Idiopathic Pulmonary Fibrosis in West Highland White Terriers

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KEYWORDS

- Dog • Interstitial lung disease • Bronchoalveolar lavage • Arterial blood gases
- HRCT • Biomarker

KEY POINTS

- Canine idiopathic pulmonary fibrosis (CIPF) is a chronic, progressive, interstitial lung disease of unknown cause affecting mainly middle-aged and old West Highland white terriers.
- Typical findings are cough, exercise intolerance, Velcro crackles, an abdominal breathing pattern, and hypoxemia.
- Bronchial changes are present in many dogs and bronchoalveolar lavage fluid analysis usually shows an increased total cell count.
- Diagnosis is one of exclusion and often requires either high-resolution CT imaging or histopathology of the lung tissue, which is seldom performed on living dogs.
- CIPF shares several clinical findings with human idiopathic pulmonary fibrosis (IPF); however, in histopathology, CIPF has features of human IPF but also of human nonspecific interstitial pneumonia.
- No effective treatment exists, but corticosteroids and theophylline can ease clinical signs in dogs. Pirfenidone is the only licensed drug to treat IPF in humans, but it does not result in cure.

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive interstitial lung disease (ILD) of unknown cause.[1] The disease is recognized in humans,[1,2] cats,[3,4] and dogs.[5–8] The prevalence and incidence of canine IPF (CIPF) are currently unknown and can be difficult to estimate. Recognizing a dog with early CIPF is challenging

because the slowly progressive clinical signs can be confused with aging. Additionally, confirming CIPF requires very thorough examinations.

The first case series of CIPF in West Highland white terriers (WHWTs) was published in the late 1990s.[5] Reports of CIPF in other dog breeds (Staffordshire bull terrier, Schipperke, and Bull terrier) were described around the same time.[6,9] More recent studies of CIPF have aimed at defining the clinicopathologic findings of diseased WHWTs compared with controls matched by age and breed,[8] revealing histopathologic features,[7,10] findings detected on high-resolution CT (HRCT),[11] and assessing pulmonary hypertension (PHT) with Doppler.[12] Other studies include an investigation of surfactant protein (SP) C,[13] different potential fibrosis biomarkers,[14,15] and proteomic analysis of bronchoalveolar lavage (BAL) fluid (BALF) of WHWTs with CIPF.[16] Many questions regarding the disease remain unanswered. Cause and pathogenesis of the disease and the role of genetics are poorly understood and, therefore, are under active research.

DEFINITION AND HISTOPATHOLOGIC FEATURES

IPF belongs to a heterogenous group of ILDs that consist of several noninfectious and nonmalignant pulmonary diseases with overlapping clinicopathologic and radiographic features. ILDs affect the pulmonary interstitium, which is the space between the capillary endothelial and alveolar epithelial basement membranes.[17] In humans, more than 200 ILDs are recognized,[17] whereas far fewer ILDs are known to affect dogs.[18] In addition to CIPF, other described ILDs in dogs include diseases such as eosinophilic pneumonia, lymphocytic interstitial pneumonitis, bronchiolitis, obliterans with organizing pneumonia, endogenous lipid pneumonia, pulmonary alveolar proteinosis, silicosis, and asbestosis.[18] In humans, IPF belongs to an ILD subgroup named idiopathic interstitial pneumonias (IIPs). These are diseases of unknown causes resulting from damage to the pulmonary interstitium due to varying pattern of inflammation and fibrosis.[19] In dogs, such a subgroup and classification do not yet exist.

Currently, CIPF is probably the best-described canine ILD. It causes collagenous thickening of the pulmonary interstitium leading to impairment in the gas exchange.[7,8,10] Although CIPF is known to share clinical features with human IPF, the resemblance between the histopathologic pictures of human and canine disease was long in debate. Based on the recent (2013) study of Syrjä and colleagues,[10] CIPF seems to have histopathologic features of the two most common subtypes of human IIP, the usual interstitial pneumonia (UIP) and nonspecific interstitial pneumonia (NSIP). UIP is the histopathologic pattern of human IPF, and NSIP is the second most common IIP in humans and an important differential diagnosis for human IPF.[19]

CIPF is characterized histopathologically by two different patterns of interstitial fibrosis. All dogs appear to have mild-to-moderate, diffuse, mature fibrosis of the alveolar wall.[10] This pattern resembles the fibrosis pattern detected in human NSIP more than the patchy appearance of fibrosis in UIP. In addition to the mature fibrosis, most dogs have multifocal areas of fibrosis accentuation. In these areas, the fibrosis appears more severe, more cellular, and, therefore, less mature. This finding is more characteristic of human UIP than NSIP. In dogs, areas of fibrosis accentuation are either peribronchial or subpleural.[10] Honeycombing, profound alveolar epithelial changes, bronchial metaplasia of alveolar epithelium, and alveolar luminal changes, such as diffuse alveolar damage, can also be present in areas of more severe fibrosis. Fibroblast foci, very characteristic of human UIP, have not been found in dogs. Nevertheless, multifocal, scattered myofibroblasts have been detected in fibrotic

interstitium. In addition to fibrosis, mild-to-moderate interstitial lymphoplasmacytic inflammation is present (**Figs. 1** and **2**).[10]

Histopathologic studies of CIPF have focused on describing the findings in WHWTs.[7,10] The only report of histopathologic features in breeds other than WHWTs was published by Lobetti and colleagues.[6] Whether there are differences in the histopathologic picture between WHWTs and other breeds is not yet clear.

CAUSE AND PATHOGENESIS

The causes of CIPF and IPF are currently unknown. In dogs, the strong predisposition of the WHWT to CIPF raises suspicion for a genetic background. In humans, familial and sporadic forms of IPF are recognized, with the familial form being less common.[1] However, family history of IPF was shown to be the strongest risk factor for human IPF in a recent study.[20] Other factors, such as environmental exposures,[20,21] cigarette smoking,[21,22] gastroesophageal reflux,[20,23] and possibly chronic viral infections,[24,25] have been recognized as potential risk factors for human IPF. Nevertheless, no unifying etiologic factor has been found.[26]

The pathogenetic mechanisms behind CIPF are not yet understood but are likely to be complex. Human IPF is hypothesized to arise from a chronic, repetitive, yet unknown insult to the distal lung parenchyma leading to injury and apoptosis of the alveolar epithelial cells. This is followed by an abnormal healing process, fibroblast and myofibroblast accumulation, and deposition of excess extracellular matrix, leading finally to the architectural changes seen in the IPF lung.[26–28] It is likely that IPF is the end result of a complicated dialogue between genetic and environmental factors.[20,29] This is also suspected in dogs although no epidemiologic studies have been performed.

Mutations in the SPs C and A2, and in the genes that maintain telomere length, have been associated with development of IPF in humans, but they explain only a small proportion of the population. Recent genetic studies suggest that mutations resulting in
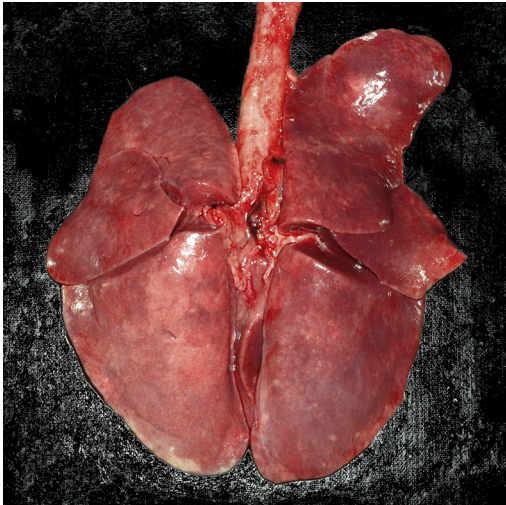
Fig. 1. Diffuse interstitial fibrosis of the lung in CIPF, with loss of pulmonary retraction and patchy multifocal accentuation of the lesions. (*Courtesy of* Pernilla Syrjä, DVM, Dipl ECVP, University of Helsinki, Finland.)
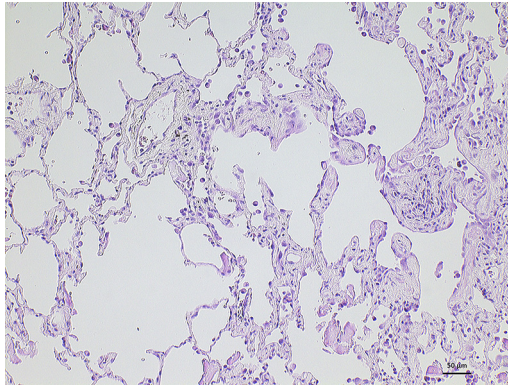
Fig. 2. The histopathology of CIPF in WHWTs is characterized by mild diffuse interstitial fibrosis (*left*) with multifocal areas of more severe interstitial fibrosis, alveolar epithelial atypia and hyperplasia, along with alveolar proteinosis and minimal interstitial inflammation (*right*). (*Courtesy of* Pernilla Syrjä, DVM, Dipl ECVP, University of Helsinki, Finland.)

defects in host defense and cell–cell adhesion could play an important role in IPF pathogenesis.[29,30] To date, only a single genetic study of CIPF has been published. After analyzing SP B and C in association with CIPF, Erikson and colleagues[13] (2009) found that SP C was absent in BALF from one of three dogs evaluated. In this dog, a mutation was detected at *SFTPC* exon 5.

As in humans, genetic factors could predispose a dog to development of disease, but other etiologic agents such as inhaled irritants are likely to be involved. Etiologic factors are difficult to trace because they may damage the lung for several years before CIPF is eventually diagnosed. Inbreeding of dogs, in this case WHWTs, offers a good resource to study these genetic mechanisms and their penetrance in CIPF.

SIGNALMENT AND CLINICAL SIGNS

CIPF usually affects middle-aged to older WHWTs. Occasionally, other terriers or other small breed dogs can be affected.[6,9,11,15,31] Human IPF more often affects males[1]; however, no sex predisposition has been reported in dogs. The usual age at the time of diagnosis varies from 8 to 15 years, but younger WHWTs with CIPF have also been reported.[5,12] Some of the non-WHWTs with CIPF have been substantially younger, with the youngest being only 3 years of age.[6] In humans, IPF typically manifests in the sixth and seventh decades and diagnosis in patients less than 50 years is rare.[1]

CIPF is considered an inevitably progressive disease. At the early phase of the disease affected dogs are probably quite normal. The mean duration of clinical signs when presented to the veterinarian has been estimated to be 8 to 13 months with great individual variation.[5,8,32] The most typical clinical signs are exercise intolerance and chronic cough in otherwise bright and alert dogs. Syncope, gagging, panting, and tachypnea are also reported. Not all affected dogs cough. Eventually, CIPF can cause respiratory difficulty, cyanosis, and respiratory failure.[5,8] Some dogs develop CIPF-related complications such as secondary respiratory tract infection or PHT. The authors are also aware of cases of pulmonary carcinoma in WHWTs with CIPF. In humans, an association exists between IPF and pulmonary carcinomas.[33] Pulmonary neoplasia coincident with IPF has also been reported in cats.[3]

In dogs with CIPF, mean survival time has been reported as 18 months from the beginning of clinical signs and less than 1 year from the time of diagnosis.[5] Nevertheless, survival time seems to vary greatly between individuals from some months to some years. Most human patients with IPF die within 5 years of diagnosis. However, several different progression patterns are recognized. In some patients, progression is slow whereas, in others, stable phases are interrupted by acute exacerbations. An accelerated variant of the disease also exists.[34] Whether these progression patterns also occur in dogs is currently not known.

DIAGNOSIS AND CLINICAL EXAMINATIONS

The diagnosis of CIPF is based on anamnestic information, findings in clinical examinations and diagnostic imaging, and exclusion of other respiratory diseases. Only histopathologic examination of lung tissue provides a definite diagnosis, but lung biopsies are seldom taken due to expense and the need for invasive surgery. The diagnosis if often confirmed at necropsy.

Dogs with CIPF are usually bright and alert due to adaptation to slowly developing respiratory impairment, but some severely affected dogs can be dyspneic and cyanotic. Bilateral, inspiratory Velcro crackles are a characteristic finding on lung auscultation,[5] but they might not be audible if the dog is breathing very shallowly.[8] In some dogs, crackles can even be heard without stethoscope when the dog is breathing with an open mouth. An abdominal breathing pattern is commonly present. A murmur, usually low-grade, right-sided, and systolic, can be heard in those dogs with tricuspid regurgitation due to PHT. Blood hematological and biochemical analyses do not show specific changes for CIPF but are commonly taken to rule out other reasons for exercise intolerance. The alkaline phosphatase concentration is frequently increased but, because such a change has also been found in healthy aged WHWTs, it is unlikely to be caused by hypoxemic liver damage.[8,32] Fecal examinations including the flotation and Baermann sedimentation methods are performed to rule out pulmonary parasites.

ARTERIAL OXYGENATION

Arterial blood gas analysis can be used to objectively estimate lung function. The method is easy to perform and gives a measurement of oxygenation capacity. It also provides an estimate of disease severity. Subsequent analyses can then be used to assess disease progression and possible treatment response. However, an arterial blood gas analysis cannot distinguish between lung function impairment due to fibrosis and inflammation. Measurement of hemoglobin saturation with oxygen by use of pulse oximetry is also used to estimate oxygenation. In the authors' opinion the pulse oximetry measurement can be misleading and offers at its best only an approximation of arterial oxygenation.

The sample for arterial blood gas analysis is drawn either from the femoral or the metatarsal artery into a heparinized syringe, any air bubbles are evacuated, and the sample is analyzed as soon as possible by a blood gas analyzer. The analysis provides measurements of PaO_2 and $PaCO_2$, and allows calculation of the alveolar-arterial oxygen gradient, $P(A-a)O_2$.[35]

Hypoxemia is a common finding in dogs with CIPF. In our previous study,[8] 90% of the WHWTs with CIPF were hypoxemic (PaO_2 less than 80 mm Hg[36]), and 45% had severe hypoxemia (PaO_2 less than 60 mm Hg[36]). Values for PaO_2, $PaCO_2$, and $P(A-a)O_2$ of WHWTs with CIPF and healthy control WHWTs are given in **Table 1**.

Table 1
Arterial blood gas analysis in WHWTs with CIPF (9 dogs) and healthy control WHWTs (11 dogs)

	WHWTs with CIPF	Healthy WHWTs
PaO_2[a]	65.5 ± 15.4 (33.5–87.4) mm Hg	99.1 ± 7.8 (89.6–113.0) mm Hg
$P(A-a)O_2$[a]	50.1 ± 17.3 (28.0–84.7) mm Hg	17.5 ± 4.9 (10.7–26.8) mm Hg
$PaCO_2$	29.3 ± 3.8 (25.0–35.7) mm Hg	28.7 ± 3.8 (20.5–34.6) mm Hg

Results are given as mean ± SD and range.
[a] Statistically significant difference, $P<.001$.
Data from Heikkilä HP, Lappalainen AK, Day MJ, et al. Clinical, bronchoscopic, histopathologic, diagnostic imaging, and arterial oxygenation findings in West Highland white terriers with idiopathic pulmonary fibrosis. J Vet Intern Med 2011;25:433–9.

Despite such low oxygen levels, most of the dogs were bright, alert, and not in respiratory distress, indicating adaptation to a chronic, slowly progressing disease.

Hypoxemia resulting from IPF has a multifactorial background. In examinations on human IPF, only 20% of the hypoxemia was explained by alveolocapillary diffusion impairment due to thickened alveolocapillary membrane whereas the main reason for hypoxemia was ventilation–perfusion mismatch.[37]

DIAGNOSTIC IMAGING

Thoracic radiographs of dogs with CIPF commonly show a bronchointerstitial pattern, but only interstitial or predominantly bronchial patterns are also reported.[8,31,32] Usually radiographic changes are already moderate-to-severe when the animal is presented to the veterinarian (Fig. 3). Identifying early radiographic changes of CIPF can be problematic. Based on our previous study, healthy older WHWTs can also have mild bronchial or bronchointerstitial patterns in thoracic radiographs. Additionally, the thick skin typical for WHWTs can make the interpretation of subtle changes difficult.[8] Changes in thoracic radiographs are not sensitive or specific for CIPF.

A   **B**
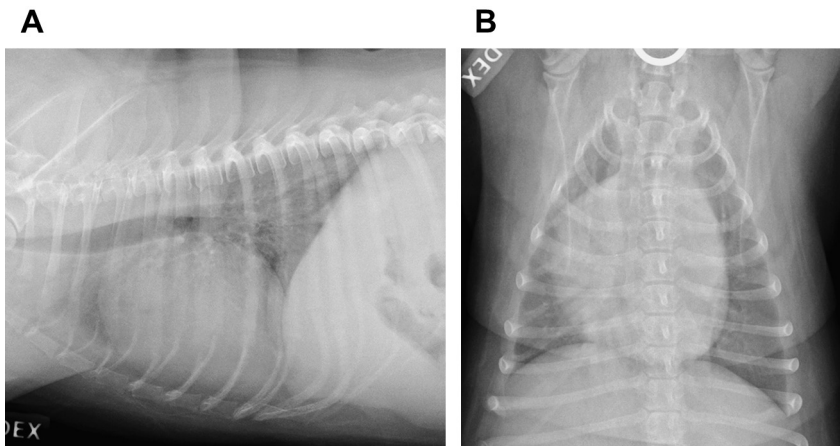
Fig. 3. Thoracic radiographs of a 12-year-old WHWT with CIPF and a PaO_2 of 64 mm Hg. Right lateral (*A*) and ventrodorsal (*B*) radiographs demonstrate a generalized bronchointerstitial lung pattern and large cardiac shadow. Extreme skin folds increase the overall opacity of the lungs. (*Courtesy of* Anu K. Lappalainen, DVM, PhD, University of Helsinki, Finland.)

Therefore, the main reason for taking them is to rule out other lung diseases such as neoplasia.

In dogs with CIPF, cardiac enlargement can be present in thoracic radiographs and is mainly caused by right-sided changes. This finding, together with lung densities and abnormal auscultation findings, sometimes results in false estimation of the presence of a primary heart disease. However, WHWT is not a breed typically affected by primary acquired heart diseases such as myxomatous mitral valve disease or cardiomyopathy. Therefore, an increased size of the heart shadow, especially in the dorsoventral view resulting in a reverse-D shaped cardiac silhouette and main pulmonary artery enlargement, should raise a suspicion of right-sided cardiac hypertrophy and possible presence of PHT. Further examination by Doppler echocardiography is required in these cases.[38] PHT is thought to result from an imbalance between pulmonary arterial vasoconstriction and vasodilatation, vascular remodeling due to an advanced lung disease, and chronic hypoxemia. Nevertheless, the pathogenesis of PHT is likely to be more complex than this and is not yet thoroughly understood.[39] PHT develops in a large number of WHWTs with CIPF. Schober and Baade[12] (2006) studied a group of WHWTs suffering from a chronic interstitial pulmonary disease with clinical signs and findings typical for CIPF. They estimated that PHT was a frequent finding affecting more than 40% of the WHWTs in their study. Similarly, PHT is very common in humans with IPF and is related to increased mortality.[39,40]

HRCT provides superior evaluation of the lung parenchyma compared with conventional thoracic radiographs. In human IPF, HRCT plays a crucial role in the diagnostic decision making and an HRCT diagnosis of IPF has a very high positive predictive value.[1] HRCT is also very useful in diagnosing CIPF.[8,11,32] Currently, the technique requires general anesthesia that might not be suitable for the most severely affected dogs due to increased anesthetic risk. The HRCT findings described in CIPF are ground glass opacity (a hazy increase in lung opacity), parenchymal bands, subpleural lines, subpleural interstitial thickening, peribronchovascular interstitial thickening, the interface sign, traction bronchiectasis, and honeycombing.[8,11,32] Consolidation can also occur[8,11] and, in some dogs, the bronchial walls can appear thickened.[32] Imaging findings in an individual dog are typically a combination of the above mentioned features (**Fig. 4**). The distribution of the lesions can be patchy[11] and the predilection site is reported to be the dorsocaudal lung lobes.[8] When attenuation of x-rays in lung tissue is evaluated quantitatively by measuring CT values, WHWTs with CIPF have significantly higher values than healthy WHWTs.[8]

In our previous study[8] and in the study of Johnson and colleagues[11] (2005), ground glass opacity was detected in all dogs with CIPF. The latter study suggested that honeycombing and traction bronchiectasis could be related to a more advanced CIPF; however, the authors have noticed that honeycombing and traction bronchiectasis can be present in dogs that lack severe hypoxemia. Honeycombing and traction bronchiectasis seem to be more common in human IPF, than in CIPF.

BRONCHOSCOPY AND BAL

Bronchoscopy and BAL provide useful information about the lung and airways. As for HRCT studies, the general condition and the severity of hypoxemia in the dog determine whether it is fit enough for the procedure. In the authors' experience, careful planning of anesthesia with supplemental oxygen before, during, and after bronchoscopy will make scoping possible even in severely hypoxemic dogs with CIPF.

Bronchoscopic findings detected in dogs with CIPF are nonspecific. Many dogs with CIPF seem to have some degree of bronchial involvement. It is not known
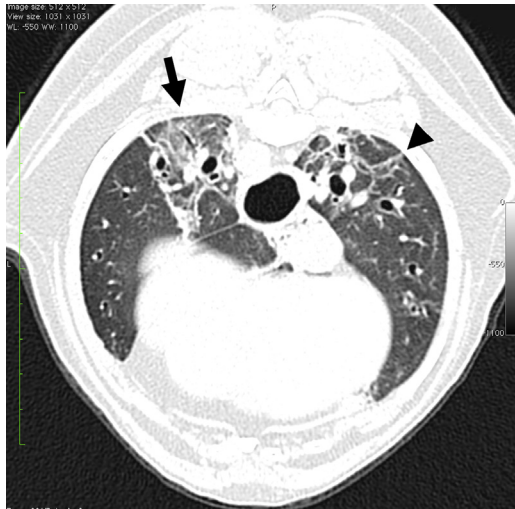
Fig. 4. A transverse HRCT image at the level of caudal lung lobes in an 11-year-old WHWT with CIPF and a PaO$_2$ of 57 mm Hg. Areas of ground glass opacity (*arrow*) and traction bronchiectasis (*arrowhead*) are seen dorsally. In this dog, the mean CT-value of all lung lobes was −709 HU, which is considerably higher than what is reported in healthy WHWTs. (*Courtesy of* Anu K. Lappalainen, DVM, PhD, University of Helsinki, Finland.)

whether this is an individual phenomenon or related to underlying CIPF. The presence of bronchoscopic changes cannot be used differentiate CIPF from chronic bronchitis (CB); however, bronchial changes such as hyperemia, mucus accumulation, and mucosal irregularities are usually more profound in CB than in CIPF.

Bronchoscopic changes reported in dogs with CIPF are tracheal collapse, bronchial mucosal irregularity, increased amount of bronchial mucus, bronchomalacia, dynamic airway collapse, and bronchiectasis.[8,32] Tracheal collapse and the increase in bronchial mucus are usually graded as mild-to moderate. Bronchial mucosal irregularity can at least partly be explained by age-related changes because it has also been detected in healthy, aged WHWTs and beagles.[8,41]

According to a survey of academic physicians, bronchoscopy is not commonly used in the diagnostic workup of human IPF.[42] The American Thoracic Society has provided clinical practice guidelines for BAL cellular analysis in ILDs only recently. Based on this, the usual BAL cell pattern in IPF is defined by increased macrophages and neutrophils, and mild-to-moderate eosinophilia can also be present. The lack of prominent lymphocytosis supports the diagnosis of IPF.[43]

In CIPF, BALF analysis usually shows an increase in the total cell count due to increased numbers of macrophages, neutrophils, and mast cells. In the differential cell counts, only a lower lymphocyte percentage was detected in dogs with CIPF compared with healthy dogs. Bacterial growth is not common.[8] A comparison of BALF analyses from WHWTs with CIPF with those obtained from healthy WHWTs is presented in **Table 2**.

TREATMENT

At the moment, there is no effective treatment of CIPF. Treatment is mainly used to reduce clinical signs on an individual basis and, secondly, to alleviate possible complications that can develop during the course of the disease. No clinical treatment

Table 2
BALF analysis in WHWTs with CIPF (11 dogs) and healthy control WHWTs (12 dogs)

	WHWTs with CIPF	Healthy WHWTs
Total cell count (cells/μL)[a]	765, IQ 450–1120 (280–3115)	350, IQ 280–380 (265–420)
Macrophages (%)	84, IQ 66–88 (64–93)	78, IQ 76–82 (69–89)
Cells/μL[b]	672, IQ 304–1000 (178–2500)	269, IQ 225–289 (194–375)
Lymphocytes (%)[b]	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[a]	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[b]	3.3, IQ 1.2–11 (0.0–64)	1.1, IQ 0.0–1.6 (0.0–3.2)

Results are given as median, interquartile range, and range.
[a] Statistically significant difference, $P<.01$.
[b] Statistically significant difference, $P<.05$.
Data from Heikkilä HP, Lappalainen AK, Day MJ, et al. Clinical, bronchoscopic, histopathologic, diagnostic imaging, and arterial oxygenation findings in West Highland white terriers with idiopathic pulmonary fibrosis. J Vet Intern Med 2011;25:433–9.

trials have been performed on dogs with CIPF and only anecdotal evidence exists for an effect of any drug. Expert opinions are based on recommendations for the treatment of human IPF as well as on the veterinarian's and owner's experience of treatment response.

Major effort has been put into finding novel medications for human IPF during the last decade. The developing knowledge about IPF pathogenesis has shifted treatment targets from inflammation toward the aberrant wound healing process. Several studies have investigated the use of immunomodulatory therapies, anticoagulant agents, endothelin receptor antagonists, vasodilators, antifibrotics, and cytokine inhibitors, without success.[44] The use of corticosteroids was found to be of no benefit, and a standard-of-care combination therapy with prednisone, azathioprine, and N-acetylcysteine was revealed to be harmful in a recent study.[45] This is no longer recommended for treatment of human IPF; however, a trial on N-acetylcysteine monotherapy is ongoing. In pilot studies, this antioxidant precursor has shown potential beneficial effects, but there is not yet enough data to support its use. At the moment, there is no treatment that can reverse the chronic fibrotic changes of human IPF. Lung transplantation is the only therapeutic modality known to increase survival.[44]

A major turning point was reached when pirfenidone was approved for the clinical treatment of human IPF in Asia and Europe. Pirfenidone has well-established antifibrotic, antioxidant, and antiinflammatory effects in experimental rodent models of fibrosis.[28] In Japanese studies on human patients with IPF, pirfenidone slowed the decline in lung function. Due to concerns related to the lack of survival benefit, more clinical studies are currently underway to further clarify its effect.[44] Pirfenidone could possibly be considered for treatment of CIPF. Although the pharmacokinetics of pirfenidone have been studied in dogs,[46] the safety of the drug in dogs is not known and there are no published reports of its clinical use in dogs.

Corticosteroids are used in the treatment of humans with NSIP. Patients with the cellular variant of NSIP have a better treatment response and prognosis than those

with IPF.[19] Based on the potential benefit of corticosteroids in human NSIP and because many dogs have concurrent bronchial changes, oral corticosteroids might have a role in the treatment of CIPF. Corcoran and colleagues[5] (1999) reported previously that some dogs with CIPF seem to respond to corticosteroid treatment. Based also on the authors' experience, corticosteroids seem to alleviate cough in many dogs although no clear effect on arterial oxygenation is detected. Because the combination of a high dose of corticosteroids and azathioprine was shown to be potentially deleterious in humans with IPF,[47] this combination should probably not be used in dogs either.

In CIPF, antitussives can be used if cough is irritating. Bronchodilators such as theophylline may be tried. Theophylline causes mild bronchodilatation, enhances mucociliary clearance, and increases contractibility of the diaphragmatic muscle.[48] Combination therapy with theophylline and corticosteroids has previously been recommended for treatment of CIPF.[5] Theophylline should be administrated with caution in hypoxemic animals and in combination with various drugs, including enrofloxacin and corticosteroids.[49]

Dogs with CIPF can experience worsening of respiratory function during the course of the disease. The cause for worsening should be diagnosed, if possible, and treated accordingly. Pneumonia should be suspected if leukocytosis or a left shift is detected together with newly developed alveolar density in thoracic radiographs. Unfortunately, the reason for the acute worsening is not always found. In humans with IPF, an unexpected, accelerated phase of lung function decline in the absence of any causative factor is called an acute exacerbation of IPF. Despite intensive care and empiric treatment with high doses of corticosteroids, cytotoxic agents, broad-spectrum antibiotics, and mechanical ventilation, the mortality of acute exacerbation in IPF approaches 50%.[47]

Usually, treatment of PHT is focused on treating the underlying disease. Because no efficacious treatment exists for CIPF, treatment is directly targeted to reduce pulmonary arterial pressure.[38] Studies on the treatment of PHT in dogs are scarce, but use of sildenafil, a phosphodiesterase-5 inhibitor, has been evaluated.[50,51] There is a theoretical concern that hypoxemia could worsen with PHT treatment because selective pulmonary arterial vasodilatation caused by medication could potentially increase ventilation perfusion mismatch.[39] However, the official statement for human IPF management notes that patients with moderate-to-severe PHT might benefit from PHT treatment.[1] The authors' have experienced that treatment with sildenafil can improve exercise tolerance in dogs with CIPF and PHT, and dogs appear brighter and more alert after starting treatment. The authors use a starting dose of approximately 1 mg/kg by mouth three times a day.

Treatment with proton pump inhibitors or histamine-2 receptor blockers could be considered if corticosteroid therapy is started because hypoxemia can make the dog more prone to adverse gastrointestinal effects. In human patients with IPF, gastroesophageal reflux, either symptomatic or occult, is very common, and microaspiration is speculated to have a role in the pathogenesis of IPF.[23,52] It is currently unknown whether gastroesophageal reflux is as prevalent in dogs with IPF.

BIOMARKERS

Diagnosing CIPF requires laborious examinations and can be challenging, especially when differentiating it from the main differential diagnosis, CB. CB carries a better prognosis and responds better to treatment. Both CIPF and CB can cause cough and exercise intolerance, and diseased dogs are usually of similar age and are small breed dogs.[15,48] There are no specific findings in thoracic radiographs for either of the

diseases, and differentiation with bronchoscopy is not possible because bronchial changes can be encountered in both. Reaching the CIPF diagnosis can require HRCT, which is expensive and not always applicable, or histologic investigation of the lung tissue. Identification of a noninvasive, measurable biomarker of fibrosis could help with the diagnosis.

A good biomarker is sensitive, specific, cost-effective, and practical to use.[53] In CIPF, search for suitable biomarkers is ongoing and some potential markers have already been found. Procollagen type III amino terminal propeptide (PIINP) is a marker of fibroblast activity and enhanced collagen turnover. PIIINP levels are elevated in humans with IPF. In dogs with CIPF, PIIINP levels are elevated in BALF and can be used to differentiate CIPF from CB with reasonable accuracy. However, serum PIIINP concentrations cannot distinguish between different chronic lung diseases. Although BALF biomarker probably better represents the production of collagen in the lungs and is less influenced by other factors than serum markers, its use is less practical.[15]

Endothelin-1 (ET-1) is a vasoactive, proinflammatory, and profibrotic peptide that is elevated in humans with IPF, both in serum and BALF. Serum ET-1 is also significantly elevated in dogs with CIPF compared with dogs with eosinophilic bronchopneumopathy, healthy dogs, or dogs with CB. ET-1 could be useful in diagnosing CIPF and differentiating it from other lung diseases. A clear advantage is that it can be measured from serum.[14]

Proteomics has also been used to examine a large scale of expressed proteins in BALF to find those specific for CIPF. Lilja-Maula and colleagues[16] (2013) performed a gel-based quantitative two-dimensional differential gel electrophoresis proteomic study followed by mass spectrometry in WHWTs with CIPF. Unfortunately, comparison of BALF proteomes between healthy dogs and dogs with CIPF or CB revealed no CIPF-specific proteins. Results showed similar changes in CIPF and CB groups, suggesting a common response to disease in otherwise different lung diseases.

In addition to using biomarkers in diagnostics, biomarker research could better define the pathogenesis of CIPF in dogs. Further studies using combinations of biomarkers could clarify the disease process in CIPF and help define the course of the disease in dogs. It is hoped that, in the near future, a biomarker that differentiates WHWTs that will later develop CIPF from those that will not could even be used in selecting dogs for breeding.

REFERENCES

1. Raghu G, Collard HR, Egan JJ, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med 2011;183(6):788–824.
2. Liebow AA. Definition and classification of interstitial pneumonias in human pathology. Prog Respir Res 1975;8(1):21–31.
3. Cohn LA, Norris CR, Hawkins EC, et al. Identification and characterization of an idiopathic pulmonary fibrosis-like condition in cats. J Vet Intern Med 2004;18(5): 632–41.
4. Williams K, Malarkey D, Cohn L, et al. Identification of spontaneous feline idiopathic pulmonary fibrosis: morphology and ultrastructural evidence for a type II pneumocyte defect. Chest 2004;125(6):2278–88.
5. Corcoran BM, Cobb M, Martin MW, et al. Chronic pulmonary disease in West Highland white terriers. Vet Rec 1999;144(22):611–6.
6. Lobetti RG, Milner R, Lane E. Chronic idiopathic pulmonary fibrosis in five dogs. J Am Anim Hosp Assoc 2001;37(2):119–27.

7. Norris AJ, Naydan DK, Wilson DW. Interstitial lung disease in West Highland White Terriers. Vet Pathol 2005;42(1):35–41.

8. Heikkilä HP, Lappalainen AK, Day MJ, et al. Clinical, bronchoscopic, histopathologic, diagnostic imaging, and arterial oxygenation findings in West Highland white terriers with idiopathic pulmonary fibrosis. J Vet Intern Med 2011;25(3): 433–9.

9. Corcoran BM, Dukes-McEwan J, Rhind S, et al. Idiopathic pulmonary fibrosis in a Staffordshire bull terrier with hypothyroidism. J Small Anim Pract 1999;40(4): 185–8.

10. Syrjä P, Heikkilä HP, Rönty M, et al. The histopathology of idiopathic pulmonary fibrosis in West Highland white terriers shares features of both nonspecific interstitial pneumonia and usual interstitial pneumonia in man. J Comp Pathol 2013; 149:303–13.

11. Johnson VS, Corcoran BM, Wotton PR, et al. Thoracic high-resolution computed tomographic findings in dogs with canine idiopathic pulmonary fibrosis. J Small Anim Pract 2005;46(8):381–8.

12. Schober KE, Baade H. Doppler echocardiographic prediction of pulmonary hypertension in West Highland white terriers with chronic pulmonary disease. J Vet Intern Med 2006;20(4):912–20.

13. Erikson M, von Euler H, Ekman E, et al. Surfactant protein C in canine pulmonary fibrosis. J Vet Intern Med 2009;23:1170–4.

14. Krafft E, Heikkilä H, Jespers P, et al. Serum and bronchoalveolar lavage fluid endothelin-1 concentrations as diagnostic biomarkers of canine idiopathic pulmonary fibrosis. J Vet Intern Med 2011;25:990–6.

15. Heikkilä HP, Krafft E, Jespers P, et al. Procollagen type III amino terminal propeptide concentrations in dogs with idiopathic pulmonary fibrosis compared with chronic bronchitis and eosinophilic bronchopneumopathy. Vet J 2013; 196:52–6.

16. Lilja-Maula LI, Palviainen MJ, Heikkilä HP, et al. Proteomic analysis of bronchoalveolar lavage fluid samples obtained from West Highland White Terriers with idiopathic pulmonary fibrosis, dogs with chronic bronchitis, and healthy dogs. Am J Vet Res 2013;74(1):148–54.

17. Cushley M, Davison A, du Bois R, et al. The diagnosis, assessment and treatment of diffuse parenchymal lung disease in adults. Thorax 1999;54:S1–30.

18. Reinero CR, Cohn LA. Interstitial lung diseases. Vet Clin North Am Small Anim Pract 2007;37(5):937–47.

19. American Thoracic Society, European Respiratory Society. American Thoracic Society, European Respiratory Society. International multidisciplinary consensus classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med 2002;165(2):277–304.

20. García-Sancho C, Buendía-Roldán I, Fernández-Plata MR, et al. Familial pulmonary fibrosis is the strongest risk factor for idiopathic pulmonary fibrosis. Respir Med 2011;105(12):1902–7.

21. Taskar VS, Coultas DB. Is idiopathic pulmonary fibrosis an environmental disease? Proc Am Thorac Soc 2006;3(4):293–8.

22. Baumgartner KB, Samet JM, Stidley CA, et al. Cigarette smoking: a risk factor for idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 1997;155(1): 242–8.

23. Gribbin J, Hubbard R, Smith C. Role of diabetes mellitus and gastro-oesophageal reflux in the aetiology of idiopathic pulmonary fibrosis. Respir Med 2009;103(6):927–31.

24. Tang YW, Johnson JE, Browning PJ, et al. Herpesvirus DNA is consistently detected in lungs of patients with idiopathic pulmonary fibrosis. J Clin Microbiol 2003;41(6):2633–40.
25. Calabrese F, Kipar A, Lunardi F, et al. Herpes virus infection is associated with vascular remodeling and pulmonary hypertension in idiopathic pulmonary fibrosis. PLoS One 2013;8(2):e55715.
26. Kottmann RM, Hogan CH, Phipps RP, et al. Determinants of initiation and progression of idiopathic pulmonary fibrosis. Respirology 2009;14:917–33.
27. Harari S, Caminati A. IPF: new insight on pathogenesis and treatment. Allergy 2010;65(5):537–53.
28. Loomis-King H, Flaherty KR, Moore BB. Pathogenesis, current treatments and future directions for idiopathic pulmonary fibrosis. Curr Opin Pharmacol 2013; 13(3):377–85.
29. Fingerlin TE, Murphy E, Zhang W, et al. Genome-wide association study identifies multiple susceptibility loci for pulmonary fibrosis. Nat Genet 2013;45:613–20.
30. Seibold MA, Wise AL, Speer MC, et al. A common MUC5B promoter polymorphism and pulmonary fibrosis. N Engl J Med 2011;364(16):1503–12.
31. Webb JA, Armstrong J. Chronic idiopathic pulmonary fibrosis in a West Highland white terrier. Can Vet J 2002;43(9):703–5.
32. Corcoran BM, King LG, Schwarz T, et al. Further characterisation of the clinical features of chronic pulmonary disease in West Highland white terriers. Vet Rec 2011;168:355.
33. Aubry MC, Myers JL, Douglas WW, et al. Primary pulmonary carcinoma in patients with idiopathic pulmonary fibrosis. Mayo Clin Proc 2002;77(8):763–70.
34. Selman M, Carrillo G, Estrada A, et al. Accelerated variant of idiopathic pulmonary fibrosis: clinical behavior and gene expression pattern. PLoS One 2007; 2(5):e482–6.
35. Day TK. Blood gas analysis. Vet Clin North Am Small Anim Pract 2002;32(5): 1031–48.
36. Haskins SC. Interpretation of blood gas measurements. In: King LG, editor. Textbook of respiratory disease in dogs and cats. St Louis (MO): Saunders Elsevier; 2004. p. 181–93.
37. Erbes R, Schaberg T, Loddenkemper R. Lung function tests in patients with idiopathic pulmonary fibrosis. Chest 1997;111(1):51–7.
38. Campbell FE. Cardiac effects of pulmonary disease. Vet Clin North Am Small Anim Pract 2007;37(5):949–62.
39. Smith JS, Gorbett D, Mueller J, et al. Pulmonary hypertension and idiopathic pulmonary fibrosis—a dastardly duo. Am J Med Sci 2013;346:221–5.
40. Frankel SK, Schwarz MI. Update in idiopathic pulmonary fibrosis. Curr Opin Pulm Med 2009;15(5):463–9.
41. Mercier E, Bolognin M, Hoffmann AC, et al. Influence of age on bronchoscopic findings in healthy beagle dogs. Vet J 2011;187:225–8.
42. Collard HR, Loyd JE, King TE Jr, et al. Current diagnosis and management of idiopathic pulmonary fibrosis: a survey of academic physicians. Respir Med 2007;101(9):2011.
43. Meyer KC, Raghu G, Baughman RP, et al. An official American Thoracic Society clinical practice guideline: the clinical utility of bronchoalveolar lavage cellular analysis in interstitial lung disease. Am J Respir Crit Care Med 2012;185(9): 1004–14.
44. Rafii R, Juarez MM, Albertson TE, et al. A review of current and novel therapies for idiopathic pulmonary fibrosis. J Thorac Dis 2013;5(1):48–73.

45. Raghu G, Anstrom KJ, King TE Jr, et al. Prednisone, azathioprine, and N-acetyl-cysteine for pulmonary fibrosis. N Engl J Med 2012;366(21):1968–77.
46. Bruss ML, Margolin SB, Giri SN. Pharmacokinetics of orally administered pirfenidone in male and female beagles. J Vet Pharmacol Ther 2004;27(5):361–7.
47. Adamali HI, Maher TM. Current and novel drug therapies for idiopathic pulmonary fibrosis. Drug Des Devel Ther 2012;6:261–71.
48. Kuehn NF. Chronic bronchitis in dogs. In: King LG, editor. Textbook of respiratory disease in dogs and cats. St Louis (MO): Saunders; 2004. p. 379–87.
49. Plumb DC. Plumb's veterinary drug handbook. 7th edition. Ames (IA): Wiley-Blackwell; 2011.
50. Kellum HB, Stepien RL. Sildenafil citrate therapy in 22 dogs with pulmonary hypertension. J Vet Intern Med 2007;21(6):1258–64.
51. Brown AJ, Davison E, Sleeper MM. Clinical efficacy of sildenafil in treatment of pulmonary arterial hypertension in dogs. J Vet Intern Med 2010;24(4):850–4.
52. Raghu G, Freudenberger T, Yang S, et al. High prevalence of abnormal acid gastro-oesophageal reflux in idiopathic pulmonary fibrosis. Eur Respir J 2006; 27(1):136–42.
53. Louhelainen N, Myllärniemi M, Rahman I, et al. Airway biomarkers of the oxidant burden in asthma and chronic obstructive pulmonary disease: current and future perspectives. Int J Chron Obstruct Pulmon Dis 2008;3(4):585–602.