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Clinical, Bronchoscopic, Histopathologic, Diagnostic Imaging, and Arterial Oxygenation Findings in West Highland White Terriers with Idiopathic Pulmonary Fibrosis

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Background: Idiopathic pulmonary fibrosis (IPF) is a chronic, interstitial lung disease primarily affecting West Highland White Terriers (WHWTs).

Objective: To describe the clinicopathological and diagnostic imaging features in WHWTs with IPF.

Animals: Twelve WHWTs with IPF and 14 healthy control WHWTs.

Method: Prospective study. Clinical signs and findings of physical examination, blood and arterial blood gas analyses, radiography, high-resolution computed tomography (HRCT), bronchoscopy and bronchoalveolar lavage (BAL) of IPF dogs were obtained and compared with controls. Histopathologic changes in IPF dogs were evaluated.

Results: Mean partial pressure of oxygen was significantly lower in IPF (mean ± SD, 65.5 ± 15.4 mmHg) than in controls (99.1 ± 7.8 mmHg, $P < .001$). The alveolar-arterial oxygen gradient was significantly higher in IPF (50.1 ± 17.3 mmHg) than in controls (17.5 ± 4.9 mmHg, $P < .001$). In HRCT, ground glass opacity (GGO) was detected in all IPF dogs, traction bronchiectasis in 4, and honeycombing in 1. Bronchoscopic airway changes were noted in all IPF dogs. On BAL fluid (BALF) cytology, the total cell count (TCC) was higher in IPF dogs, and the numbers but not the percentages of macrophages, neutrophils, and mast cells were increased. On histopathology, multifocal or diffuse interstitial fibrosis, type II pneumocyte hyperplasia, prominent intraalveolar macrophages, distortion of alveolar architecture, and emphysematous change were detected.

Conclusion and Clinical Importance: IPF causes substantial hypoxemia. In HRCT, GGO is a consistent finding. IPF dogs have concurrent airway changes and an increase in BALF TCC.

Key words: Arterial blood gases; Bronchoalveolar lavage; Dog; High-resolution computed tomography; Interstitial lung disease.

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive interstitial lung disease that carries a poor prognosis. IPF has been described in humans, and despite being actively investigated, its pathophysiology remains poorly understood and its etiology is unknown.[1] An interstitial lung disease with many similar features also occurs in dogs[2–5] and cats.[6] In both humans and dogs, diseased individuals tend to be middle aged or older and respond poorly to treatment.[2,7]

IPF is characterized by an abnormal accumulation of collagen in the pulmonary interstitium.[4,8] This hampers gas exchange and leads to clinical signs such as dry cough, exercise intolerance, and respiratory difficulties. Despite clinical similarities, it is not known whether the histopathologic pattern in canine IPF resembles that of usual interstitial pneumonia (UIP),[2,4,5] which is the histopathological pattern of IPF in humans.[7]

Canine IPF occurs mainly in terriers and is most common in the West Highland White Terrier (WHWT).[2,3,9] The diagnosis is based on clinical findings, diagnostic imaging, and the exclusion of other cardiac and respiratory illnesses. A definite diagnosis of interstitial fibrosis is obtained by histopathologic examination.

In IPF, the emphasis of thoracic imaging has shifted from radiography to high-resolution computed tomography (HRCT), which can detect subtle changes in the lung parenchyma. HRCT is considered crucial for the diagnosis of IPF in humans.[10,11] In a previous study, the lung changes in canine IPF were reported to resemble those of human patients.[12] Ground glass opacity (GGO) appeared in early IPF, whereas interstitial thickening, honeycombing, and traction bronchiectasis became evident at a later stage.[12]

Abbreviations:

ALP	alkaline phosphatase
BAL	bronchoalveolar lavage
BALF	BAL fluid
GGO	ground glass opacity
HRCT	high-resolution computed tomography
HU	Hounsfield unit
IPF	idiopathic pulmonary fibrosis
TCC	total cell count
UIP	usual interstitial pneumonia
WHWT	West Highland White Terrier

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Bronchoscopy and bronchoalveolar lavage (BAL) provide important information about the respiratory tract. Previously, only minimal airway changes and low-grade inflammatory reactions have been reported in dogs with IPF.[2] However, the diseased lung tissue should be histopathologically examined in order to clarify whether more prominent airway involvement indicates an alternative diagnosis. Additionally, BAL fluid (BALF) cellularity has not yet been quantitatively assessed in this disease.

Arterial blood gas analysis can be used to evaluate lung function. Hypoxemia and an increased alveolar-arterial oxygen gradient ($P[A\text{-}a]O_2$) have been associated with canine IPF,[2,5] but no reports about the severity of the changes exist.

The purpose of this study was to describe the clinicopathological and diagnostic imaging features in WHWTs with IPF. Clinical signs and findings of physical examination, blood and arterial blood gas analyses, radiography, HRCT, bronchoscopy, and BAL cytology are reported and compared with healthy control WHWTs. Histopathologic findings of IPF dogs also are described.

Materials and Methods

Study Population

Twenty-six privately owned WHWTs were prospectively recruited. Twelve WHWTs had a diagnosis of IPF and 14 healthy WHWTs were chosen as controls. The owners provided written consent for participation. The study was performed at the Veterinary Teaching Hospital of the University of Helsinki, Finland. The study protocol was approved by the Committee of Experimental Animals of Western Finland.

Diagnosis of IPF

The diagnostic evaluation of IPF dogs consisted of history and physical examination (12/12), hematology and serum biochemistry (11/12), fecal examination (8/12), arterial blood gas analysis (9/12), thoracic radiography (10/12), echocardiography (10/12), HRCT (6/12), and bronchoscopy and BAL (11/12). All of the examinations described above also were performed on all controls, except for arterial blood gas analysis (11/14), HRCT (12/14), and bronchoscopy and BAL (12/14). In 11/12 IPF dogs, the diagnosis was later verified by histopathologic examination of lung tissue. In the remaining 1 dog, IPF diagnosis was based on the aforementioned thorough clinical evaluation.

Clinical Signs and Physical Examination

The owners were questioned about clinical signs and a thorough physical examination was carried out by one of the authors (H.P.H.).

Biochemical, Hematologic, and Fecal Examination

Venous blood was collected for serum biochemistry and CBC. A 3-day fecal sample was examined for parasites by the Baermann and flotation methods.

Arterial Blood Gas Analysis

Arterial blood samples were taken from the femoral or dorsal metatarsal artery. The dogs were not sedated and were breathing room air. The partial pressures of oxygen (PaO_2) and carbon dioxide, $P(A\text{-}a)O_2$, pH, bicarbonate, and acid-base excess were analyzed immediately with a blood gas analyzer[a] at 37°C.

Thoracic Radiography, Echocardiography, and HRCT

Right and left lateral and ventrodorsal radiographs were obtained and echocardiography was performed.[b] Afterward, the dogs were premedicated with butorphanol.[c] Anesthesia was induced with midazolam[d] and propofol.[e]

An HRCT study was performed under isoflurane inhalation anesthesia.[f] The dogs either were in dorsal or ventral recumbency and were ventilated before scanning. Data were obtained with a helical dual slice scanner[g] during the respiratory pause. Slice thickness was 1.0 mm with 7.5 mm table movement. The images were viewed in Syngo Multi Modality Workplace[h] by one of the authors (A.K.L.), who was blinded to the dog's disease status. The HRCT findings were categorized according to a classification scheme published previously.[12] Each radiographic and HRCT finding was scored as normal, mild, moderate, or severe. A HRCT finding was considered mild when it was subtle and only present in 1 lung lobe. When subtle lesions were present in several lobes or the lesion was distinct it was assessed as moderate. A widespread and extensive lesion was evaluated as severe even if present in 1 lung lobe only. Additionally, quantitative CT values of the nondependent parts of the lung lobes were measured and mean CT values were calculated.

Bronchoscopy and BAL

Bronchoscopy and BAL were performed after HRCT with a videoendoscope[i] with IV propofol anesthesia. The presence of tracheal collapse, bronchial mucus, bronchial mucosal irregularity, bronchiectasis, and bronchomalacia was reported. The right and left caudal lung lobes were lavaged with sterile, warmed (37°C) saline (2 mL/kg, divided in 2 aliquots). The BALF sample was processed as described previously.[13] A quantitative bacterial culture was performed. The limit of infection was set to bacterial growth of 10^4 CFU/mL.[14]

Histopathology

Multiple samples of mainly subpleural lung tissue from 2 to 6 lung lobes were collected from each dog by H.P.H. immediately after euthanasia. Samples were fixed in 10% neutral buffered formalin, processed routinely, and sections were stained with hematoxylin and eosin. All of the samples were evaluated by 1 author (M.J.D.).

Statistical Analysis

Analyses were performed by a commercial statistical program.[j] Normality was evaluated by the Shapiro-Wilk test. An unpaired Student's *t*-test was used when distribution was Gaussian (blood and arterial blood gas results) and the Mann-Whitney *U*-test was used for nonnormally distributed data (BALF results). Spearman's rank correlation was used for all correlations. All comparisons were performed 2-tailed. The differences were considered significant if $P < .05$.

Results

Signalment, Clinical Signs, and Physical Examination

The IPF group consisted of 6 intact males, 5 intact females, and 1 neutered female. There were 2 intact males, 3 neutered males, 5 intact females, and 4 neutered females in the control group. The mean age and weight were 13 years (range, 10–15 years) and 9 kg (range, 8–13 kg) in the IPF group, and 9 years (range, 3–14 years)

and 9 kg (range, 8–12 kg) in controls. The control dogs did not have any signs or findings indicating disease.

At presentation, 8 dogs with IPF were receiving medications (eg, prednisolone, theophylline, furosemide, benazepril, pimobendan, or thyroxine). One dog had hypothyroidism, one had urinary tract infection, and another had pyelonephritis. One control dog was receiving prednisolone and cyclosporine for dermatologic problems.

The most common clinical sign was a combination of cough and exercise intolerance, described in 5/12 IPF dogs. Exercise intolerance as the sole problem was reported in 3/12 and cough in 2/12 dogs. One dog had only been gagging and another panting. The mean duration of signs was 13 months (range, 2–29 months).

The general condition of 10/12 dogs was good, and the dogs were bright and alert. Both of the remaining 2 dogs were dyspneic and tachypneic, and 1 of them additionally was cyanotic. Abdominal breathing was reported in 8/12 dogs with IPF, including both of the dyspneic dogs. Diffuse inspiratory pulmonary crackles described as ''Velcro crackles'' were detected bilaterally in 9/12 dogs. Two dogs were normal on auscultation and 1 had rhonchi. In 2 dogs, the ''Velcro crackles'' were audible without a stethoscope. None of the dogs had wheezes on auscultation.

Biochemical, Hematologic, and Fecal Examination

Only serum concentration of alkaline phosphatase (ALP) and platelet count were not within reference ranges. After excluding the dogs receiving prednisolone medication and the dog with pyelonephritis, the ALP concentration was increased in 6 of the remaining 7 dogs with IPF and in 5 of the remaining 13 controls. Similarly after exclusion, thrombocytosis was seen in 6/7 dogs with IPF and in 12/13 controls. The mean ALP concentration was 454 U/L (range, 190–827 U/L) in IPF and 282 U/L (range, 54–654 U/L) in controls (reference range, 33–215 U/L). The mean thrombocyte count was 534,000 $\times$ $10^3/\mu$L (range, 370,000–720,000 $\times$ 10^3 μ/L) in IPF and 556,000 $\times$ 10^3 μ/L (range, 356,000–880,000 $\times$ 10^3 μ/L) in controls (reference range, 102,000–395,000 $\times$ 10^3 μ/L). The mean hematocrit was 52% (range, 33–53%) in IPF and 51% (range, 38–59%) in controls (reference range, 38–57%). The ALP concentration, thrombocyte count, and hematocrit did not differ between the 2 groups.

All fecal samples were negative for parasites. The dogs were not tested for heartworm (*Dirofilaria immitis*) antigen because it is not endemic in Finland. Histopathologic examination of lung tissue did not disclose changes consistent with *Angiostrongylus vasorum* infection.

Arterial Blood Gas Analysis

Results are given in Table 1.

Table 1. Arterial blood gas values in IPF dogs (n = 9) and healthy control dogs (n = 11), given as mean $\pm$ SD and range.

	Dogs with IPF	Controls
PaO_2 (mmHg)*	65.5 $\pm$ 15.4 (33.5–87.4)	99.1 $\pm$ 7.8 (89.6–113.0)
$P(A\text{-}a)O_2$ (mmHg)*	50.1 $\pm$ 17.3 (28.0–84.7)	17.5 $\pm$ 4.9 (10.7–26.8)
$PaCO_2$ (mmHg)	29.3 $\pm$ 3.8 (25.0–35.7)	28.7 $\pm$ 3.8 (20.5–34.6)
pH	7.451 $\pm$ 0.040 (7.407–7.529)	7.467 $\pm$ 0.053 (7.407–7.569)
HCO_3^- (mmol/L)	21.1 $\pm$ 2.6 (17.9–5.9)	20.4 $\pm$ 1.9 (17.6–3.0)
ABE (mmol/L)	-1.5 ± 3.0 (-6.0–3.1)	-1.5 ± 2.1 (-5.0–1.3)

ABE, acid-base excess; HCO_3^-, bicarbonate; IPF, idiopathic pulmonary fibrosis; $P(A\text{-}a)O_2$, alveolar-arterial oxygen gradient; $PaCO_2$, partial pressure carbon dioxide; PaO_2, partial pressure of oxygen.

*Statistically significant difference, $P < .001$.

Thoracic Radiography, Echocardiography, and HRCT

The most common radiographic finding was a bronchointerstitial pattern seen in 7/10 IPF dogs (moderate in 3/10, severe in 4/10). Three of 10 IPF dogs had patchy alveolar opacities with indistinct margins in 1 or 2 lung lobes. The most common pattern in controls was mild bronchial or bronchointerstitial pattern, which was considered normal.

Mean vertebral heart score was 10.0 in IPF dogs (range, 9.1–11.1) and 10.2 in controls (range, 9.3–11.0). Echocardiography disclosed right-sided cardiac enlargement in 6/10 IPF dogs. Tricuspid valve dysplasia and pulmonary stenosis were eliminated in all dogs. Left-sided heart disease also was not detected.

On HRCT, several lesions were detected in each dog with IPF. In the majority of the dogs, the predilection site for the lesions was the dorsocaudal lung lobes. GGO was seen in all dogs (severe in 4/6, moderate in 2/6). Parenchymal bands were visible in 4/6 dogs (mild in 1/6, moderate in 3/6), subpleural lines in 1/6, moderate subpleural interstitial thickening in 1/6, moderate peribronchovascular interstitial thickening in 3/6, consolidation in 4/6, traction bronchiectasis in 4/6, and honeycombing in 1/6 dogs (Fig 1). Traction bronchiectasis and honeycombing occurred simultaneously in 1 dog. In 4/12 controls, no changes were recorded. Eight of 12 controls had only 1 or 2 focal lesions in the dependent part of the lung. Consolidation, traction bronchiectasis, subpleural lines, subpleural interstitial thickening, or honeycombing was not seen in any of the controls. The CT values were significantly higher in IPF (mean $\pm$ SD, -735 ± 55 Hounsfield unit [HU]; range, -645 to -789 HU) compared with controls (-821 ± 36 HU, -761 to -862 HU, respectively; $P = .001$). No correlation with PaO_2 was detected.

Bronchoscopy and BAL

Bronchoscopic results were available from 8/12 dogs with IPF and 11/14 control dogs. The findings in dogs with IPF were mucosal irregularity (8/8), tracheal collapse (5/8) (grade I in 3/8, grade III in 2/8), mild to moderate amount of bronchial mucus (2/8), mild

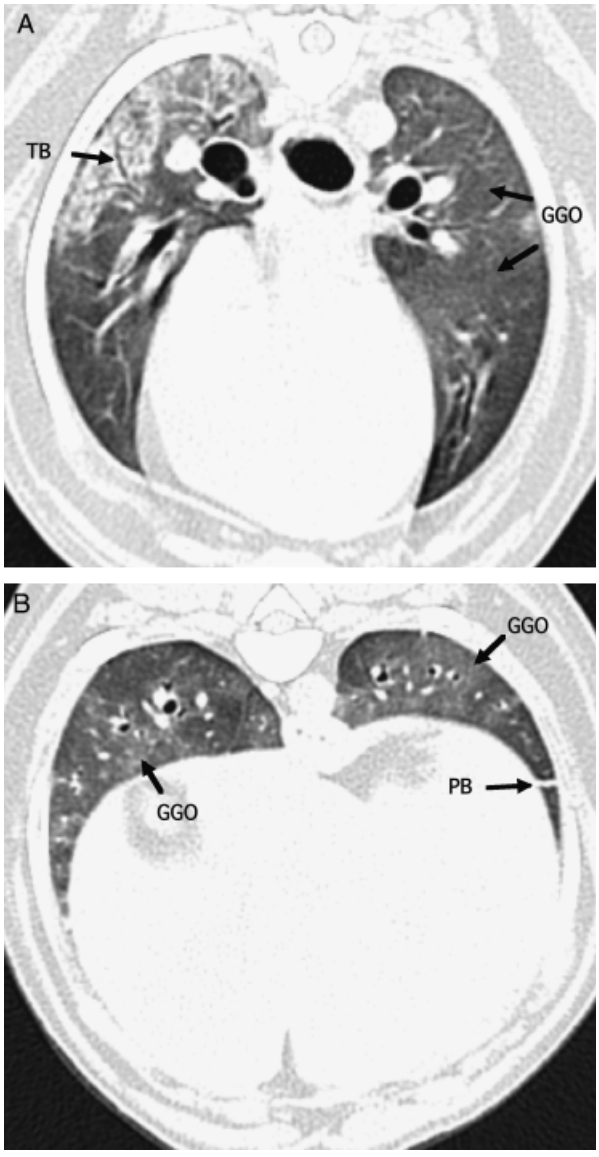

Fig 1. Idiopathic pulmonary fibrosis. Lung high-resolution computed tomography images of 2 affected dogs. (**A**) Image demonstrates areas of ground glass opacity (GGO) and traction bronchiectasis (TB). Scan was obtained from a 10-year-old West Highland White Terrier (WHWT) with severe hypoxemia (partial pressure of oxygen [PaO_2] 50.6 mmHg). Scanned in dorsal recumbency. (**B**) Image shows a parenchymal band (PB) and areas of GGO in an 11-year-old WHWT (PaO_2 61.3 mmHg). Scanned in ventral recumbency.

bronchiectasis (3/8), and bronchomalacia (4/8) (mild in 2/8 and severe in 2/8). Three of 11 controls had grade I tracheal collapse. Mild mucosal irregularity was seen in 7/11 controls.

Analyses of BALF are shown in Table 2. BALF total cell count (TCC), macrophages, neutrophils, and mast cell percentage correlated negatively with PaO_2 ($r = -0.626$, $P = .005$; $r = -0.558$, $P = .016$; $r = -0.644$, $P = .004$; $r = -0.507$, $P = .032$, respectively). Lymphocyte percentage had a positive correlation with PaO_2 ($r = 0.610$, $P = .007$). No bacterial growth was detected.

Histopathology

Within each section there was either multifocal or diffuse evidence of moderate to severe expansion of the interstitium by accumulation of dense fibrous connective tissue. This matrix often was sparsely cellular and there was no clear evidence of active fibroblastic proliferation. This change was accompanied by prominent foci of type II pneumocyte hyperplasia (Fig 2). Distortion of alveolar architecture and emphysematous change in adjacent areas of relatively unaffected lung often were observed. Alveolar spaces generally contained prominent macrophages and in some cases there also were occasional multinucleated giant cells. In most cases, there was no evidence of inflammatory change affecting either the parenchyma or airways apart from 3 dogs in which there was either mild interstitial pneumonia, severe interstitial pneumonia associated with secondary bacterial infection, or a discrete granulomatous reaction centered upon aspirated debris. The lung from 3 dogs had evidence of incidental anthracosis.

Discussion

The goal of this study was to further define the clinicopathological and diagnostic features of IPF in dogs. We were able to quantify the degree of hypoxemia and the cellular changes in BALF. The study was prospective and included a control group of healthy dogs of the same breed. Eleven of the 12 dogs with IPF had histopathologic confirmation of the diagnosis.

The signalment, clinical signs, and physical examination findings were consistent with those reported previously.[2] "Velcro crackles" are a distinctive finding in canine IPF,[2] and are heard in the majority of human patients.[7] In this study, "Velcro crackles" were not heard in 3 dogs with IPF, including the most severely and the least affected dogs. The absence of this finding might be because of an early phase of the disease, or shallow, tachypneic breathing present in the severely affected dog. In humans, slow breathing from near-residual lung volume helps detect the abnormal sounds.[15]

In this study, increased ALP activity was seen frequently in dogs with IPF, although alanine aminotransferase examined was within reference range. Because similar increases also were noted in controls, it is unlikely that the reason for high ALP activity would be hypoxemic liver damage, as is described in dogs with severe tracheal collapse.[16]

Arterial blood gas analysis is an objective means of estimating lung function and it proved to be useful in this population of dogs. Hypoxemia has been reported previously in dogs with IPF,[2,5] but the severity of the change has not been quantified. We detected notably low PaO_2 and high $P(A\text{-}a)O_2$,. Still, most IPF dogs were bright and alert, and only 2 dogs were dyspneic. The slow progression of the disease enables the dogs to accommodate to progressively lower oxygen levels. Although $P(A\text{-}a)O_2$ values of the IPF dogs were substantially increased, the controls also had mildly higher values than the reference range (<15 mmHg).[17] Part of this increase can be explained by the measurement temperature being 37°C

Table 2. Cytological findings in BALF of IPF dogs (n = 11) and healthy control dogs (n = 12), given as median, IQ, and range.

	IPF Dogs	Controls
Recovered volume (%)	59, IQ 49–63 (35–65)	56, IQ 49–69 (40–76)
Total cell count (cells/μL)**	765, IQ 450–1,120 (280–3,115)	350, IQ 280–380 (265–420)
Macrophages (%)	84, IQ 66–88 (64–93)	78, IQ 76–82 (69–89)
Cells/μL*	672, IQ 304–1,000 (178–2,500)	269, IQ 225–289 (194–375)
Lymphocytes (%)*	6.4, IQ 4.4–13 (1.7–30)	16, IQ 14–19 (9.2–21)
Cells/μL	51, IQ 28–83 (14–335)	56, IQ 42–63 (39–79)
Neutrophils (%)	3.4, IQ 3.5–24 (3.0–30)	4.5, IQ 3.1–4.7 (0.9–6.2)
Cells/μL**	32, IQ 24–124 (10–753)	14, IQ 11–17 (2.8–18)
Eosinophils (%)	0.0, IQ 0.0–0.0 (0.0–2.0)	0.4, IQ 0.0–0.6 (0.0–2.0)
Cells/μL	0.0, IQ 0.0–1.8 (0.0–14)	1.5, IQ 0.0–1.8 (0.0–5.6)
Mast cells (%)	0.4, IQ 0.4–1.0 (0.0–2.5)	0.3, IQ 0.0–0.4 (0.0–0.9)
Cells/μL*	3.3, IQ 1.2–11 (0.0–64)	1.1, IQ 0.0–1.6 (0.0–3.2)
Epithelial cells (%)	0.0, IQ 0.0–1.4 (0.0–9.7)	0.2, IQ 0.0–0.4 (0.0–1.8)
Cells/μL	0.0, 0.0–6.6 (0.0–78)	0.9, IQ 0.0–1.4 (0.0–6.3)
Plasma cells (%)	0.0, IQ 0.0–0.0 (0.0–0.6)	0.0, IQ 0.0–0.0 (0.0–0.6)
Cells/μL	0.0, IQ 0.0–0.0 (0.0–3.3)	0.0, IQ 0.0–0.0 (0.0–2.1)

BALF, bronchoalveolar lavage fluid; IPF, idiopathic pulmonary fibrosis; IQ, interquartile range.
*Statistically significant difference, $P < .05$.
**Statistically significant difference, $P < .01$.

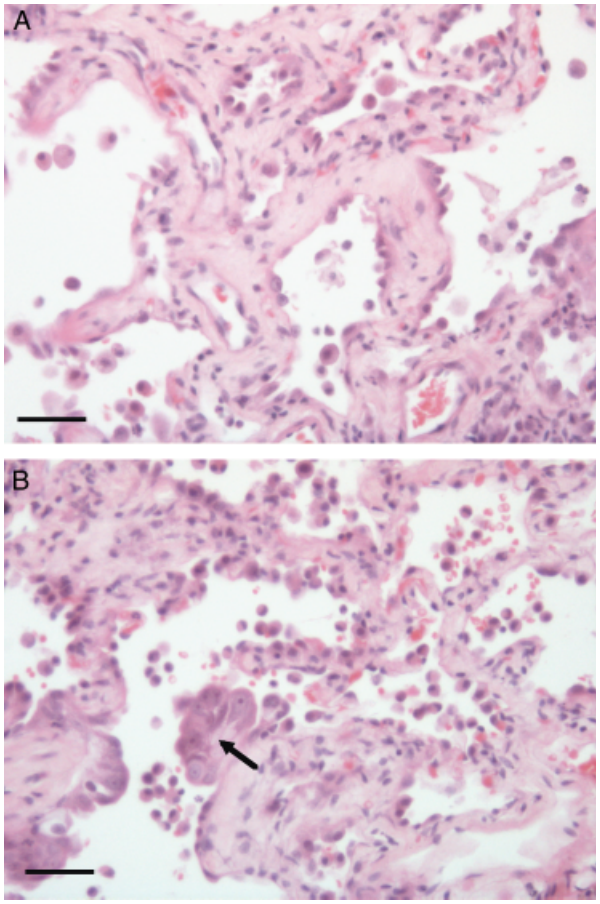

Fig 2. Representative histopathological changes from a 13-year-old West Highland White Terriers with idiopathic pulmonary fibrosis. (**A**) Distortion of alveolar microarchitecture with prominent fibrosis of the interstitium and scattered alveolar macrophages. (**B**) A focus of type II pneumocyte hyperplasia is indicated. Bar 100 μm, hematoxylin and eosin.

instead of the dog's body temperature, and part by the age of the dogs, because older dogs can have higher values.[18] Given the lack of practical and more sensitive pulmonary function tests in dogs, arterial blood gas analysis can be considered a suitable method for assessing the severity of IPF and, when repeated, for monitoring the course of the disease.

Radiographic signs of IPF are nonspecific, and in addition to lung pathology, the opacity of the images can be increased by thick skin typical for the breed and SC fat. A bronchointerstitial pattern was the most common radiographic finding in IPF dogs, which is in accordance with previous studies.[2,3,12] Alveolar opacities were detected in 3 diseased dogs. In one of them, HRCT was performed and no such change was seen. This suggests that alveolar opacity in the radiograph could at least partly be related to poor inflation of the lung.

Pulmonary hypertension is common in WHWTs with IPF, affecting more than 40% of the diseased dogs.[19] In our study, 6/10 dogs with IPF undergoing echocardiography showed right-sided ventricular dilatation with hypertrophy, which in the absence of cardiac causes could indicate pulmonary hypertension. However, because pressure gradients across the tricuspid valve were not calculated, the presence of pulmonary hypertension could not be confirmed.

HRCT is widely used in diagnosing IPF in human patients.[10] GGO, described as a hazy increase in lung opacity without obscuration of the underlying vessels,[12] was visible in all dogs with IPF, which also was noted in a previous study.[12] Because IPF is the most commonly reported interstitial lung disease in WHWTs, we believe the HRCT finding of GGO contributes to the clinical diagnosis of IPF in this breed. These findings contrast with those of human patients with IPF in whom extensive GGO is considered atypical and more indicative of an inflammatory process, and only honeycombing, traction

bronchiectasis, coarse reticulation, and architectural distortion are associated with a definite diagnosis.[10,20] Here, traction bronchiectasis and honeycombing were detected in 4 and 1 affected dogs, respectively. Reticular opacities such as parenchymal bands and subpleural lines were seen in almost all dogs with IPF. Consolidation in the dependent parts of the lung also was common in dogs with IPF, but was not seen in control dogs. Whether the change was caused by the underlying lung pathology or positional atelectasis is not known. The predilection site for all lesions was the dorsocaudal lung lobes in most dogs.

The dogs with IPF had higher CT values than did controls. CT values are nonspecific and express the attenuation of X-rays in the tissue. The values depend on respiratory phase and therefore are not used in evaluating diffuse lung pathology in humans. However, in the present study the scans were carried out in a more standardized way during the respiratory pause. Therefore, the difference between control and IPF dogs was not because of different respiratory phases, but instead it may be caused by decreased expansile capacity of fibrotic lungs or diffuse lung pathology.

Bronchoscopy with BAL is an important tool in eliminating differential diagnoses in dogs with a suspected diagnosis of IPF. However, because changes seen on bronchoscopy only reflect abnormalities in the airways, the usefulness in the diagnosis of IPF is otherwise limited. In this study, all dogs with IPF undergoing bronchoscopy showed some signs of airway involvement. Mucosal irregularity, which was seen in all dogs with IPF but also in 7/11 controls, could be partly explained by the older age of the dogs.[21] The criteria used for detecting airway abnormality also may have been excessively sensitive. Corcoran et al[2] described bronchial changes in approximately one third of dogs with IPF, suggesting a combination of bronchial and interstitial lung disease. In our study, despite the degree of the airway changes, all of the dogs examined had a similar histopathologic picture of interstitial pulmonary fibrosis. This indicates that bronchoscopic findings commonly associated with airway disease, such as mucosal irregularity and tracheobronchomalacia, do not eliminate a diagnosis of canine IPF. In humans, acquired tracheomalacia and tracheal dilatation can occur as a complication of pulmonary fibrosis and are thought to be because of increased traction on the tracheal wall.[22] In dogs, the cause for malacic airways in chronic lung diseases is unclear,[23] and whether the bronchial changes seen in IPF occur secondarily to the underlying interstitial lung disease or as an independent phenomenon is not known.

Dogs with IPF had an increase in the BALF TCC because of increased numbers of macrophages, neutrophils, and mast cells. The only change in the relative differential counts was detected in the lymphocyte percentage, which was lower in dogs with IPF than in controls. On histopathologic examination of lung tissue, macrophages were prominent in alveolar spaces reflecting their role in IPF pathology. Because TCC also was increased in those dogs with IPF that did not cough, this change likely is a consequence of the interstitial lung disease rather than solely a secondary bronchial reaction to cough. In human patients with IPF, BALF TCC is increased, and neutrophilia and mild or moderate eosinophilia are described in most patients whereas lymphocytosis is less common.[k,7,24] In humans, although differential cell counts correlate with severity of disease, BALF cellularity does not have prognostic value.[24,25] We correlated TCC, individual, and differential cell counts with PaO_2 and detected only weak correlations, which may not be of clinical value.

In this study, pulmonary tissue from each affected dog had microscopic features consistent with most of the previous descriptions of IPF in the WHWT.[2,4] The extent to which the histopathologic picture of canine IPF resembles human UIP, or other forms of idiopathic interstitial lung disease, still remains unclear. Both canine and human disease share features such as accumulation of collagen in the pulmonary interstitium, distortion of alveolar architecture, type II pneumocyte hyperplasia, prominent alveolar macrophages, and minimal inflammatory change.[2–4,8] Fibroblast foci, one of the key criteria for UIP diagnosis in humans,[26] were detected in dogs in a study by Erikson et al,[5] but were neither seen in our study or in the study of Norris et al.[4]

Although we present a large number of histopathologically confirmed cases of canine IPF, one of the limitations of this study is the lack of histopathology in 1 dog. Because of the comprehensive examinations, such as BAL and HRCT, all indicating IPF, we were confident in including this dog. The control dogs were thoroughly examined, but no histopathology was obtained from them either. Although unlikely, subclinical respiratory disease cannot be completely eliminated. Bronchoscopy and HRCT could not be performed in all IPF dogs because of risk of anesthetic complications because of advanced disease.

In summary, we conclude that canine IPF does not induce specific hematologic or serum biochemical alterations and leads to hypoxemia. IPF dogs have bronchoscopically detectable airway changes, and an increase in BALF TCC. On HRCT, GGO appears to be typical of canine IPF. On histopathology, interstitial fibrosis, type II pneumocyte hyperplasia, prominent intraalveolar macrophages, distortion of alveolar architecture, and emphysematous change are detected.

Footnotes

[a] ABL800 FLEX, Radiometer, Copenhagen, Denmark
[b] Philips iE33, Philips, Bothell, WA
[c] Torbugesic, Fort Dodge Animal Health, Fort Dodge, IA
[d] Midazolam Halemn, Algol Pharma, Espoo, Finland
[e] PropoVet, Abbot Logistics, Zwolle, the Netherlands
[f] Isoba Vet, Schering-Plough Ltd, Uxbridge, UK
[g] Somatom Emotion Duo, Siemens AG, Forchheim, Germany
[h] Siemens AG, Erlagen, Germany
[i] Olympus GIF-N180, Olympus Europa GmbH, Hamburg, Germany
[j] PASW Statistics 18.0 for Windows, SPSS Inc, Chicago, IL
[k] Domagala-Kulavik J, Skirecki T, Chazan R. Diagnostic value of total cell count in bronchoalveolar lavage fluid from patients with interstitial lung diseases. Eur Respir J 2009;34(Suppl):107 (abstract)

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