally extensive to diffuse, subacute to chronic, proliferative interstitial pneumonia. The pneumonia was characterized by the presence of a moderate number of mixed-type inflammatory cells within thickened alveolar walls; proliferation of and occasional filling of alveoli by alveolar macrophages with marked microvesicular cytoplas-
mic change; variable type II pneumocyte hyperplasia; patchy alveolar filling with protein-rich, deeply hyaline fluid; moderate multifocal alveolar emphysema; moderate peribronchiolar and perivascular edema; and moderate hyperplasia of the smooth muscle around the terminal bronchioles. In addition, coalescing foci and fibrous tracts were present, mainly beneath the pleura, where the alveoli were replaced by mature, fibrous connective tissue and were infiltrated with a moderate number of lymphoplasmacytic inflammatory cells. Remaining bronchioles were collapsed, lined by hyperplastic and often bizarrely shaped epithelial cells, and surrounded by loose lymphoplasmacytic cuffs [Figure 2]. Moderate subpleural fibrosis, moderate hyperplasia of the mesothelial pleural cells, and marked subpleural lymphatic dilatation were also evident. Special stains for infectious agents (i.e., periodic acid-Schiff, Ziehl-Neelsen, Gram) were all negative.

Due to the poor prognosis, the owners opted for euthanasia. No postmortem examination was performed.

**Case No. 2**

A three-year-old, fully vaccinated, female Staffordshire bull terrier was referred to the OVAH for chronic, progressive dyspnea and exercise intolerance over a three-month period. On clinical examination, cyanotic mucous membranes, severe polypnea, and inspiratory dyspnea were present. On thoracic auscultation, inspiratory crackles were audible,
especially over the caudoventral lung lobes. Complete blood count showed absolute polycythemia (hematocrit, 71%; reference range, 37% to 55%; red blood cell count [RBC], 10.44 x10^{12} /L; reference range, 5.5 to 8.5 x10^{12} /L), with albumin within reference ranges.

Survey thoracic radiographs showed a severe, generalized, mixed-bronchial and interstitial pattern and pleural thickening. On TTA cytopathology, mucus, few macrophages, and alveolar epithelial cells were evident. Culture of a TTA specimen was negative for bacterial and fungal growth. Fine-needle aspirate of the lung showed fibroblasts, macrophages, and plaques of alveolar epithelial cells. An ANA titer was negative.

An open-chest lung biopsy was done. Macroscopically, there was lung fibrosis with decreased compliance. Histopathology showed severe, focally extensive, subacute to chronic, proliferative interstitial pneumonia characterized by the presence of a small number of mixed-type inflammatory cells; mature, fibrous connective tissue in irregularly thickened alveolar walls; and mild, patchy hyperplasia of type II pneumocytes. In scattered foci, often associated with bronchioles, alveolar wall thickening virtually obliterated alveolar spaces [Figure 3]. Alveolar spaces, where present, were either overdistended or variably filled with protein-rich edema fluid and macrophages with abundant, finely vacuolar cytoplasm. Peribronchiolar smooth muscle was moderately hyperplastic, as was the bronchiolar epithelium of terminal bronchioles. Special stains for infectious agents (i.e., periodic acid-Schiff, Ziehl-Neelsen, Gram) were negative.

The animal was treated with prednisolone (2 mg/kg body weight, q 24 hrs and tapered over a two-month period to 0.5 mg/kg body weight, alternate days) and the antifibrotic drug, colchicine (0.03 mg/kg body weight, q 24 hrs), to possibly aid in slowing progression of the disease. Six weeks after discharge, the dyspnea was unchanged. Three months later, the owners opted for euthanasia. No autopsy was performed.

**Case No. 3**

A three-year-old, fully vaccinated, male bull terrier was referred to OVAH with a four-month history of lethargy as well as panting and cyanotic mucous membranes when excited. Clinical evaluation showed mildly elevated body temperature, polypnea, inspiratory and expiratory dyspnea, and cyanotic mucous membranes. The only abnormality on CBC was a mature neutrophilia (12.01 x10^{9} /L; reference range, 3.0 to 11.5 x10^{9} /L). Serum biochemistry and urine and fecal analyses all were within reference ranges. Survey radiographs of the thorax showed a bronchoalveolar to interstitial pattern, affecting both lung fields. Transtracheal aspirate, bronchial lavage, and FNA of the lung were all cytopathologically unrewarding, with few cells seen. Bacterial and fungal cultures from all three specimens were negative. An ANA titer was negative.

An open-chest biopsy was done. During the biopsy procedure, the dog underwent cardiac arrest and died. On autopsy, the lungs were incompletely collapsed, firm, mottled cream-gray and red, and exuded small amounts of foam from cut surfaces. On histopathology, there was severe, focally extensive to diffuse, subacute to chronic, proliferative interstitial pneumonia characterized by moderate to marked alveolar wall thickening by mature, fibrous connective tissue, infiltration of a small number of mixed-type inflammatory cells, and marked, often bizarre hyperplasia of type II pneumocytes [Figure 4]. The remaining alveolar spaces contained protein-rich fluid and, often, small numbers of necrotic inflammatory cells, fibrin, and alveolar macrophages. Greatly enlarged macrophages with abundant, finely vacuolar cytoplasm filled...
many of the subpleural alveoli. Moderate perivascular edema, mild to moderate hyperplasia of the smooth muscle surrounding bronchioles, and a few, scattered, loose lymphoplasmacytic foci were also present. Special stains for infectious agents (i.e., periodic acid-Schiff, Ziehl-Neelsen, Gram) were negative.

Case No. 4
A five-year-old, female, fully vaccinated Staffordshire bull terrier was referred to the OVAH for chronic respiratory disease. On clinical examination, a dry, hacking cough could be easily elicited on tracheal palpation, and polypnea was detected. A full CBC, serum biochemistry profile, urinalysis, and ANA titer were all within reference ranges. Survey thoracic radiographs showed possible cardiomegaly and an interstitial to bronchial lung pattern [Figure 5]. Echocardiography and electrocardiogram (EKG) tracings showed no cardiac abnormalities. Transtracheal aspirate, tracheobronchoscopy, and bronchoalveolar lavage were all within reference ranges. Based on the above findings, a diagnosis of chronic, interstitial pneumonia was made. The dog was discharged on supportive therapy consisting of nebulization, an antitussive (codeine, 1 mg/kg body weight, q 12 hrs), and prednisolone (2 mg/kg body weight, q 24 hrs and tapered down over a two-month period to 0.5 mg/kg body weight, alternate days). The dog progressively deteriorated and was readmitted four months later. At this point, she showed inspiratory dyspnea with no cough. Survey radiographs of the thorax showed a severe, diffuse, interstitial lung pattern [Figure 6]. Transtracheal aspirate was within reference ranges. Two days after being admitted, the dog went into respiratory arrest and died.

At autopsy, the lungs did not collapse on opening the thoracic cavity and showed areas of consolidation and hepatization with multifocal, whitish-gray, peribronchiolar areas that felt firm and exuded foam on cut surface. Histopathological examination revealed chronic and proliferative interstitial pneumonia throughout the parenchyma with marked alveolar wall thickening due to proliferation of type II pneumocytes, fibrous connective tissue, and various inflammatory cells. The latter consisted predominately of macrophages, some giant cells, and lesser numbers of lymphocytes and plasma cells [Figure 7]. A similar inflammatory cell infiltrate and fibrin filled the alveolar spaces. There was marked bronchiolar epithelial hyperplasia and peribronchiolar smooth-muscle hyperplasia and fibrosis.

Case No. 5
A three-year-old, fully vaccinated, female Staffordshire bull terrier was referred to the OVAH for chronic, progressive dyspnea over a 12-month period. On clinical examination, cyanotic mucous membranes, severe polypnea, and dyspnea were present. On thoracic auscultation, inspiratory crackles were audible throughout the lung fields. Complete blood count showed absolute polycythemia (hematocrit, 72%; RBC, 11.50 x10¹²/L) and an albumin of 36 g/L (reference range, 27 to 35 g/L). Survey thoracic radiographs showed a moderate, generalized alveolar pattern. Before any further diagnostic tests could be done, the dog died.

At autopsy, the lungs were congested, failed to collapse on opening the thoracic cavity, and were markedly increased in consistency. Histopathology showed severe, extensive, multifocal to coalescing pulmonary fibrosis; mixed-type
inflammatory cells; mature, fibrous connective tissue within irregularly thickened alveolar walls; and mild, patchy hyperplasia of type II pneumocytes. A lung sample was negative for bacterial and fungal growth.

Discussion

The five dogs described in this report showed clinical, radiographic, and histopathological changes compatible with IPF.

Idiopathic pulmonary fibrosis is thought to occur secondary to any lower respiratory tract insult in which the inflammatory response to the insult cannot be controlled. Interstitial fibrosis is seen in the lung in response to a variety of insults and often appears stereotypical in terms of its clinical and pathological features. However, exposure to a known etiological factor does not always lead to fibrosis. In humans, the etiopathogenesis of idiopathic pulmonary fibrosis is not known, but a possible role for immune complexes (i.e., unidentified antigens), which are chemotactic for polymorphonuclear leukocytes and active macrophages, has been postulated.

Pulmonary fibrosis resulting from an interstitial pneumonia may either be attributable to acute damage or to chronic inflammatory conditions involving a proliferative cellular response. During the acute phase, the most dramatic features of the lesion are the flooding of alveoli with serofibrinous exudate and the congestion and edema of alveolar walls. Replacement of degenerative type I pneumocytes takes place on intact basement membranes by proliferation of type II pneumocytes. This resultant epithelialization of the alveoli is a common feature of subacute to chronic interstitial pneumonia. Proliferation of alveolar type II pneumocytes marks the shift from the exudative to the proliferative stage of interstitial pneumonia. Onset of fibrosis is a critical feature of the proliferative phase, because it is irreversible.

Stimulation or up-regulation of fibroblast proliferation and collagen synthesis is induced by macrophage-derived cytokines.

Alveoli are lined by two types of epithelial cells: type I and II pneumocytes. Type I pneumocytes have a large surface-to-volume ratio and cover a large area of the alveolar wall. The morphological features of these cells make them highly sensitive to injury, whereas type II pneumocytes are more compact and are thus less vulnerable. When alveolar injury occurs following an acute exudative phase of inflammation, type II pneumocytes proliferate to fill denuded areas of alveoli. If inflammation abates and scarring is not severe, type II pneumocytes can later be transformed into type I pneumocytes. Acute pulmonary injury, whether toxic, metabolic, or infectious in origin, causes damage principally to alveolar endothelial cells and type I pneumocytes. Whether the endothelium or epithelium is damaged first is dependent on the nature, portal of entry, and intensity of the insult and, to some extent, the species affected.

Several parts of the alveolar structure are affected in IPF, including the alveolar walls lined with type I and type II pneumocytes, and the interstitial supporting structure composed of fibroblasts, myofibroblasts, collagen, adhesive proteoglycans, and capillary endothelium [Figure 8]. In the early stage of the disorder, there is patchy alveolitis with mild to moderate thickening of the alveolar walls. As the disease progresses, the inflammation persists, and progressive derangement of the alveolar structures occurs, including loss of type I pneumocytes, proliferation of type II pneumocytes, migration of bronchoalveolar epithelial cells to the alveoli, loss of capillaries, and thickening of the walls of the
small airways and arteries. The interstitial matrix is expanded with large numbers of fibroblasts, myofibroblasts, smooth-muscle cells, and masses of twisted, deranged fibers (particularly type I collagen). These histopathological changes were evident in the lung sections from all five dogs.

Idiopathic pulmonary fibrosis is thought to represent a stereotyped inflammatory response of the alveolar wall to injuries of different types, durations, and intensities. In humans, detailed evaluations for a specific etiology have been fruitless. Studies have also shown that T-lymphocytes from patients with this disorder proliferate in response to a variety of “self” components, including type I pneumocytes, collagen, and deoxyribonucleic acid (DNA). There is evidence that proliferating type II pneumocytes in regenerating alveolar epithelium are implicated in the pathogenesis of this disorder. Several studies in humans have suggested a genetic link for IPF, but definitive evidence is lacking. No obvious clinical or historical cause could be identified in these five cases. Although the dogs in this report were not related, four of the dogs were bull terrier-type dogs, and the one case reported in the veterinary literature was a dog of a similar breed. Therefore, it is possible that bull terrier breeds are at an increased risk for the development of IPF.

In humans, all age groups can be affected with IPF; however, it is more common between the ages of 20 to 40 years. This correlates to the age group of these dogs, as their ages ranged from three to six years. In humans, an irritative, nonproductive cough is present in approximately 15% of patients. An interstitial pneumonia is not usually associated with a cough, and manifestations of this disease would not be expected until pulmonary gas exchange has already been impaired. In the dogs, there was marked congestion and thickening of the alveolar walls, with proliferation of type II pneumocytes. The presence of mainly histiocytic inflammatory cells was evident on histopathological examination.

Figure 7—Histopathological section from an autopsy from case no. 4, showing marked congestion and alveolar wall thickening due to proliferation of type II pneumocytes and the presence of mainly histiocytic inflammatory cells (Hematoxylin and eosin stain, 10X; bar=130 µm).

Figure 8—Schematic representation of the pathogenic mechanisms within the alveolar space, alveolar walls, and pulmonary interstitium that can lead to inflammation and eventual fibrosis. The focus is the pulmonary macrophage that is activated by inhaled antigens (Ag), circulating immune complexes, or circulating antigens (Cf). The net result is that the macrophage, through mediators such as chemotaxins, attracts inflammatory cells from the circulation into the alveolar space, as well as stimulates fibrogenesis and muscle cell proliferation. Interstitial fibrosis may result. (Reproduced with permission from: Reynolds HY. Interstitial lung diseases. In: Isselbacher KJ, Braunwald E, Wilson JD, Martin JB, Faurer AS, Kasper DL, eds. Harrison’s principles of internal medicine. 13th ed. New York: McGraw-Hill, 1994:1206–11).
been severely compromised. One dog was initially presented with a cough, whereas the other four did not have a history of coughing.

In humans, the physical examination may be entirely normal. Loud, dry, and basilar, so-called velcro crackles are virtually diagnostic in advanced disease. A patient with end-stage IPF presents with the physical findings of cor pulmonale. Clinical findings in these dogs were limited to the respiratory system and consisted of polypnea, dyspnea, and inspiratory crackles. Cyanosis was present in two cases.

In humans, typical chest radiographic changes demonstrate diffuse reticular or reticulonodular infiltrates that have lower-zone predominance. In the advanced stages of IPF, a fine honeycombing (i.e., small, cystic spaces) and reduced lung volume are evident. Radiographically, interstitial lung disease in the dog may appear as a diffuse increase in overall pulmonary density; indistinct, smaller, pulmonary vascular structures; indistinct linear or reticular densities; or as a combination of short linear and small nodular (i.e., reticulonodular) densities throughout the lung. However, unstructured increases in interstitial density may reflect past or current disease. An increased interstitial opacity on thoracic radiographs is usually the only indication that interstitial disease exists, but this type of pattern is associated with a disparate group of thoracic conditions including acute fibrosing alveolitis, cardiogenic and noncardiogenic pulmonary edema, infection, pulmonary infiltration with eosinophilia, certain infiltrative neoplasms, exposure to toxins such as paraquat, and certain systemic illnesses. Most of these conditions have a rapid clinical onset (hours to days) and rarely have a slow, chronic-progressive course. Survey thoracic radiographs in these dogs showed an interstitial lung pattern tending to be bronchial to nodular and involving all lung fields.

In humans affected with IPF, changes in CBC, routine serum biochemistry, and urinalysis are not seen. Approximately 40% of human patients with IPF have positive rheumatoid or antinuclear factors. These findings suggest that an immunopathogenetic mechanism may be operative in some cases of IPF. Some cases of IPF may, in fact, represent a limited connective-tissue disease of the lung. Antinuclear antibody was negative in four of the dogs tested in this report, thus reducing the possibility of an immune-mediated collagen-vascular disorder.

Classically in human patients, spirometry demonstrates a reduction of the total lung capacity that is a restrictive ventilatory defect. The flow rates are usually preserved, provided the patient does not have a complicating airway problem. The diffusing capacity for carbon monoxide is reduced, especially after exercise. The compliance of the lung (i.e., elastic recoil) is also reduced. Although not specifically measured, decreased lung compliance was evident macroscopically during thoracotomy in the dogs of this report. The most important and probably the earliest pathophysiological derangements are hypoxemia and hyperventilation, made worse by exercise. Exercise intolerance and polypnea were present in all five cases of this report. These result from both an increased alveolar-arterial oxygen gradient and increased dead-space ventilation.

A lung biopsy is necessary to confirm the diagnosis and determine prognosis. An open-lung biopsy is preferred because of the ability to obtain a greater amount of tissue and the opportunity for the surgeon to select areas of obvious involvement. It is well known that while some areas of the lung may demonstrate fibrosis, other areas may show an active process. Histopathology of the lung from humans affected with IPF typically showed severe, chronic, interstitial pneumonia; marked fibrosis; lymphoplasmacytic and macrophage infiltration; epithelialization; patchy alveolar edema; and hypertrophy/hyperplastic type II pneumocytes. These changes are similar to the changes present in the lungs of the dogs described in this report and to what has been reported in another affected dog.

The principal therapy for IPF is corticosteroids. In approximately 20% of human cases, corticosteroid therapy not only provides symptomatic relief but also increases survival in these diseases. In humans, another guide to the effectiveness of corticosteroid therapy appears to be the histopathological findings: if dense fibrosis with honey-combed lung is present, the results of therapy are likely to be minimal; however, if examination reveals an active cellular process (neutrophils and macrophages), then beneficial results from corticosteroid therapy can be expected. Symptomatology, chest radiographs, and lung function studies can judge improvement. Maintenance therapy with corticosteroids after the first two to four weeks should be titrated to the lowest dose that maintains clinical benefits. Should the disease not respond or be progressive, immunosuppression with cyclophosphamide or azathioprine should be considered. Other antifibrotic or immunosuppressive agents such as colchicine, penicillamine, and cyclosporine have not been thoroughly evaluated in humans. In the literature, it has been reported that a proportion of canine cases show good clinical response to corticosteroid therapy, but the condition eventually results in respiratory failure. Concurrent use of azathioprine may be of additional benefit. Two of the dogs in this report did not respond to corticosteroids.

Although oxygen administration may improve clinical signs, it may in fact worsen the pulmonary lesions. Oxygen toxicity is emerging as an important form of inhaled injury, as concentrations over 50% can produce damage in already compromised lungs after two to three days of exposure. Proliferating type II pneumocytes are sensitive to the toxic effects of oxygen.

Conclusion
Although not a common disease, IPF should be considered in all dogs with chronic dyspnea and radiographic changes suggestive of interstitial pneumonia. Evaluation of lung tissue, obtained either antemortally (via thoracotomy or thoracoscopy) or postmortally, is necessary to further elucidate this disease in the dog.
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References