

FIBROSING INTERSTITIAL LUNG DISEASES INVOLVE DIFFERENT PATHOGENIC PATHWAYS WITH SIMILAR OUTCOMES

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ABSTRACT. Fibrosing interstitial lung diseases (ILDs) are a large group of diseases triggered by external or internal stimuli that can have similar outcomes, i.e. lung fibrosis. Some ILDs are primarily fibro-proliferative disorders in which alveolar loss and epithelial/fibroblastic proliferation and dysplasia lead to lung fibrosis and architectural derangement, while other ILDs are considered inflammatory disorders in which specific underlying conditions (with either an external or an internal origin) can shift the pathogenic process to the fibro-proliferative pathway. The treatment of primarily inflammatory ILDs, regardless of their tendency to switch to lung fibrosis usually consists of anti-inflammatory drugs (e.g. corticosteroids, cytostatic + immunosuppressive agents), targeted 'biologic treatment' (e.g. anti TNF-alpha, anti CD20) and combinations thereof. However, we have entered an era in which new drugs that specifically target fibrosing ILDs, namely IPF, have emerged. Continuing laboratory research and clinical studies will hopefully provide us with a more complete understanding of the pathogenesis of fibrosing ILDs. Additionally, we are optimistic about the discovery of new pharmacological targets for the treatment of these serious diseases. The complex issues concerning fibrosing ILDs were addressed and passionately discussed during the Prague postgraduate course and conference devoted to these diseases (June 19th – 21th, 2014). (*Sarcoidosis Vasc Diffuse Lung Dis* 2015; 32: 246-250)

KEY WORDS: pulmonary fibrosis- pathogenesis- diagnosis- treatment

COMMON FEATURES OF IDIOPATHIC PULMONARY FIBROSIS AND INFLAMMATORY INTERSTITIAL LUNG DISEASES

Fibrosing interstitial lung diseases (ILDs) are a large group of diseases triggered by external or internal stimuli that can have similar outcomes, i.e. lung fibrosis. Some ILDs are primarily fibro-proliferative disorders in which alveolar loss and epithelial/fi-

broblastic proliferation and dysplasia lead to lung fibrosis and architectural derangement, while other ILDs are considered inflammatory disorders in which specific underlying conditions (with either an external or an internal origin) can shift the pathogenic process to the fibro-proliferative pathway. Though idiopathic pulmonary fibrosis (IPF) and inflammatory ILDs have different etiologies, in certain cases they can result in a common pattern that is typical of usual interstitial pneumonia (UIP). This is most likely to happen in cases with a modified cytokine milieu, which can influence the behaviour of immune cells (mainly macrophages) and enhance fibroblast formation in the lungs. Cigarette smoking is involved in the pathogenesis of different ILDs and is probably the factor that drives ILDs toward the chronic fibrosing form of the diseases.

Received: 20 October 2014

Accepted after revision: 28 October 2014

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PATHOGENESIS OF FIBROSING ILDs

Pathogenetic features of idiopathic pulmonary fibrosis

An example of a primarily fibrosing ILD is IPF. IPF can arise in genetically susceptible individuals and is probably triggered by repeated alveolar injury from multiple origins (1). One of the typical features of IPF is altered fibro-proliferative healing of lung tissue, which results in a UIP radiologic and histopathologic pattern (2). Fibroblasts and myofibroblasts found in the UIP lung can have several possible origins, including bone marrow, or they can arise from epithelial-mesenchymal transition (EMT) of alveolar cells. These processes involve activation of the Wnt pathway and transforming growth factor (TGF)-beta, both of which appear to be important factors (3-6). Additionally, a milieu containing T_H2 cytokines and chemokines also seems to be involved in the pathogenesis of IPF. This modified profibrotic cytokine milieu (aside from the genetic influence) might be supported by transcription factor Nrf2, which augments the production of interleukin (IL)-4 and ENA-78 (7). Recent studies have shown that the pathogenesis of IPF is more complex than first thought and may involve mechanisms of cell senescence (including telomere shortening) and oxidative stress (8,9).

Genetic susceptibility to IPF: The genetic loci associated with an increased probability of IPF development comprise several groups of genes. An underlying genetic cause, in cases of familial IPF, has been found involving gene mutations associated with surfactant proteins and telomerases. The dysfunction of telomeres or mutations of genes coding for surfactant proteins can cause early senescence and endoplasmic reticulum stress (resulting from unfolded proteins) that leads to epithelial stem cell exhaustion (10). External harmful stimuli may accelerate this process. With regard to the sporadic form of IPF, an important recent finding describes a correlation between sporadic mutations of the gene that codes for mucin and the pathogenesis of IPF (*pro-MUC5B rs.35705950 polymorphism*) (11). The morphologic correlate for this genetic variation might be found in the overexpression of MUC5B in honeycomb cysts layered with mucociliary epithelium in patients with IPF. Polymorphisms of genes for cytokines, namely IL-4, IL-6, IL-1 alpha, tumor necrosis factor alpha

(TNF-alpha), TGF-beta and IL-10 have been found to be associated with disease manifestations and prognosis; these compounds lead to increased production of the above mentioned cytokines and a shift in the immune balance, which creates a milieu conducive to fibro-proliferative healing (12).

Pathogenetic features of primarily inflammatory ILDs

Non-specific interstitial pneumonia: From the prognosis perspective, nonspecific interstitial pneumonia (NSIP) is a potentially less severe form of fibrosing ILD, which is more often associated with connective tissue diseases (CTDs), hypersensitivity pneumonitis (HP), and drug induced pneumonitis compared to idiopathic NSIP. The pathogenesis of NSIP probably differs from that of IPF; this idea is supported by proteomic analysis data showing a greater expression of vascular endothelial growth factor (VEGF)-A and matrix metalloproteinase-2 (MMP-2) in IPF compared to NSIP (13-15).

Hypersensitivity pneumonitis: Hypersensitivity pneumonitis (HP) is a typical primarily inflammatory ILD that sometimes shifts to chronic fibrosing ILD. The pathogenesis of HP assumes a 'two hit' theory, which means that the disease likely occurs in genetically prone individuals, but only after repeated exposures to a specific inhaled organic antigen. In contrast to IPF, class II MHC molecules appear to be a genetic susceptibility loci in HP and polymorphisms associated with HLA-DR and DQ (TAP1 gene-transporters associated with antigen processing 1) have been associated with increased risk of HP in populations with different genetic backgrounds (16). Additionally, viral infections can play a role in acute manifestations of the disease. Sometimes it is very difficult to distinguish chronic HP from IPF, since the same radiologic and histopathologic UIP pattern can be seen in both. Probably both host factors (i.e. genetic predisposition to fibro-proliferative response in lung tissue (e.g. TNF- alpha and IL-6 polymorphisms) as well as external environmental factors (i.e. antigen exposure, smoking) play a role in the evolution from the acute, reversible form, to the chronic form of the disease. The transition to the chronic form is frequently accompanied by unfavorable outcomes (17).

Pneumoconioses: Similarly, exogenous ILDs caused by inorganic dusts, mainly asbestosis and sil-

icosis, can also result in irreversible fibrosis. Fortunately, the incidence and prevalence of these types of disease have been sharply reduced due to improved work conditions in high-risk industries (e.g. asbestos and silica mines and plants). The clinical picture and outcome in patients with these diseases depends on the type of dust and cumulative exposure. To date, a genetic predisposition has not been demonstrated; nonetheless, there are certain susceptible groups of genes that might be involved in the disease pathogenesis, mainly the genes associated with oxidant/antioxidant balance and those linked to the inflammatory response (18,19).

Lung involvement in connective tissue diseases:

Lung involvement in CTDs can easily present as fibrosing ILDs with a UIP pattern that resembles IPF. Sometimes it is difficult to diagnose the underlying CTD due to the limited manifestation of the disease (also called “sine syndromes,” in which even typical symptoms of the CTD are absent). Thus, every patient presenting with ILD should also be evaluated for a possible underlying CTD (e.g. autoantibody screening, looking for extrapulmonary symptoms). In patients with rheumatoid arthritis (RA), cigarette smoking is frequently a factor contributing not only to the development of lung involvement but also to the complex pathogenesis of RA itself (20-22).

Sarcoidosis: Sarcoidosis is mostly considered a benign systemic disorder with prevailing lung manifestation. Nevertheless, in some genetically predisposed individuals the chronic fibrosing form of the disease can develop. On the positive side, most patients with fibrotic sarcoidosis (stage IV) have a rather good prognosis, which is probably related to a different type of fibro-proliferative process, despite the fact that honeycombing is sometimes identified in these patients as well (23).

Drug induced ILDs: Reactions to certain drugs can also lead to fibrosing ILDs, which can be indistinguishable from other idiopathic interstitial pneumonias (24).

CLINICAL FEATURES OF FIBROSING ILDs

Most chronic fibrosing ILDs have similar clinical features, with progressive shortness of breath being particularly noteworthy. Some cases are also characterized by an auscultation phenomenon con-

sisting of fine crackles (crepitus, Velcro-rales) that are usually heard in the basal regions of the lungs. In patients with IPF, Velcro-rales are an important clinical marker, found in more than two-thirds of patients, and frequently present along with finger clubbing. Patients must always be actively assessed for signs of connective tissue diseases (i.e. skin and joint symptoms, Raynaud phenomenon, difficulty with swallowing, etc.). In addition, signs of extrapulmonary sarcoidosis should not be overlooked (e.g. granulomas in scars, enlarged lymph nodes, erythema nodosum, and arrhythmias).

DIAGNOSTIC APPROACH TO FIBROSING ILDs

The guiding principle for diagnosis of all ILDs is the use of a multidisciplinary approach (clinical + radiologic + histopathologic), which tends to be less invasive than previous diagnostic approaches. The last statement on IPF from 2011 recommends surgical lung biopsy only in cases where HRCT changes do not correspond to IPF and importantly, does not recommend bronchoalveolar lavage (BAL) as a regular part of an IPF investigation (1). With new developments in the field of bronchology and in BAL fluid processing, the comeback of bronchoscopic techniques in ILDs investigations, including BAL, was inevitable. One of the most important advances in bronchoscopic procedures has been the inclusion of the transbronchial cryobiopsy among the standard bioptic methods in ILDs. The technique is minimally invasive and provides samples of lung tissue for histopathologic evaluation with an acceptable rate of complications even in “high-risk” elderly patients with advanced forms of the disease (25).

Treatment approaches to fibrosing ILDs; status and future insights

The treatment of primarily inflammatory ILDs, regardless of their tendency to switch to lung fibrosis, is usually the same and consists of anti-inflammatory drugs (e.g. corticosteroids, cytostatic + immunosuppressive agents), targeted ‘biologic treatment’ (e.g. anti TNF-alpha, anti CD20) and combinations thereof. However, we have entered an era in which new drugs that specifically target fibrosing ILDs, namely IPF, have emerged. Only a few years

ago, IPF was thought to be untreatable (1). Presently, we are at a point where other fibrosing ILDs, not just IPF, can be treated using antifibrotic drugs like pirfenidone and nintedanib (26). Continuing laboratory research and clinical studies will hopefully provide us with a more complete understanding of the pathogenesis of fibrosing ILDs. Additionally, we are optimistic about the discovery of new pharmacological targets for the treatment of these serious diseases (27).

The complex issues concerning fibrosing ILDs were addressed and passionately discussed during the Prague postgraduate course and conference devoted to these diseases (June 19th – 21th, 2014). Invited speakers gave edifying lectures and authors of original works presented posters; additionally there were stimulating discussions that ranged from the pathogenesis and molecular background to the clinical course, treatment, and prognosis of fibrosing ILDs. The abstracts of original papers are available in this issue of *Journal of Sarcoidosis Vasculitis and Diffuse Lung Diseases Supplement*, thanks to the efforts of Prof. Robert Baughman (chief editor).

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