UPDATE ON CANINE AND FELINE PULMONARY FIBROSIS

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INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a poorly understood constellation of chronic respiratory diseases that affect people, dogs, and cats. While there are histologic and epidemiologic differences in IPF across all three species, one unfortunate similarity is that the condition carries a poor prognosis in both veterinary and human medicine. In veterinary medicine, our current diagnostic and therapeutic approach to IPF in dogs and cats is heavily based on similarities and differences between the canine and feline forms and IPF in people. The purpose of this session will be to review the current understanding of IPF pathogenesis in people, to describe the clinical presentation of canine and feline IPF, and to discuss diagnostic and treatment options for dogs and cats with IPF.

IDIOPATHIC PULMONARY FIBROSIS IN PEOPLE

Fibrotic interstitial lung diseases (ILDs) in people are described as a heterogeneous group of lung disorders that affect epithelial cells, basement membrane, and capillary endothelial cells, and that feature interstitial fibrosis as a significant histologic component. These can be due to a variety of causes, including infections, drugs, inhaled toxins, lung tumors, inflammatory lung disease, and immune-mediated conditions. Idiopathic pulmonary fibrosis is the clinical descriptive term for a subset of fibrotic ILD patients exhibiting a specific histologic lung pattern (usual interstitial pneumonia), and meeting specific clinical criteria, including a poorer response to therapy.

Histologically, the hallmark finding in IPF in people is evidence of progressive fibrosis with temporal heterogeneity [1]. This characterized by regions of chronic injury contrasting acute lesions and normal lung. Regions of chronic injury exhibit smooth muscle hyperplasia, alveolar epithelial metaplasia, and interstitial fibrosis surrounding “fibroblastic foci,” discrete regions of intense fibroblast and myofibroblast proliferation. This lung injury exhibits a subpleural distribution, and may also be associated with mild inflammation [2]. Co-morbid lung malignancies, including bronchogenic carcinomas and squamous cell carcinomas, are a frequent finding in human IPF patients [3].

The cause of IPF in people remains unknown, but several hypotheses have been supported with experimental evidence. Chronic inflammation, or cycles of recurrent inflammation, has been proposed as a trigger for cycles of lung injury, wound healing, and progressive fibrosis [1]. Another hypothesis is that a respirable agent, such as exposure to cigarette smoke or occupational exposure to metal or wood dusts, may serve as an inciting stimulus [4]. A third hypothesis is that IPF is the result of a fibroproliferative disorder, or a deranged or neoplastic fibroblast response [5].

IPF affects middle-aged to older people (40-70 years of age), and affects men more than women. Patients typically present with exertional dyspnea and a non-productive cough, with an insidious onset [4]. Therapeutic options for IPF in people include anti-inflammatory therapy (corticosteroids), cytotoxic agents (cyclophosphamide), immunosuppressives (azathioprine), and anti-fibrotics (colchicine), none of which has been associated with significant success. Lung transplantation has been successful for patients with late stage disease or severe diffusion capacity defects. Overall, IPF carries the worst prognosis among fibrotic interstitial lung diseases in people, with clinical response rates between 10-40% [4], and a median survival time of 3-4 years [6].

IDIOPATHIC PULMONARY FIBROSIS IN DOGS

Canine IPF occurs most commonly in terrier breeds. The West Highland White Terrier is overrepresented [7,8], and cases have also been reported in Staffordshire bull terriers, Cairn terriers, Jack Russell terriers, and schipperkes [9,10]. The canine form is histologically distinct from IPF in people. IPF in dogs is typically characterized by diffuse, uniform interstitial fibrosis and type II pneumocyte hyperplasia [8]. Fibroblastic foci, myofibroblast proliferation, and temporal heterogeneity, the hallmarks of human IPF, are not prominent features of the canine form.
Canine patients with IPF typically present with slowly progressive exercise intolerance and mild cough. Canine patients may exhibit a restrictive breathing pattern, characterized by rapid, shallow breathing, equilibration of inspiratory and expiratory times, and minimization of extraneous movements. Thoracic auscultation commonly reveals fine, “Velcro” crackles in all lung fields [8].

Confirmation of the diagnosis requires histologic demonstration of fibrotic interstitial lung disease. However, computed tomography (CT) findings in dogs with IPF may be useful surrogates in making a presumptive diagnosis [11]. CT alterations in dogs with IPF include ground glass opacities and traction bronchiectasis. Honeycombing, a common feature in both the human and feline form (see below) is not a common feature of canine IPF [8]. Bronchoscopic and bronchoalveolar lavage findings are not specific to IPF, but may be useful in eliminating other causes of progressive respiratory dysfunction. Arterial blood gas at the time of presentation typically reveals hypoxemia with an elevated alveolar-arterial gradient [8].

**IDIOPATHIC PULMONARY FIBROSIS IN CATS**

A form of fibrotic interstitial lung disease with many similarities to human IPF has recently been described and characterized in cats [12,13]. Feline IPF affects middle-aged to older cats. Clinical presentation commonly includes tachypnea, respiratory difficulty, cough, lethargy, anorexia, and weight loss. The duration of respiratory signs can vary tremendously, from 2 days to 1 year. Additionally, there are reports of three cats with IPF that died prior to showing any respiratory clinical signs [12].

Thoracic auscultation commonly reveals crackles, wheezes, or both. The “classic” radiographic pattern for IPF in cats is a heterogeneous or patchy distribution of interstitial disease, with areas of locally extensive interstitial disease coalescing to alveolar disease. Bronchiectasis, lung nodules, and cavitary lung lesions have also been reported [12].

The clinical presentation of cats with IPF may mimic other common bronchopulmonary diseases. However, as is the case with dogs, the routine diagnostic tests typically employed for evaluation of bronchopulmonary disease are not rewarding, other than to rule out concurrent, possibly treatable causes of lower respiratory dysfunction. Histologically, feline IPF is characterized by a temporally heterogeneous interstitial fibrosis with fibroblastic foci, alveolar epithelial metaplasia, and smooth muscle hyperplasia, similar to histologic findings in people. Co-incident lung tumors have also been reported, including bronchogenic carcinomas, multifocal adenomas, and a histiocytic sarcoma [12, 13].

**TREATMENT OF CANINE AND FELINE IPF**

Anti-inflammatory corticosteroid therapy has been the mainstay of therapy for both canine and feline IPF. Methylxanthine bronchodilators can be added in dogs for both their synergistic action with corticosteroids, and for respiratory muscle stimulation in dogs with exercise intolerance or respiratory muscle fatigue. Both dogs and cats can develop pulmonary hypertension as a consequence of chronic interstitial lung disease. When this can be documented and monitored, therapy with sildenafil (0.5 mg/kg) can be implemented. In general, the response to therapy in both dogs and cats is poor.

**SUMMARY**

Clinicians should be aware of fibrotic interstitial lung diseases in dogs and cats, with many features consistent with IPF in people. Although no clinical signs are uniformly observed, common clinical abnormalities may include tachypnea, cough, and inspiratory dysfunction. The typical diagnostic tests used for bronchopulmonary disease may be useful in ruling out other co-morbid conditions. However, results of these routine diagnostics are not specific to interstitial lung disease. Lung histology is necessary to confirm the diagnosis. The decision to pursue lung biopsy can be a difficult one, particularly in the face of severe cardiopulmonary compromise. However, regular lung biopsy in interstitial lung diseases will be necessary to confirm diagnoses, recommend lifelong therapy, and further our understanding of the pathogenesis of idiopathic pulmonary fibrosis.

7. Corcoran et al, Vet Rec 144, 1999
8. Heikkila et al., JVIM 25, 2011
10. Lobetti et al, JAAHA 37, 2001