

Respiratory System

Idiopathic Pulmonary Fibrosis – “Westie Lung Disease”

In order to appreciate the effects of pulmonary fibrosis, it first is important to understand the basic anatomy and physiology of the pulmonary system. The pulmonary system is comprised of the airways and the lungs. The airways include the trachea, the bronchi and their divisions into the very small bronchioles. The lungs are comprised of the alveoli (air sacs) and their surrounding capillaries, where exchange of oxygen and carbon dioxide take place, and the tissues and spaces that surround the alveoli. Collectively, these latter components of the lung, which are called the interstitium, are made up of elastin, collagen, smooth muscle cells, mast cells and a few other types of less common cells. The purpose of the interstitium is to provide both structure and strength to the lungs.

Breathing problems can arise from a number of factors including developmental problems, injury, obstruction of airways, circulation problems, viral, bacterial and fungal infections, and interstitial disease. Acute interstitial pneumonia is a disease affecting the interstitium in which the cells and fibers comprising the interstitium are damaged and eventually are replaced with scar tissue. The body’s response to injury that results in scarring is called fibrosis. Consequently, the disease is called pulmonary fibrosis. Because the underlying cause for the injury remains unknown, the disease also is referred to as idiopathic (“unknown cause”) pulmonary fibrosis. This disease, which also is known as “Westie Lung Disease”, prevents the lungs from functioning normally, resulting in difficulty breathing and, eventually, death. In a recent study of affected Westies with this disease, the median survival time from onset of clinical signs was 32 months. This condition

primarily affects middle-aged to older Westies, and individual survival time varies considerably. A similar chronic and ultimately fatal disease also affects humans.

While it was once thought that idiopathic pulmonary fibrosis was the result of an inflammatory reaction to an individual injury, it is now understood that fibrosis most likely occurs as the result of repeated injuries caused by some unknown agent or agents. It may be that these agents are a combination of allergens in the air, pollution, and infectious organisms. The body’s natural response to injury is to replace damaged cells and fibers with fibrous connective (scar) tissue. While the scar tissue fills in the space where damage occurred, it leaves the area less flexible and less functional than normal. Excessive and repeated scarring, as occurs in pulmonary fibrosis, leaves the lungs unable to expand fully or to contract properly. As a result, they lose their ability to bring oxygen into the body or to expel waste gases. There appears to be a genetic component to pulmonary fibrosis and Westies appear, in particular, to be at risk.

The Westie Foundation of America (WFA) sponsored a 1-day meeting in October 2007 at Purdue University. As a result, a paper “An Official American Thoracic Society Workshop Report: Comparative Pathobiology of Fibrosing Lung Disorders in Humans and Domestic Animals” was published and is available online (<http://www.atsjournals.org/doi/full/10.1513/AnnalsATS.201309-321ST>). The purpose as cited in this publication was “to improve awareness and communication regarding spontaneous progressive fibrotic lung disorders in mammals and to stimulate interaction between human and veterinary medical professionals”.

Common Clinical Findings

Difficulty Breathing (Dyspnea)

Coughing

Exercise Intolerance

Abnormal Lungs on Radiographs

As a next step, the WFA fundraised approximately \$125,000 to host a second meeting “Fibrosis Across Species Workshop” on April 27-29, 2014 convening almost 70 human and veterinarian pulmonologists, pathologists, geneticists, radiologists, immunologists to discuss the “One Health” concept comparing disease in the Westie breed and humans. Several research studies resulted from this meeting to determine if pulmonary fibrosis in the Westie is comparable to the disease in humans. Continued research using the Westie as a naturally occurring model of pulmonary fibrosis will further treatment options in humans as well as our beloved Westies. A paper of this meeting is forthcoming and planned for both veterinary and human scientific journals.

Clinical Symptoms and Diagnosis

The major symptom of dogs with pulmonary fibrosis is difficulty in breathing – a clinical symptom known as “dyspnea”. Some canine patients will also cough frequently and may have a fever. These dogs tire quickly and lose their ability to do strenuous activities, such as running around or going up and down stairs. Veterinarians will note that lung sounds heard through a stethoscope are abnormal, and the heart will enlarge

as the disease progresses. The part of the heart that pumps blood into the lungs, the right ventricle, enlarges the most. This occurs as that part of the heart works harder to pump blood into the increasingly resistant lungs. Because of dysfunction of their heart and blood vessels, affected dogs may also have blood become congested in the veins around their organs.

Hypersensitivity pneumonitis, a chronic condition in which a dog has an allergic reaction to inhaled organic dusts, results in symptoms that are very similar symptoms to those associated with pulmonary fibrosis and can lead to debilitating scarring of the lungs. If hypersensitivity pneumonitis is the cause of the problem, it can be prevented by eliminating exposure to the allergen. In some cases, skin testing may be used to identify the allergen responsible (see previous section on *Atopic Skin Disease*).

The diagnosis of idiopathic pulmonary fibrosis will be made based on the clinical signs, history, results of lung function tests and findings on radiographs (x-rays). Radiographs of the thorax typically reveal abnormalities in the lungs (e.g., loss of clear air space) and evidence of right ventricular enlargement.

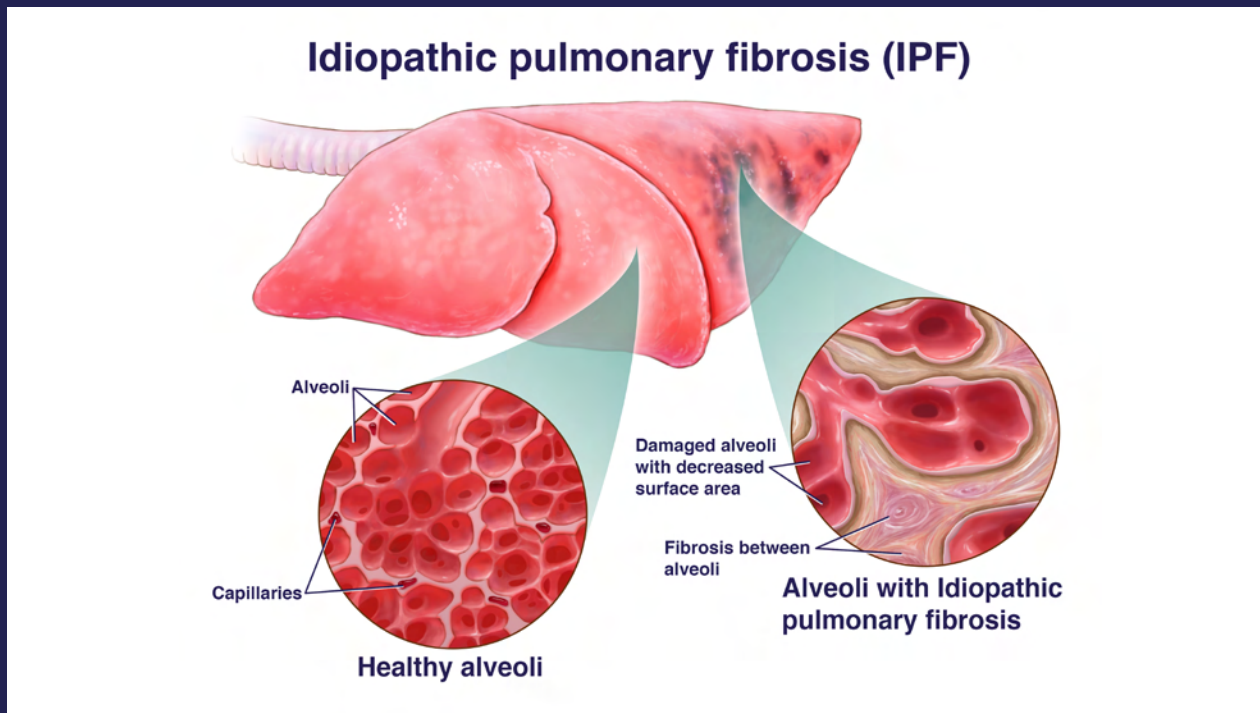


Figure 1 - In this illustration, differences between normal healthy alveoli within the lung are contrasted against those affected by idiopathic pulmonary fibrosis. The scar tissue between the alveoli and reduces alveolar surface area compromise the ability of the lungs to oxygenate the blood.

The veterinarian also may decide to measure the levels of oxygen and carbon dioxide in the patient's arterial blood.

In some cases, veterinarians may consider doing a lung biopsy, to collect tissue for microscopic examination and interpretation by a veterinary pathologist. In fact, biopsy of lung tissue is the gold standard used to make the diagnosis of idiopathic pulmonary fibrosis in humans.

While this procedure is invasive (it requires sedation /anesthesia and surgical preparation, at a minimum), it is the only way to examine the lung itself for abnormal changes indicating disease. Veterinarians may also use a technique called bronchiolar lavage to collect cells from inside the bronchioles and alveoli. This diagnostic procedure involves sedating the dog, instilling dilute physiologic sterile saline solution into the patient's lungs, and then suctioning it out with a syringe. When the fluid sample is then retrieved, it contains cells and debris from the lungs and airways. Experienced veterinary clinical pathologists can then examine the cellular makeup of this fluid to learn more about the types of disease that may be present. In many dogs with idiopathic pulmonary fibrosis, this fluid contains an increased total number of white blood cells, principally macrophages, neutrophils and mas cells. Typically bacteria are not isolated from the fluid.

Prevention and Treatment

Idiopathic pulmonary fibrosis is a serious and progressive disease that primarily affects older Westies. Because of the strong breed predisposition for this disease, prevention of this devastating disease starts with careful decisions regarding breeding. Current research studies are being performed to identify which of a particular dog's offspring are at risk for developing the condition. While in most affected dogs pulmonary fibrosis remains idiopathic, smoking is a common cause of the disease in humans. The hot gases from cigarette

“ The body's natural response to injury is to replace damaged cells and fibers with fibrous connective (scar) tissue. ”

smoke damage lung tissues and this leads to scarring, lung remodeling and emphysema. Living with a human who smokes will dramatically increase any dog's risk of developing pulmonary fibrosis and other lung diseases.

There is no cure for pulmonary fibrosis, and treatment is difficult. Currently, affected dogs can be helped by the use of corticosteroids, which reduce inflammation, suppress the immune system and help interrupt the cycle that leads to fibrosis. Non-steroidal anti-inflammatory drugs, such as aspirin or ibuprofen, have not been shown to be particularly effective in reducing the signs of disease or arresting the progressive scarring associated with the disease. Without a good understanding of the cause of this disease, therapies are not specific to the disease and do not completely alleviate symptoms. Bronchodilators, such as theophylline, and cough suppressants may help make some patients more comfortable, but there is evidence that different dogs respond differently to therapy. In recent years, pirfenidone, a drug that has antifibrotic, antioxidant and anti-inflammatory effects, has been used in human patients with the disease. The results of a small number of clinical trials with this drug suggest that it slows, but does not prevent, disease progression in these patients. Dogs diagnosed in earlier stages of the disease can often be managed more successfully than those that have progressed significantly by the time the diagnosis is made. Dogs with longstanding disease may be at risk for developing heart problems and these, too, will need to be identified and managed.

Current Research About Canine Idiopathic Pulmonary Fibrosis

Because idiopathic pulmonary fibrosis occurs primarily in Westies, a genetic basis for the disease is strongly suspected. As a result, several research studies have been performed in an effort to determine whether or not this is true, and, if so, which genes might be associated with development of the disease. In this section, we summarize the results of five recent studies, one of which describes a test for evaluating exercise tolerance in affected dogs.

Roels E, Dourcy M, Holopainen S, et al. No evidence of herpesvirus infection in West Highland White Terriers with canine idiopathic pulmonary fibrosis. *Vet Pathol* 2016, April 22 Epub ahead of print.

This study was performed to determine if there is an association between idiopathic pulmonary fibrosis in Westies and the presence of herpesvirus infection. The rationale for this study was that Epstein Barr virus infection has been associated with a similar disease in people and equine herpesvirus has been consistently isolated from lung tissue of horses with pulmonary fibrosis. To see if a similar association exists in Westies with idiopathic pulmonary fibrosis, blood and lung samples from Westies with the disease and age-matched controls without the disease were studied to determine if they contained different amounts of a specific gene associated with herpesvirus. The herpesvirus gene could not be amplified by PCR from any of the blood or lung samples from either population of dogs. Therefore, it is highly unlikely that an association exists between the disease and herpesvirus infection.

L. Lilja-Maula, P. Syrja, H.P. Laurila, E. Sutinen, M. Palviainen, O. Ritvos, K. Koli, M.M. Rajamaki and M. Myllarniemi. Upregulation of alveolar levels of activin B, but not activin A, in lungs of West Highland White Terriers with idiopathic pulmonary fibrosis and diffuse alveolar damage. *J Comp Path* 2015; 152: 192-200.

Activins are cellular products that play important roles in inflammation and fibrosis, and have been implicated in the development of idiopathic pulmonary fibrosis in people. Westies with canine idiopathic pulmonary fibrosis often have acute exacerbations of the disease that are characterized by diffuse damage to the alveoli. This study was performed to compare the concentrations of two activins, A and B, in lung tissue of Westies with idiopathic pulmonary fibrosis, Westies with other severe pulmonary diseases, and healthy Westies. Activin B, but not activin A, was strongly increased in the pulmonary alveoli of Westies with idiopathic pulmonary fibrosis and in dogs with other severe pulmonary diseases. Activin B was detected in the fluid from Westies with the disease, particularly during acute exacerbations. It was not detected in fluid from healthy Westies. These findings suggest that activin B may be important in the development of idiopathic pulmonary fibrosis and could be used as an indicator of alveolar damage. Additional studies will be needed to further characterize the role of activin B in this disease.

L. Lilja-Maula, H.P. Laurila, P. Syrja, A.K. Lappalainen, E. Krafft, C. Clercx, and M.M. Rajamaki. Long-term outcome and use of 6-minute walk test in West Highland White Terriers with idiopathic pulmonary fibrosis. *J Vet Intern Med* 2014; 28:379–385.

In this 5-year study, survival time, prognostic factors, and use of a standardized 6-minute walk test were compared for two groups of West Highland White Terriers, 15 with idiopathic pulmonary fibrosis and 11 without the disease. Although dogs with the disease had a significantly increased risk of death than the control dogs, the survival time for affected dogs was 32 months from the onset of clinical signs. Because the effects of a very similar diseases in humans is monitored using a standardized 6-minute walk test that determines how far a patient can walk in 6 minutes, the investigators used this test to compare the exercise tolerance of Westies with idiopathic pulmonary fibrosis to Westies without the disease. The investigators also examined a large number of laboratory assay results and severity of changes on thoracic radiographs to see if any of these could be used as factors to evaluate prognosis. However, there were no significant prognostic factors identified in this study. The investigators determined that Westies with idiopathic pulmonary fibrosis walked a significantly shorter distance (~435 yards) than control dogs (~540 yards) in 6 minutes, making this a good, non-invasive test to evaluate lung function and exercise tolerance in affected dogs.

Krafft E, Laurila HP, Peters IR, Bureau F, Peeters D, Day MJ, Rajamäki MM, Clercx C. Analysis of gene expression in canine idiopathic pulmonary fibrosis. *Vet J.* 2013 Nov;198(2):479-86.

This study was performed to characterize the expression of different genes in pulmonary tissues from dogs with idiopathic pulmonary fibrosis and dogs without the disease, with the aim of learning more about the development of the disease and to identify possible biomarkers. More than 700 genes were identified as having greater than two-fold difference in expression between affected and non-affected dogs. The biological functions associated with these genes were related to cellular growth and proliferation, developmental processes, cellular movement, cell-to-cell interactions, and antigen presentation. Genes whose expression levels were of particular interest encoded specific mediators of inflammation and fibrosis (various chemokines and fibroblast activation protein). Serum concentrations of one of the chemokines (CCL2) were significantly higher in Westies with idiopathic pulmonary fibrosis than in unaffected Westies, suggesting that this chemokine might serve as a candidate biomarker for the disease.

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

This study compared the microscopic findings in lung tissue from six Westies diagnosed with idiopathic pulmonary fibrosis to those typically seen in humans with the similar disease. The primary feature of the canine form of the disease was the deposition of extracellular matrix (connective tissue) around the capillaries that surround the alveoli in the lungs. This excessive amount of connective tissue impairs the normal diffusion of oxygen between the air in the alveoli and the blood in the alveolar capillaries, making it more difficult to properly oxygenate blood in the lungs. The authors reported seeing evidence of mild inflammation, which suggests that the fibrosis does not occur as the result of an overly aggressive inflammatory response to infection. Given these findings, it was suggested that additional research must be performed about the mechanisms that regulate collagen formation and degradation, as alterations in these processes may be important in the development of the disease.



Acknowledgements

Mr. Matthew Crotts, a medical illustrator in Educational Resources in the College of Veterinary Medicine at the University of Georgia, created the illustration used in this chapter.

Relevant References

- Heikkilä HP, Lappalainen AK, Day MJ, Clercx C, Rajamäki MM. Clinical, bronchoscopic, histopathologic, diagnostic imaging, and arterial oxygenation findings in West Highland White Terriers with idiopathic pulmonary fibrosis. *J Vet Intern Med.* 2011 May-Jun;25(3):433-9.
- Heikkilä-Laurila HP, Rajamäki MM. Idiopathic pulmonary fibrosis in West Highland white terriers. *Vet Clin North Am Small Anim Pract.* 2014 Jan;44(1):129-42.
- Krafft E, Heikkilä HP, Jespers P, Peeters D, Day MJ, Rajamäki MM, McEntee K, Clercx C. Serum and bronchoalveolar lavage fluid endothelin-1 concentrations as diagnostic biomarkers of canine idiopathic pulmonary fibrosis. *J Vet Intern Med.* 2011 Sep-Oct;25(5):990-6.
- Krafft E, Laurila HP, Peters IR, Bureau F, Peeters D, Day MJ, Rajamäki MM, Clercx C. Analysis of gene expression in canine idiopathic pulmonary fibrosis. *Vet J.* 2013 Nov;198(2):479-86.
- Lilja-Maula L, Syrjä P, Laurila HP, Sutinen E, Palviainen M, Ritvos O, Koli K, Rajamäki MM, Myllärniemi M. Upregulation of alveolar levels of activin B, but not activin A, in lungs of west highland white terriers with idiopathic pulmonary fibrosis and diffuse alveolar damage. *J Comp Pathol.* 2015 Feb-Apr;152(2-3):192-200.
- Lilja-Maula L, Syrjä P, Laurila HP, Sutinen E, Rönty M, Koli K, Rajamäki MM, Myllärniemi M. Comparative study of transforming growth factor- β signaling and regulatory molecules in human and canine idiopathic pulmonary fibrosis. *J Comp Pathol.* 2014 May;150(4):399-407.
- Lilja-Maula LI, Laurila HP, Syrjä P, Lappalainen AK, Krafft E, Clercx C, Rajamäki MM. Long-term outcome and use of 6-minute walk test in West Highland White Terriers with idiopathic pulmonary fibrosis. *J Vet Intern Med.* 2014 Mar-Apr;28(2):379-85.
- Lilja-Maula LI, Palviainen MJ, Heikkilä HP, Raekallio MR, Rajamäki MM. 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 Jan;74(1):148-54.
- Norris AJ, Naydan DK, Wilson DW. Interstitial lung disease in West Highland White Terriers. *Vet Pathol.* 2005 Jan;42(1):35-41.
- Roels E, Dourcy M, Holopainen S, et al. No evidence of herpesvirus infection in West Highland White Terriers with canine idiopathic pulmonary fibrosis. *Vet Pathol* 2016, April 22 Epub ahead of print.
- Syrjä P, Heikkilä HP, Lilja-Maula L, Krafft E, Clercx C, Day MJ, Rönty M, Myllärniemi M, Rajamäki MM. The histopathology of idiopathic pulmonary fibrosis in West Highland white terriers shares features of both non-specific interstitial pneumonia and usual interstitial pneumonia in man. *J Comp Pathol.* 2013 Aug-Oct;149(2-3):303-13.