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Laurila, Henna P.; Rajamäki, Minna M.

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Update on Canine Idiopathic Pulmonary Fibrosis in West Highland White Terriers

Henna P. Laurila, DVM, PhD*, Minna M. Rajamäki, DVM, PhD

KEYWORDS

• Dog • Interstitial lung disease • Idiopathic interstitial pneumonia
• Arterial blood gas analysis • HRCT • Bronchoalveolar lavage • Biomarker

KEY POINTS

- Canine idiopathic pulmonary fibrosis (CIPF) is a chronic, progressive, interstitial lung disease of unknown etiology affecting mainly middle-aged and old West Highland white terriers.
- Typical findings are cough, exercise intolerance, Velcro crackles, abdominal breathing pattern, and hypoxemia.
- Diagnosis is often requires either high-resolution computed tomography (HRCT) or histopathology of the lung tissue, which is seldom performed on live dogs.
- CIPF shares several clinical findings with human idiopathic pulmonary fibrosis, but in HRCT and histopathology, CIPF has features of human idiopathic pulmonary fibrosis as well as nonspecific interstitial pneumonia.
- No curative treatment exists, and clinical treatment trials are lacking in dogs. Symptomatic treatment with corticosteroids and theophylline may alleviate clinical signs.

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a devastating interstitial lung disease (ILD) with no known cure. It is chronic, is inevitably progressive, and leads to death. IPF is recognized in humans and in their animal companions, cats and dogs.[1–3] The term, *canine IPF* (*CIPF*), is used to separate the human and canine diseases.

CIPF affects mainly the West Highland white terrier (WHWT). Corcoran and colleagues[3] published the first case series describing the clinical features of this disease in WHWTs. More reports of CIPF in a WHWT and other dog breeds were described around the same time.[4–6] CIPF was found to carry striking similarities to human IPF. The key feature of both diseases is the abnormal accumulation of collagen in the

Discipline of Small Animal Internal Medicine, Department of Equine and Small Animal Medicine, Faculty of Veterinary Medicine, University of Helsinki, PO Box 57 (Viikintie 49), Helsinki 00014, Finland
* Corresponding author.
E-mail address: henna.laurila@helsinki.fi

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lung parenchyma for no known reason.[7,8] This hampers gas exchange causing cough, exercise intolerance, and, finally, respiratory failure. In humans, IPF diagnosis signifies a worse prognosis than most cancers. During the past 2 decades, CIPF has been the subject of several studies.[9] The possibility that dogs could serve as a spontaneous animal model for human IPF has increased interest in CIPF.

Currently, CIPF is the best-described ILD affecting dogs. Studies on CIPF have focused on detailed clinicopathologic findings, histopathologic features, concomitant pulmonary hypertension (PH), high-resolution computed tomography (HRCT) findings, and outcome and prognostic factors.[8,10–18] Potential blood and bronchoalveolar lavage fluid (BALF) biomarkers of CIPF have been targeted, namely procollagen type III amino-terminal propeptide (PIIINP), endothelin-1 (ET-1), serotonin, vascular endothelial growth factor, serum Krebs von den Lungen-6, and matrix metalloproteinases (MMPs).[9,19–22] New insight has been brought to the pathogenesis and etiology by investigating surfactant protein C, BALF proteome, transforming growth factor ß (TGF-ß) signaling pathway, gene expression profiles, chemokine concentrations, respiratory microbiota, presence of reflux aspiration, association with herpesvirus infection, and potential fungal etiology and by surveying the environment and care of WHWTs with and without CIPF.[9,22–31]

The potential role of dogs in modeling of human respiratory disease has been considered in meetings and reviews of comparative medicine.[32,33] The correlation between CIPF and human IPF is only partially understood at present. Even though CIPF is not identical to human IPF, as a disease model, it is likely superior to models of induced fibrosis in the mouse used today.[33] Several aspects of the disease remain, however, unanswered. The incidence and prevalence of CIPF are not known. A better understanding of the etiology and pathogenesis could help find new therapeutic agents. Finally, the role of genetics in this disorder is still poorly understood but is under active research.

DEFINITION

CIPF and IPF belong to a heterogenous group of ILDs, which consist of several noninfectious and nonmalignant pulmonary diseases with overlapping clinicopathologic and radiographic features. A majority of the ILDs have an unknown etiology. More than 200 ILDs are recognized in humans, but many fewer are reported in dogs.[34] Because diagnosing ILD requires a thorough clinical work-up, histopathologic examination of lung tissue, and a multidisciplinary approach, it is likely that cases are undiagnosed.[34] A classification scheme modified from human medicine was proposed for canine and feline ILDs recently. It divides ILDs into (1) idiopathic interstitial pneumonias (IIPs), (2) ILDs of known cause, and (3) miscellaneous ILDs.[34] CIPF belongs to IIPs. In humans, the IIPs are a group of non-neoplastic disorders that result from damage to the lung parenchyma with varying patterns of inflammation and fibrosis.[35] Canine and feline IIPs are further classified into sporadic and familial fibrotic ILD, nonspecific interstitial pneumonia (NSIP) and lymphocytic interstitial pneumonitis, acute interstitial pneumonia, cryptogenic organizing pneumonia, and other IIPs.[34] CIPF in WHWTs is a familial fibrotic ILD. For the details of the proposed classification and the description of the other IIPs and ILDs affecting dogs and cats, readers are referred to reviews.[34,36]

CIPF is not the only term that has been used to describe this disease affecting WHWTs. Other names include IPF, chronic IPF, canine pulmonary fibrosis, chronic pulmonary disease in WHWTs, and ILD in WHWTs.[3,6,10,13,15,23] By CIPF, the authors refer to a chronic, progressive, familial fibrotic ILD of unknown cause, limited to the lungs, and occurring mainly in older WHWTs.

HISTOPATHOLOGICAL FEATURES

CIPF is characterized histopathologically by 2 different patterns of interstitial fibrosis. All affected dogs have diffuse and mature uniform fibrosis of the alveolar wall.[8,10] This varies from mild to moderate in severity and is distributed throughout the lung (**Fig. 1**A, B).[8] Most affected WHWTs also have multifocal areas of more severe, more cellular, and less mature fibrosis.[3,8,23] These areas of fibrosis occur with pronounced alveolar epithelial and luminal changes, interstitial smooth muscle hyperplasia, proliferating myofibroblasts, and occasional honeycombing (**Fig. 1**C, D).[8] Fibrosis appears accentuated either adjacent to the bronchioli or under the pleura. Only mild to moderate interstitial lymphoplasmacytic inflammation is present.[8]

When compared with human diseases, CIPF in WHWTs shares features of both human usual interstitial pneumonia (UIP), the histopathologic pattern of human IPF, and

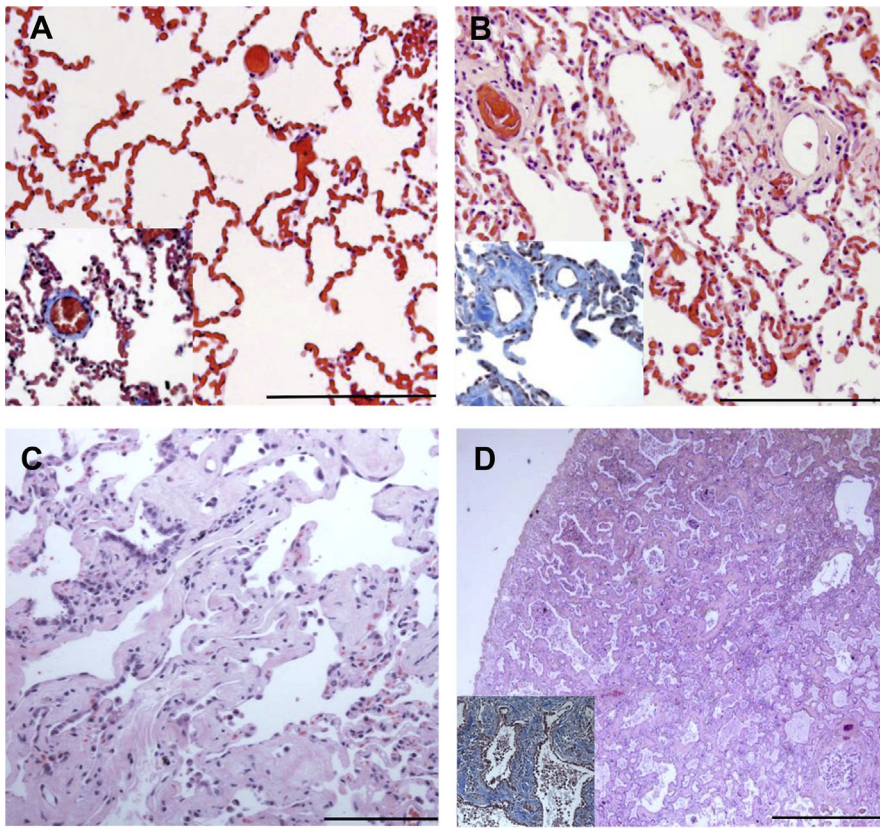


Fig. 1. Histopathologic features of CIPF in WHWTs. (*A*) Lung histology of a healthy WHWT (hematoxylin-eosin [HE]); bar, 200 μm. (*Inset*) Vessel of a healthy WHWT (Masson trichrome). (*B*) Mild diffuse mature interstitial fibrosis (HE); bar 200 μm. (*Inset*) Perivascular concentric fibrosis (Masson trichrome). (*C*) Focus of accentuated disease with severe interstitial fibrosis and type II pneumocyte hyperplasia (HE); bar, 200 μm. (*D*) Subpleural area of honeycombing and severe interstitial fibrosis (HE); bar, 1 mm. (*Inset*) Cystic fibrotic airspace within areas of honeycombing (Masson trichrome). (*From* Laurila HP. Canine idiopathic pulmonary fibrosis - clinical disease, biomarkers and histopathological features. [PhD]. Helsinki, Finland: University of Helsinki; 2015: 3-76; with permission.)

NSIP. The diffuse, mature fibrosis closely resembles the fibrosis pattern of NSIP whereas the accentuation areas are more characteristic of human UIP.[8] Fibroblast foci are a hallmark of human UIP and indicate active, ongoing fibrosis.[1,7] Although not organized in such foci, myofibroblasts likely also participate in fibrogenesis in CIPF.[8]

Whether there are differences in the histopathologic picture between CIPF, the familial fibrotic ILD affecting WHWTs, and a sporadic fibrotic ILD affecting other dog breeds remains to be investigated.

PATHOGENESIS AND ETIOLOGY

As the word idiopathic implies, the etiology of CIPF and IPF is unknown and pathologic processes are incompletely understood. The early idea of IPF as an inflammatory disease has been negated by recent research and the current hypothesis focuses on a repetitive insult to distal lung parenchyma followed by an aberrant wound healing process.[7] The injured alveolar epithelium seems to be the key player in the fibrotic lung response. Increased epithelial cell death, abnormal re-epithelialization, pneumocyte type II hyperplasia, and activation of alveolar epithelial cells participate in creating a profibrotic microenvironment.[7] The abnormally activated alveolar epithelial cells secrete growth factors, such as TGF-ß, cytokines, and other chemotactic mediators, inducing fibroblast proliferation, migration, and recruitment of fibroblast progenitor cells. After epithelial injury, the coagulation cascade is activated, which in turn has profibrotic effects. Exposure to different stimuli, including TGF-ß and wound clotting, transforms epithelial cells into fibroblasts in a process called epithelial mesenchymal cell transition. In humans, fibroblasts form small clusters, the so-called fibroblast foci, and differentiate to myofibroblasts.[7] The reasons why they organize into such foci are unknown. In WHWTs with CIPF, myofibroblasts appear scattered in the interstitium.[8] The final result is an abnormal accumulation of fibroblasts and myofibroblasts and exaggerated production of collagen and other extracellular matrix components, leading to architectural distortion characteristic of IPF lung.

The trigger for this fibrosis cascade is not known. In human IPF, research has revealed several potential epidemiologic risk factors that might contribute to the epithelial injury and apoptosis, such as cigarette smoking, exposure to environmental and occupational agents, gastroesophageal reflux leading to microaspiration, and chronic viral infections, in particular, herpesviruses.[7,37] In dogs, no association between CIPF and herpesvirus infection was found in a recent study.[30] Considering the histopathologic aspect of CIPF, the proximity of the fibrosis accentuation areas to bronchioli could indicate that an inhaled etiologic factor is involved in the pathogenesis of CIPF.[8] An epidemiologic survey for owners of WHWTs with CIPF revealed that living in an old house, lack of ventilation system, and frequent grooming in dedicated grooming facilities were associated with increased risk for CIPF.[9] Määttä and colleagues[31] detected bile acids in BALF of WHWTs with CIPF and healthy WHWTs but not in BALF of healthy dogs of other breeds. The results suggest that microaspiration due to gastroesophageal reflux could be a predisposing factor for CIPF in WHWTs.[31]

Although a majority of human IPF cases are sporadic, several genetic mutations are known to increase the risk for IPF; however, none of these has consistently been associated with IPF.[1,7] In dogs, accumulation of diseased individuals within one breed suggests that CIPF is hereditary in WHWTs. Genetic relationship to another WHWT with CIPF was associated with CIPF in the recent epidemiologic survey.[9] Despite ongoing studies, a unifying genetic factor has not yet been discovered and the strong breed

predisposition of WHWTs to CIPF requires further research. One factor predisposing WHWTs to CIPF could be an increase in serum TGF-ß concentration detected both in diseased and healthy WHWTs.[26] TGF-ß is a key mediator of fibrosis and is involved in pathogenesis of CIPF.[26,27]

The diffuse mature, uniform fibrosis detected in the CIPF lung is characteristic of human NSIP. In addition to being an idiopathic disease in humans, NSIP occurs in conjunction with other conditions, such as systemic connective tissue diseases.[35] Such a disease, however, has not been reported in WHWTs to date.

It is likely that CIPF is the result of a complex puzzle of environmental insults, a specific genetic background, and other host factors contributing to the development of the disease.

SIGNALMENT AND CLINICAL SIGNS

CIPF affects mainly WHWTs. Dogs of other breeds, mainly terriers, occasionally can be affected; however, it is unclear whether the fibrotic ILD in these dogs is similar to that of WHWTs. WHWTs tend to be middle-aged or old when they first display signs. The median age at the time of clinical diagnosis varies between 8 years and 13 years in different studies,[3,11,14,16,17] although affected WHWTs as young as 3 years of age have been reported.[11,12] Human IPF typically manifests in the sixth and seventh decades and diagnosis in patients less than 50 years is rare.[1] IPF affects male humans more often than female humans, but there is no sex predisposition in dogs.[1,37]

Commonly, dogs already suffer from advanced disease when they are presented to the veterinarian. The clinical signs develop slowly and at first the affected dogs probably appear normal. The duration of clinical signs varies but usually is between 8 months and 13 months prior to diagnosis.[37] The most common clinical sign is the combination of cough and exercise intolerance, but not all the dogs cough. Other described clinical signs are respiratory difficulty, cyanosis, tachypnea, orthopnea, and collapse.[37] Some dogs develop CIPF-related complications, such as PH. In humans, an association exists between IPF and pulmonary carcinomas,[7] and the authors are aware of some cases of pulmonary carcinoma in WHWTs with CIPF.

DIAGNOSIS AND CLINICAL EXAMINATIONS

Diagnosis of CIPF is based on signalment, anamnestic information, findings in clinical examination, and HRCT as well as exclusion of other respiratory diseases. The typical signalment of a middle-aged to older WHWT improves diagnostic confidence. A definitive diagnosis is provided only by histopathologic examination of lung tissue, but lung biopsies are seldom obtained due to the invasiveness of the procedure; therefore, diagnosis often is confirmed at necropsy. Diagnosing a fibrotic ILD without histopathology in a non-WHWT breed is challenging.

Dogs with CIPF usually are bright and alert due to adaptation to slowly developing respiratory impairment. Some severely affected dogs can be cyanotic and in distress, and an abdominal breathing pattern commonly is present. Lung auscultation reveals bilateral, inspiratory Velcro crackles and sometimes also wheezes.[37] A Velcro crackle is a distinctive pathologic lung sound that mimics the sound heard when separating 2 strips of Velcro.[38] Velcro crackles are hypothesized to result from sudden opening or closing of distorted distal airspaces. In humans, Velcro crackles can be the first sign of IPF.[38] If a WHWT with CIPF is breathing very shallowly, Velcro crackles might not be audible even in advanced CIPF, although in some dogs, crackles can be heard without a stethoscope when the dog is breathing with an open mouth.[14] The authors pay special attention to lung auscultation in older WHWTs even if they do not have clinical

signs indicating respiratory disease to provide early detection of potential disease. A soft right-sided murmur is heard in some dogs with tricuspid regurgitation due to PH. CIPF does not cause weight loss.[15]

CIPF is not associated with changes in serum biochemistry or hematology, but these analyses are performed to rule out other reasons for exercise intolerance.[3,14] The lack of polycythemia in CIPF is interesting and, in humans, polycythemia is not linked to IPF as it is to other chronic hypoxemic diseases. The reason for this is not known.[39] CIPF does not cause an elevation in serum C-reactive protein.[40] Fecal examinations, including the flotation and Baermann sedimentation methods, are performed to rule out pulmonary parasites.

ARTERIAL OXYGENATION

Arterial blood gas (ABG) analysis is used to estimate lung function objectively and to determine the severity of CIPF. Repeated ABG analyses also are an easy tool for evaluating disease progression in dogs.[15] Estimates of oxygenation obtained by pulse oximetry can be misleading in unanesthetized WHWTs and, therefore, are not recommended by the authors.[15]

Hypoxemia is a key clinical consequence of CIPF. An ABG analysis can reveal a surprisingly low Pa_{O_2} and high alveolar-arterial oxygen gradient (P_{AO_2} - Pa_{O_2}) in a WHWT with CIPF (**Table 1**). Despite this, most dogs are not in respiratory distress, indicating adaptation to a chronic, slowly progressing disease. Elevation of Pa_{CO_2} is not a feature of CIPF.[14,16,18] ABG findings of CIPF are in line with those of human IPF.[39,41]

6-MINUTE WALK TEST

A 6-minute walk test is a submaximal exercise test that measures the distance an individual is capable of walking over 6 minutes. It is used to evaluate exercise capacity in human IPF and can be used in CIPF as well without any special equipment or training.[15,16] It is not a diagnostic tool, instead, repeated $P_{(A\text{-}a)O_2}$ measurements of the distance walked in 6 minutes can be used to monitor the changes in exercise tolerance of WHWTs with CIPF and, therefore, the progression of the disease. The median distance walked was significantly lower in WHWTs with CIPF (398 m, range 273 m–519 m) compared with healthy aged WHWTs (492 m, range 420 m–568 m).[15]

Table 1
Arterial blood gas analysis in older West Highland white terriers with canine idiopathic pulmonary fibrosis (40 dogs) and healthy West Highland white terriers (32 dogs, all >7 y)

	West Highland White Terriers with Canine Idiopathic Pulmonary Fibrosis	Healthy West Highland White Terriers
Pa_{O_2}	60.1 ± 10.2 (33.5–87.4) mm Hg	97.1 ± 6.7 (86.1–113.0) mm Hg
(P_{AO_2} - Pa_{O_2})	55.0 ± 12.2 (28.0–84.7) mm Hg	18.7 ± 5.3 (9.8–29.9) mm Hg
Pa_{CO_2}	29.2 ± 3.6 (21.2–35.7) mm Hg	29.2 ± 4.3 (19.9–36.8) mm Hg

In CIPF dogs, ABG analysis was performed at the time of diagnosis. CIPF was confirmed by HRCT and/or histopathology. Healthy WHWTs had no clinical signs or HRCT findings indicating respiratory disease. Dogs participated in research projects at the Veterinary Teaching Hospital of the University of Helsinki, Finland. Results are given as mean ± SD and range.

PULMONARY HYPERTENSION

PH develops in many WHWTs with CIPF. Different studies have documented echocardiographic findings indicating PH in approximately 20% to 60% of diseased WHWTs.[12,14,16,17] Similarly, PH is estimated to affect 32% to 50% of human IPF patients and is related to increased mortality.[42] The clinical signs of PH (exercise intolerance and syncope) do not differ from the signs of CIPF.[43] Therefore, Doppler echocardiography is required to search for PH, especially if the dog has a soft right-sided murmur or if thoracic radiographs raise suspicion of right-sided cardiac enlargement. PH 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 PH is likely much more complex than this and is not yet thoroughly understood.[42]

THORACIC RADIOGRAPHY

Thoracic radiographs of WHWTs with CIPF commonly show a bronchointerstitial pattern, which is already moderate to severe when the animal is presented to the veterinarian.[37] In addition to interstitial infiltrates, predominantly bronchial and patchy alveolar patterns also are reported.[9] Changes in thoracic radiographs are neither sensitive nor specific for CIPF, and the main reason for taking them is to rule out other lung diseases, such as neoplasia.[37]

Identifying early radiographic changes of CIPF is problematic, because healthy older WHWTs also can have mild bronchial or bronchointerstitial patterns in thoracic radiographs.[14] Additionally, the thick skin typical for WHWTs can make the interpretation of subtle changes difficult. Thoracic radiography is not helpful in evaluating the progression of CIPF, because the changes vary independently of clinical signs (**Fig. 2**).[15] Cardiac and pulmonary arterial enlargement can be present in thoracic radiographs, caused mainly by PH.

HIGH-RESOLUTION COMPUTED TOMOGRAPHY

HRCT provides superior evaluation of the lung compared with conventional radiographs. If HRCT findings are characteristic, lung biopsy is not necessary to confirm IPF in humans.[1] HRCT also is useful in diagnosing CIPF. The HRCT features of WHWTs with CIPF have been assessed by several studies.[11,13,14,16–18] The most frequent finding is ground-glass opacity (GGO) described as a hazy increased opacity of the lungs, with preservation of bronchial and vascular margins. Mosaic attenuation pattern also is frequently observed[16,17] and may indicate a more advanced disease.[17] Linear and reticular opacities are common, whereas traction bronchiectasis and honeycombing are detected more rarely. Consolidation can occur, and, in some dogs, bronchial wall thickening or nodules have been described (**Fig. 3**).

In humans, extensive GGO points toward an alternative diagnosis, such as NSIP, whereas honeycombing, traction bronchiectasis, coarse reticulation, and architectural distortion are characteristic of IPF.[44] Therefore, the HRCT features of CIPF share characteristics of both human IPF and NSIP.[9]

When lung tissue attenuation is evaluated quantitatively by measuring computed tomography values, values are significantly higher in WHWTs with CIPF than in healthy WHWTs.[14,17,18]

To avoid the risks of general anesthesia, the authors use a modified VetMouseTrap positioning device (Universal Medical Systems Inc., Solon, OH) (**Fig. 4**). It limits the dog's motion and enables HR CT imaging with no or only minimal sedation. The

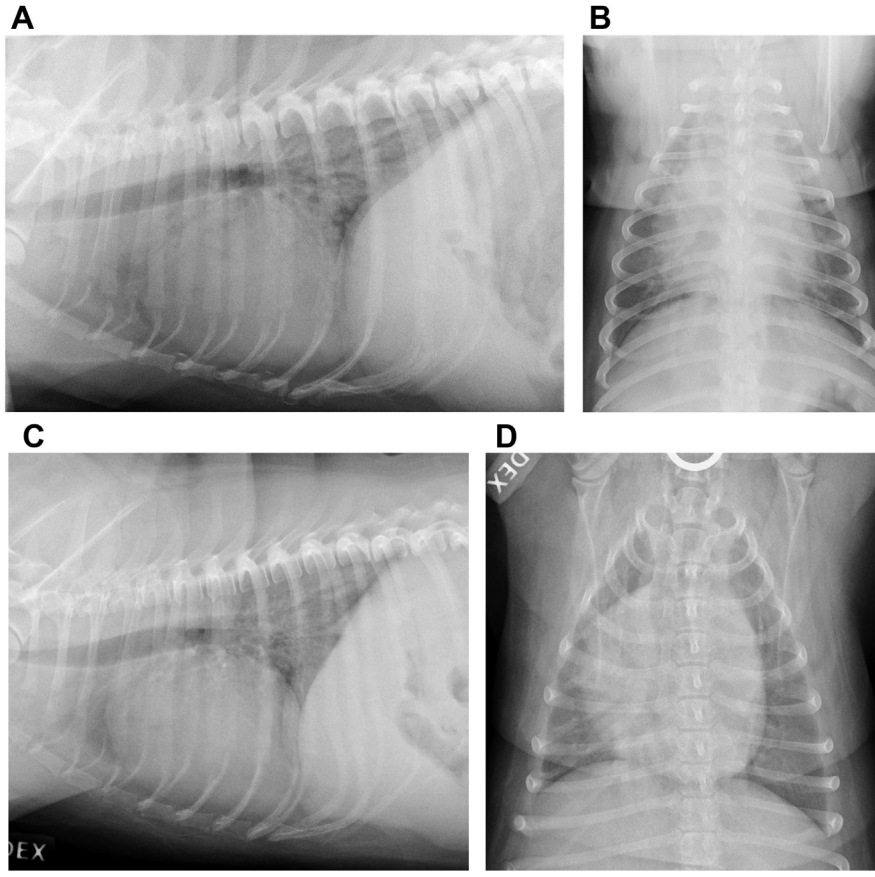


Fig. 2. Thoracic radiography is not a sensitive tool to evaluate the severity of CIPF as demonstrated by these images. Right lateral and ventrodorsal radiographs from a 12-year-old WHWT with moderate CIPF (Pao_2 82 mm Hg) (*A*, *B*) and from another 12-year-old WHWT with more severe CIPF (Pao_2 64 mm Hg) (*C*, *D*). The images show moderate (*B*) to severe (*A*, *C*, *D*) generalized bronchointerstitial lung patterns and a large cardiac shadow. Extreme skin folds increase the overall opacity of the lungs. ([*A, B*] *From* Laurila HP. Canine idiopathic pulmonary fibrosis - clinical disease, biomarkers and histopathological features. [PhD]. Helsinki, Finland: University of Helsinki; 2015: 3-76; with permission; and [*C, D*] *Courtesy of* Anu K. Lappalainen, DVM, PhD, University of Helsinki, Finland.)

method was found feasible in discriminating healthy from diseased WHWTs.[18] When HR CT images obtained under sedation were compared with those obtained under anesthesia, both underestimation and overestimation of GGO and mosaic attenuation patterns were observed.[16]

BRONCHOSCOPY AND BRONCHOALVEOLAR LAVAGE

Bronchoscopy and BALF provide useful information about the lung and airways, but the findings are not specific for CIPF. Many dogs with CIPF have some degree of bronchial involvement (Fig. 5). It is not known whether this is an individual phenomenon, related to underlying CIPF, or connected to cough. The presence of bronchoscopic

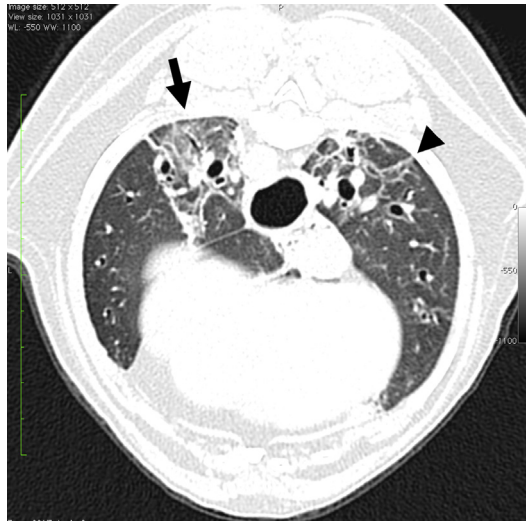


Fig. 3. A transverse HRCT image at the level of caudal lung lobes in an 11-year-old WHWT with CIPF and a Pao_2 of 57 mm Hg. Areas of GGO (*arrow*) and traction bronchiectasis (*arrowhead*) are seen dorsally. The images were obtained under general anesthesia. (*Courtesy of* Anu K. Lappalainen, DVM, PhD, University of Helsinki, Finland.)

changes cannot be used to differentiate CIPF from CB. Bronchial changes, however, such as hyperemia, mucus accumulation, and mucosal irregularities, usually are more profound in CB than in CIPF.[37] Bronchoscopy requires general anesthesia. The decision to perform bronchoscopy must be considered from the perspective of benefits versus risks. Bronchoscopy should be pursued, especially when there is discrepancy between clinical data and HRCT findings or suspicion of infection or other disease process or if CIPF is suspected in a young WHWT or in a dog of a non-WHWT breed. The general condition and the severity of hypoxemia determine whether a dog is fit for the procedure. In the authors' experience, careful planning of anesthesia with



Fig. 4. Photograph illustrating use of the modified VetMouseTrap™ (Universal Medical Systems Inc., Solon, OH.) The device is used without the lid, and padding is added inside the device. (From Holopainen S, Rautala E, Lilja-Maula L, et al. Thoracic high resolution CT using the modified VetMousetrap™ device is a feasible method for diagnosing canine idiopathic pulmonary fibrosis in awake West Highland white terriers. Vet Radiol Ultrasound. 2019; 60(5):525-532; with permission.)

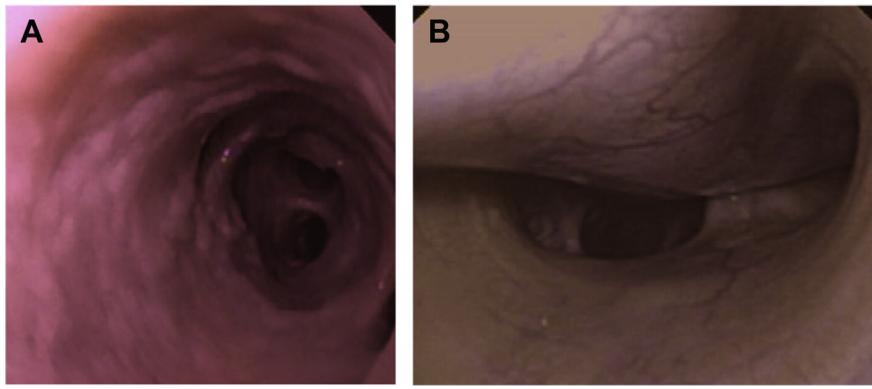


Fig. 5. Bronchoscopic images from WHWTs with CIPF. (*A*) Moderate bronchial mucosal irregularity in a 12-year-old WHWT with CIPF. (*B*) Grade II tracheal collapse viewed at the level of carina in a 12-year-old WHWT with CIPF. (*From* Laurila HP. Canine idiopathic pulmonary fibrosis - clinical disease, biomarkers and histopathological features. [PhD]. Helsinki, Finland: University of Helsinki; 2015: 3-76; with permission.)

supplemental oxygen before, during, and after bronchoscopy make scoping possible even in severely hypoxemic WHWTs with CIPF.

Bronchoscopic changes reported in CIPF are bronchial mucosal irregularity, mild to moderate increases in bronchial mucus, bronchomalacia, dynamic airway collapse, and bronchiectasis.[3,14,16] Additionally, tracheal collapse, usually mild to moderate, seems to be common in WHWTs with CIPF.[3,14,16] The significance of this finding and its possible relationship to the underlying ILD is unclear, and the authors have also detected tracheal collapse in clinically healthy old WHWTs.[14] Bronchial mucosal irregularity can be explained at least partly by age-related changes.[14,45]

BALF analysis of WHWTs with CIPF usually shows an increase in the total cell count due to increased numbers of macrophages, neutrophils, and mast cells. Bacterial growth is uncommon.[9,14] BALF analysis is not routinely recommended in the diagnostic evaluation of human IPF, but it can be useful in excluding other ILDs or evaluating infection or malignancy.[1] In human IPF, increased total cell count, BALF neutrophilia, and mild to moderate eosinophilia are described. Lack of lymphocytosis supports the IPF diagnosis. In NSIP, BALF lymphocytosis is typical.[46,47]

BIOMARKERS

Reaching CIPF diagnosis can require HRCT, which is expensive and not always applicable, or histologic investigation of lung tissue. The lack of CIPF-specific therapy, however, questions the benefits of surgical lung biopsy. Therefore, identification of a noninvasive fibrosis biomarker could be helpful. Both screening and targeted investigational approaches have been used in the biomarker search with promising results.[9]

- Biomarkers with the potential to discriminate WHWTs with CIPF from healthy WHWTs are serum and BALF ET-1, serum and BALF chemokine (C-C) ligand 2, BALF interleukin-8, BALF PIIINP, and BALF MMP-9.[19–21,29]
- Biomarkers with the potential to differentiate WHWTs with CIPF from dogs with chronic bronchitis (CB) are serum and BALF ET-1, BALF PIIINP, BALF MMP-9, and BALF MMP-2.[19–21]

- Biomarkers that might be related to the predisposition of WHWT breed for CIPF are serum TGF-ß, serum interleukin-8, and possibly serum Krebs von den Lungen-6. The concentrations of these markers were higher in serum of WHWTs compared with other breeds.[9,22,26]

Further studies are necessary to confirm these findings, to find novel biomarkers, and to investigate combinations of these that have the highest predictive values. Ideally, a biomarker that differentiates WHWTs that will develop CIPF from those that will not would be available to select WHWTs for breeding.

TREATMENT

Currently, there are no effective treatments for CIPF. No treatment trials have been performed on dogs with CIPF, and the studies published on CIPF have not been designed to evaluate any treatment effect.[37] Pharmacologic treatment options for human IPF are scarce as well. No known treatment can stop the progression or reverse the fibrotic changes. IPF is the leading indication for lung transplantation in humans worldwide.[48]

Knowledge about IPF pathogenesis has shifted treatment targets from inflammation toward the aberrant wound healing process. What used to be a standard-of-care combination therapy with prednisone, azathioprine, and *N*-acetylcysteine was revealed to be harmful in human IPF. At present, human IPF-specific therapy is based on 2 novel antifibrotics, pirfenidone and nintedanib. Both can slow the decline in lung function but do not result in cure.[49]

Pirfenidone has well-established antifibrotic, antioxidant, and anti-inflammatory effects.[49] It might be considered for treatment of CIPF. Although the pharmacokinetics of pirfenidone have been studied in dogs, the safety is not known and there are no clinical reports of its use in dogs.[37] Currently, pirfenidone is expensive: treating a WHWT would cost 12€ to 17€ ($13–$20) per day (July 2019) if the pirfenidone dose is extrapolated from humans.

Nintedanib is an intracellular inhibitor of multiple tyrosine kinases with potent antifibrotic and anti-inflammatory effects in animal models.[49] A recent study suggested that nintedanib extends life expectancy in human patients with IPF.[50] Unfortunately, in toxicology studies of nintedanib, dogs suffered from severe gastrointestinal adverse effects even with low doses of the drug.[51]

In CIPF, treatment is used mainly to reduce clinical signs on an individual basis and to alleviate complications.[37] Many WHWTs with CIPF receive corticosteroids. Corcoran and colleagues[3] reported that some dogs with CIPF seem to respond to corticosteroid treatment. Based on the authors' experience, corticosteroids reduce cough in many dogs; however, the authors have not observed any clear long-term improvement in arterial oxygenation.[15] In human IPF, corticosteroids are not recommended as disease-modifying therapy due to adverse effects and lack of efficacy.[52] In NSIP, however, oral corticosteroids form the basis of the treatment alone or in combination with other immunosuppressive agents. Human patients with a less common, cellular NSIP respond well whereas patients with a more common, fibrosing NSIP do far worse but still survive longer than patients with IPF.[53] If corticosteroids are chosen as an empirical therapy for CIPF, it is up to the veterinarian to decide whether to give it orally or via inhalation. No studies exist to support either use. Given the potential benefit of corticosteroids in human NSIP, an oral route might be elected. On the other hand, considering the lack of efficacy in human IPF, concurrent bronchial changes could be targeted instead of the interstation, and, therefore, inhaled steroids might be a better option, especially in old WHWTs with concomitant diseases.

Combination therapy with corticosteroids and theophylline has been recommended for treatment of CIPF and is also the authors' choice.[3] Theophylline causes mild bronchodilatation, enhances mucociliary clearance, and increases contractibility of the diaphragmatic muscle.[54]

WHWTs with CIPF might benefit from use of proton pump inhibitors or histamine H_2 receptor blockers. This is supported by the finding of microaspiration in WHWTs with CIPF.[31] Gastroesophageal reflux with microaspiration is common in human IPF and predisposes to lung injury. Antiacid therapy is recommended for the treatment of all human patients with IPF[1] because it could slow disease progression and reduce the risk of acute worsening of IPF in humans.[55] Because it is a low-cost treatment and unlikely harmful, it can be used in WHWTs with CIPF as well.

Treatment of PH usually focuses first on management of the underlying disease; however, because no effective treatment exists for CIPF, treatment of concurrent PH is directly targeted to reduce pulmonary arterial pressure. A recent meta-analysis in human medicine did not support the theoretic concern that hypoxemia could worsen with PH treatment because of deterioration in ventilation-perfusion mismatch.[56] Data on the use of sildenafil in human IPF-related PH are conflicting and the authors of the official management guidelines of human IPF do not take a stand for or against its use.[49] Although no study has evaluated the benefits and adverse effects of sildenafil in CIPF-related PH, sildenafil therapy has been investigated in dogs with PH in general and has been reported to improve clinical signs and quality of life. The authors prescribe sildenafil to WHWTs with CIPF that have echocardiographic measurements suggesting PH.

WHWTs with CIPF can experience acute worsening of respiratory function during the disease course. The cause for such worsening, for example, a bacterial pneumonia, should be treated appropriately. If no cause is found, the dog could be suffering from an acute exacerbation (AE) of CIPF, histopathologically characterized by diffuse alveolar damage.[15,28] The etiology of AE in human IPF is unknown, but it is likely triggered by an acute insult, for example, microaspiration, infection, or stress due to bronchoscopy or surgery, which then leads to severe acute lung injury. Despite empirical treatment with a high dose of corticosteroids and broad-spectrum antibiotics, the short-term mortality of AE of IPF in humans is very high.[57] Likewise, the expected outcome for a WHWT having AE of CIPF is poor.

Pulmonary rehabilitation and long-term oxygen therapy are recommended for humans with IPF.[1] The authors encourage the owners of WHWTs with CIPF to continue routine daily walks with their dogs, unless the dog shows signs of exhaustion. Long-term oxygen therapy is not feasible in dogs, although intermittent treatment might be possible in some dogs.

CLINICAL COURSE AND SURVIVAL

Although diseased WHWTs usually are already old at the time of disease recognition, CIPF has a negative impact on survival. Median survival was reported to be 32 months (range 2–51 months) from the onset of clinical signs and 11 months (range 0–40 months) from diagnosis (**Fig. 6**).[15] In humans, the median survival after diagnosis is 2 years to 3 years in IPF and 6 years to 13.5 years in fibrotic NSIP.[1,53] Predicting the disease course for an individual WHWT is difficult, because of the lack of prognostic markers. Only high-serum chemokine (C-C) ligand 2 at the time of diagnosis and the severity of CT findings were found to be negatively associated with survival.[9] As in human IPF, CIPF in WHWTs can have either a slow or rapid disease progression. When diseased WHWTs were followed over time, 5 of 15 WHWTs with CIPF needed to

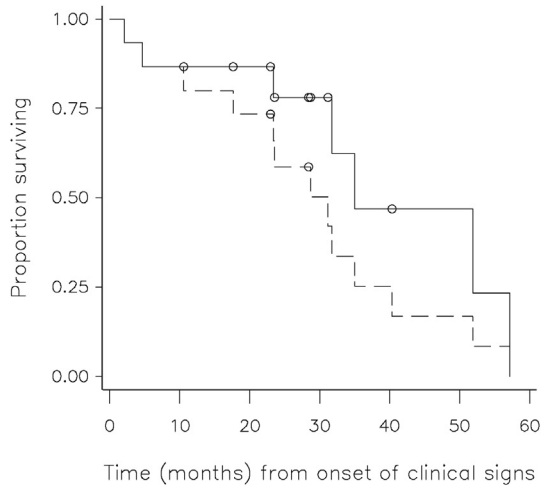


Fig. 6. Kaplan-Meier survival curves for all-cause survival (*dashed line*) and CIPF-specific survival (*solid line*) of WHWTs with CIPF from onset of clinical signs. Circles indicate censored animals (all-cause survival: WHWTs alive at study endpoint; CIPF-specific survival: WHWTs alive and those who died of non–CIPF-related causes). (*From* Lilja-Maula LIO, Laurila HP, Syrjä P, et al. Long-term outcome and use of 6-minute walk test in West Highland white terriers with idiopathic pulmonary fibrosis. J Vet Intern Med 2014;28:379-85; with permission.)

be euthanized because of AE.[15] Further research into the etiopathogenesis and genetics of CIPF is needed, along with searches for viable biomarkers for disease as well as disease progression.

DISCLOSURE

The authors have nothing to disclose.

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