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INTERSTITIAL LUNG DISEASE (ILD) IN THE DOG

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Introduction
The lung interstitium consists of the space sandwiched between the alveolar lining epithelium and is made up of connective tissue and resident fibroblasts and macrophages. It also contains the lung capillaries and lymphatics, but does not include the lining epithelium of the alveoli. When disease affects the lung interstitium it is most likely that it will involve adjacent structures at some time, and once the process has spread to the alveoli, pneumonia is present.

Diseases of the lung interstitium
True ILDs of the dog and cat are not clearly defined, unlike in human medicine where there are large numbers of such diseases (Table 1). A variety of pathological processes will affect the lung interstitium and the most convincing ILD disease entities in the dog are pulmonary infiltration with eosinophilia (also known as eosinophilic bronchopneumopathy) and idiopathic pulmonary fibrosis. However, lung parasitism, viral infection and neoplasia (lymphoma) can also affect the interstitium, but are likely to involve other lung structures as well.

The lung parasites can include *Filaroides* spp (*Olslerus osleri*, *Filaroides hirthi*, *Crenosoma vulpis*, *Aelurostrongylus abstrusus*, *Capillaria aerophila*, and the heartworms *Angiostrongylus vasorum*, and *Diriofilaria immitis*), but their importance will depend on geographical location. In humans, there is a large group of occupational, toxin and drug-induced interstitial lung diseases and connective tissue disorders that can involve the lung, but analogous conditions are difficult to recognise with certainty in dogs and cats. Without increased use of lung biopsy these ILDs are unlikely to be proven to exist in the dog and cat in the future. The only toxin-induced ILD recognised in the dog is parquet poisoning. The interstitium can also be affected by other disease processes such as pulmonary oedema (cardiogenic and non-cardiogenic), and syndrome entities such as acute respiratory distress syndrome (ARDS), but typically these conditions affect other parts of the lung and so cannot be classified as ILDs. Bacterial bronchopneumonia and the mycotic pneumonias (specific geographic locations worldwide) could be viewed similarly. Radiographic detection of non-specific interstitial lung changes is readily recognised in clinical practice and can be associated with metastatic mineralization with hyperadrenocorticalism or as a consequence of the natural ageing process. All these diseases compromise respiratory function to varying degrees and can secondarily initiate other types of respiratory pathology which make identification of the underlying disease processes problematic.

Pulmonary infiltration with eosinophilia (PIE)
PIE is also known as eosinophilic bronchopneumopathy (EBP) and is characterised by large numbers of eosinophils being present in the lung. Within the PIE syndrome, involvement of the interstitium alone or additional involvement of the alveoli and bronchi can be seen. This makes it difficult to identify a pure PIE ILD, but the initial process of eosinophil migration into the lung will involve the interstitium, and in many of these cases a distinct interstitial pattern can be identified on radiography. Typically dogs present with a cough and only if the pathology is extensive do other signs of dyspnoea and exercise intolerance become apparent. The underlying cause of PIE is unknown, but the recruitment of eosinophils to the lung suggests a hypersensitivity disorder. At the same time there is often a circulating eosinophilia suggesting the stimulation of bone marrow to satisfy a lung demand for eosinophils. The potential role of parasitism in this process also needs to be considered and in PIE cases routine anthelmintic treatment is advised as part of the treatment protocol. Bronchoscopic examination of the PIE case is usually unremarkable, but eosinophil-rich material can be collected and is a pre-requisite for diagnosis of PIE. Sometimes this material can be identified as a congealed mucus plug in the airways. If left untreated, secondary chronic airway changes similar to chronic bronchitis can occur, but this is clearly avoided by appropriate therapy early in the disease process. Routine haematology might also detect a circulating basophilia.

Since PIE can be reminiscent of kennel cough, dogs tend to be treated with antibiotics in the first instance. This may alleviate the clinical signs, either because of control of secondary infections or due to natural remission, but the clinical signs will re-appear and the dog develops a chronic cough. Once the eosinophilic nature of the lung inflammatory reaction has been documented, standard treatment is with glucocorticosteroids and this typically results in a rapid and sustained response. Dexamethasone induces apoptosis in eosinophils and when given initially will remove eosinophils from the lung and circulation. Maintenance treatment uses oral prednisolone at anti-inflammatory doses, tapering to...
alternate day dosing and ceasing therapy after 6-8 weeks. In most cases this single treatment regime is sufficient with no further recurrence. In some dogs continued intermittent therapy may be required and in particularly resistant cases addition of azathioprine may be required. Such cases can prove difficult to maintain in the long-term.

**Idiopathic pulmonary fibrosis (IPF)**
IPF has been recognised pathologically in the cat, but to date this has not been accomplished satisfactorily in the dog. However, an IPF-like disease reminiscent of IPF in humans is suggested to exist in the dog and appears to be particularly prevalent in the West Highland white terrier. Other closely related terrier breeds have also been reported to be affected. The clinical features of IPF are much better described in the dog than the cat.

Typically, affected dogs are middle aged and present with a slowly progressive chronic respiratory disease with coughing, dyspnoea and exercise intolerance. Otherwise they are in good health and despite the progressive deterioration in respiratory function, remain so until the end. The survival time from when the condition is diagnosed varies, but is usually less than 12 months. However, owners often do not present their pets for evaluation until the disease is advanced, interpreting the reduced exercise tolerance to be a consequence of ageing.

When first examined, affected dogs have distinct inspiratory crackles, suggesting the disease is advanced, and this finding is crucial to diagnosis. Thoracic radiography will demonstrate a distinct increase in interstitial density. However, the major differential diagnosis for chronic inspiratory crackles is chronic bronchitis and the presence of obvious bronchial markings with or without interstitial changes would make this diagnosis more likely. To overcome this problem bronchoscopy is necessary to exclude a diagnosis of chronic bronchitis. In some individuals it appears both conditions can exist at the same time. Bronchoscopy allows bronchoalveolar lavage to be carried out and in IPF cases there is usually little or no evidence of an inflammatory reaction.

High-resolution computed tomography (HRCT) can greatly increase the confidence of interpretation of radiographic signs, and in IPF dogs typical HRCT findings include ground glass opacity, sub-pleural bands, parenchymal bands, sub-pleural and peri-bronchovascular interstitial thickening and traction bronchietasis. These changes appear to correlate well with the severity of disease. However, the accuracy of diagnosis of IPF does not appear to be affected by the use of HRCT when thoracic radiographs are of high quality, assessed by a specialist diagnostic imager and there is good supporting bronchoscopic data. The use of radiography in the diagnosis of IPF can be a confounding factor since interstitial radiographic patterns are markedly affected by exposure settings, body conformity, obesity and stage of respiration, and close attention to obtaining good quality radiographs is paramount for accurate diagnosis. Furthermore, subtle interstitial lung patterns are extremely difficult to identify with an acceptable degree of certainty. HRCT is also useful in determining the extent and location of disease pathology and would be invaluable if diagnostic lung biopsy were to be attempted.

Abnormalities of blood gas analysis can be found in IPF affected dogs and are usually representative of ventilation-perfusion mis-match. While application of pulmonary function testing has not been assessed in IPF cases, the lung stiffness is likely to result in reduced lung compliance. This can be appreciated as difficulty in manual inflation in anaesthetised cases and end-expiratory dynamic collapse of lobar bronchi on bronchoscopy.

Confirmation of IPF requires lung biopsy, and in human IPF the pathology is that of usual interstitial pneumonitis. This pathological process has been identified in the cat, but has yet to be confirmed in the dog. The lack of suitable biopsy or necropsy material from affected dogs, and the lack of experienced veterinary respiratory pathologists, makes it difficult to know when this problem will be rectified. The patchy nature of the disease makes unguided biopsy samples of limited value. If it transpires that the dog pathology is different from that reported for humans and cats, canine IPF may have to be re-named, but a well characterised clinical entity does appear to exist. The course of this disease is predictable and results in eventual respiratory failure. However, euthanasia is usually carried out before that stage as the respiratory impairment becomes intolerable. In up to 50% of canine IPF cases pulmonary arterial hypertension develops and this further compromises respiratory function. In some case this can lead to right-sided congestive heart failure.

Treatment of canine IPF appears to be of little value and there is little that can be done to improve respiratory function or to arrest disease progression. Oral prednisolone is often tried, but is ineffective, or if an effect is noticed the concurrent existence of chronic bronchitis should be suspected. Sildenafil therapy in those dogs with pulmonary hypertension appears to benefit some cases, and this would suggest that pimobendan might be similarly beneficial. Control of obesity in IPF cases would be advisable, but in general controlling the day-to-day activity is also necessary to reduce the chances of hypoxic episodes. There is no evidence to show anti-fibrotic agents like colchicine would be of any benefit, but whether or not this would be case if the disease process could be identified earlier is unknown. Many other medications are being evaluated in human IPF, but
Cardiorespiratory

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<th>Drug or toxin-induced</th>
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<th>Primary interstitial lung diseases</th>
<th>Idiopathic fibrotic disorders</th>
<th>Connective tissue disorders</th>
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<td>Eosinophilic pneumonia</td>
<td>Idiopathic pulmonary fibrosis</td>
<td>Rheumatoid arthritis</td>
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<td>Paraquat</td>
<td>Farmers lung disease</td>
<td>Lymphoma</td>
<td>Lymphocytic interstitial Pneumonitis</td>
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<td>drugs</td>
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<td>Metastatic calcification</td>
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Table 1: Classification of interstitial lung diseases in humans (the list is not exhaustive)

the only agents that appear to have some promise are pirfenidone and hydroxyproline analogs. The possibility of these being effective in canine IPF is still unknown.

Additional reading