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REVIEW ARTICLE

REVIEW PAPER OF IDIOPATHIC PULMONARY FIBROSIS

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Abstract

Idiopathic pulmonary fibrosis is a rapidly progressive illness of unknown cause characterized by sequential acute lung injury with subsequent scarring and end-stage lung disease. IPF is triggered by an as yet unidentified alveolar injury that leads to activation of transforming growth factor-β (TGF-β) and alveolar basement membrane disruption. The resulting deposition of excess disrupted matrix by these myofibroblasts leads to the development of IPF. Till today, no drug therapy has clearly been demonstrated to benefit patients with idiopathic pulmonary fibrosis. This review highlights the current understanding of IPF, molecular mechanisms of pathogenesis and some diagnosis and possible clinical treatments of this devastating disease.

INTRODUCTION

Idiopathic pulmonary fibrosis, also known as cryptogenic fibrosing alveolitis, is one of a family of idiopathic pneumonias sharing the clinical features of shortness of breath, radiographically evident diffuse pulmonary infiltrates, and varying degrees of inflammation, fibrosis, or both on biopsy (1). Idiopathic pulmonary fibrosis (IPF) is the most common and predominantly lethal form of the idiopathic interstitial pneumonias, with an associated median survival of only 2 to 3 years (2). The etiology of this chronic and progressive fibrotic lung disease is by definition unknown, although potential risk factors such as cigarette smoking and other environmental exposures have been described (2).

Epidemiology:

Historical challenges in studying the epidemiology of IPF:

The epidemiology of IPF remains poorly described for many reasons, but changes in definitions of IPF and complex diagnostic algorithms have proven major challenges (3). In 1998, Katzenstein and Myers proposed that the term IPF be reserved for those patients with a histopathological pattern of usual interstitial pneumonia and no identifiable cause for their interstitial lung disease (ILD) (4). This concept was formalized into diagnostic criteria in the first international consensus statement on IPF in 2000(5) and revised in 2011(2). Additionally, these statements have emphasized the importance of a multidisciplinary approach to accurate diagnosis through consensus that includes discussion among pulmonologists, radiologists, and pathologists with expertise in ILDs (3). The relative rarity of IPF has challenged investigators with an interest in its epidemiology and before 1960 discouraged large-scale epidemiologic studies from being performed (6). Although Leibow and Carrington first defined a UIP pattern in 1969(7), IPF was not given a diagnostic code in the International Classification of Diseases (ICD) until the ninth revision (ICD-9) at the end of the 1970s (8).

Incidence and prevalence:

The incidence and prevalence of IPF have been difficult to define as the diagnostic criteria for this disease have changed over the years (9). A United-States population-based study published in 1994, reported the incidence of IPF to be 10.7 cases per 100,000 per year for men and 7.4 cases per 100,000 per year for women (10). In European countries, IPF prevalence ranged from 1.25 per 100,000 population in Belgium (11) to 23.4 per 100,000 population in Norway (12). In Finland, Hodgson et al (13) screened hospital databases nationwide for alveolitis fibroticans idiopathica and used the international consensus criteria published by the ATS and ERS in 2000 (14); the nationwide prevalence of IPF for the period 1997–1998 ranged from 16 to 18 cases per 100,000 population (5). In India, this was earlier considered to be a rare disease. However, it has been noted that Indian patients seem to develop the disease a decade earlier than their counterparts in the West (14). In 1979, Jindal et al published their data on 61 cases of DPLD seen over a period of five years (15). Recently the same centre published data on 76 patients with IPF diagnosed over a 16-month period showing a definite increase in the frequency of diagnosis (14). The increase in the number of studies from India may be a true reflection of the increase in the incidence or may be apparent because of increased awareness of the condition or due to better availability of diagnostic facilities like high-resolution CT and fibreopticbronchoscopy(16).

IPF is more commonly seen in patients between 40 to 70 years of age (17). Prevalence and incidence of IPF are clearly higher in older age groups, a finding consistent with the role of aging in the pathogenesis of IPF (18). The risk of death as a result of IPF also increases with age (2, 19), with a hazard ratio (HR) of 0.25 for patients younger than 50 years (20) and a longer median survival amongst those younger than 50 (116.4 months compared to 62.8 months) (21). Age-related changes affecting cell regulation are likely important in the development of IPF (22). IPF also appears to be more common in men compared to women, however, some postulate this may be due to sex differences in historical smoking patterns rather than an inherent sex-related risk for IPF (23).

Pathogenesis

IPF is the most severe chronic form of pulmonary fibrosis and results in gradual exchange of normal lung parenchyma with fibrotic tissue and in the irreversible impairment of gas exchange in the lung (24). The current concept for the development of pulmonary fibrosis including IPF is that at least three physiologically balanced processes implicated in the maintenance of lung fibroblasts populations - proliferation, apoptosis of (myo) fibroblasts and production of ECM - are disturbed (25) . A number of genetic mutations such as the surfactant protein C (SFTPC), surfactant protein A2 (SFTPA2) and telomerase (TERT and TERTC) have also been associated with the development of lung fibrosis (26-28). Morphological studies have demonstrated that subepithelial accumulation of fibroblasts in a lesion termed the “fibroblastic focus” is the sentinel morphological lesion of IPF (29).

Ultrastructural analysis of the fibroblastic focus has revealed that it is composed of alpha-smooth muscle actin-expressing myofibroblasts enmeshed in a matrix rich in polymerized type I collagen (30). Prior to the activation of myofibroblasts, it is generally believed that an initial or repetitive injury occurs to type I alveolar epithelial cells (AEC-I) which constitute the majority of the alveolar surface (31). When AEC-I is injured, type II alveolar epithelial cells (AEC-II) are undergo hyperplastic proliferation and release some growth factors, cytokines and other substance that subsequently helps to activate myofibroblasts, which secret collagen and ECMs .The accumulation of ECM and the hyper-proliferation of myofibroblasts ultimately destroy alveolar parenchyma (25). TGFβ is a central stimulator of collagen production in the pathogenesis of pulmonary fibrosis (32). Most important is the demonstration that TGF-β is an integral component of fibrotic tissue in IPF, with a known role in causing the differentiation of myofibroblasts (33, 34). Munger et al. recently showed that activation of latent TGF-β through expression of the integrin αvβ6 can generate fibrogenic conditions (35). Recent studies further revealed that β1 integrin regulates the crucial PTEN/PI3K/Akt axis, thereby altering IPF fibroblast cell phenotype in response to type I collagen matrix (36), and this signaling pathway is closely linked to cell proliferation, migration and apoptosis. Thus the precise understanding of the altered PTEN/PI3K/Akt dependent pathway is thought to be vital for the elucidation of IPF pathogenesis.

The cross talk between integrins and TGF-β signalling is of considerable interest in a wide variety of physiological and pathophysiological processes including idiopathic pulmonary fibrosis. The αVβ6 integrin-dependent activation

of TGF-β requires the binding of the β6 cytoplasmic tail to the actin cytoskeleton (37). This activation of TGF-β is highly dependent on the association of inactive (latent) forms of TGF-β and TGF-β binding protein-1 (LTBP-1) of the large latent complex with αVβ6 integrin (38).Various profibrotic factors such as PDGF, ET-1, TNF-α, heat shock protein 47 (HSP47), connective tissue growth factor (CTGF), IL-4, insulinlike growth factor (IGF) and its binding proteins are also known to be associated with the regulation of fibrosis(39). Several miRNAs are known to play a major role of conductors in the pathogenesis of fibrosis (40). Among them, miR155, miR-15b, miR-16, mir21, mir23a, miR26a/b, miR-30c and miR338 are though to be associated with lung fibrosis (41).

Diagnosis:

It is critical to obtain a complete history, including medication history, drug use, social history, occupational, recreational, and environmental respiratory exposure history, risks for the human immunodeficiency virus, and review of systems, to ensure other causes of interstitial lung disease are excluded. The diagnosis of idiopathic pulmonary fibrosis relies on the clinician to integrate and correlate the clinical, laboratory, radiologic, and/or pathologic data (42). Inflammation or scar tissue builds up in lungs, making them thick and hard. This build-up of scar tissue is called fibrosis. Lungs become stiffer and lose their elasticity, they are less able to take oxygen from the air. People with IPF can feel breathless from simple everyday activities like walking Non-productive Cough is anothercommonsymptom.

Physical Findings:

#Fine bibasilar inspiratory crackles (Velcro crackles): Dry crackles, or coarse crackels on inspiration, are usually heard at the lung bases.

#There may be tachypnea at rest, cyanosis, clubbing of the fingers and toes (25-50%), usually without hypertrophic osteoarthropathy.

#In the later stage, cor pulmonale is evident, with findings of pulmonary hypertension, such as an accentuated pulmonic second sound or a right-sided lift, and eventually signs of right-sided heart failure. The right ventricular ejection fraction determined by radionuclide ventriculography is often depressed in the face of normal left ventricular performance (43).

Laboratory testing:

Antinuclear antibodies or rheumatoid factor titers: Positive results in about 30% of patients with IPF, but the titers are generally not high (44). The presence of high titers may suggest a connective tissue disease.

C-reactive protein level and erythrocyte sedimentation rate: Elevated but nondiagnostic in idiopathic pulmonary fibrosis. Circulating immune-complex titers and serum immunoglobulin level may be increased, cryoimmunoglobulins may be present.

Complete blood cell count: polycythemia (rare)

Arterial blood gas analysis: chronic hypoxemia (common).

Pulmonary function studies: Nonspecific findings of a restrictive ventilatory defect and reduced diffusion capacity for carbon monoxide (DLCO) (45).

Imaging studies:

Chest radiography: Abnormal findings but lacks diagnostic specificity. Demonstrate peripheral reticular opacities (netlike linear and curvilinear densities) predominantly at the lung bases, honeycombing (coarse reticular pattern), and lower lobe volume loss (46).

High-Resolution Computed Tomography: HRCT has greatly enhanced the evaluation of interstitial lung diseases by increasing spatial resolution, facilitating visualization of parenchymal detail to the level of the pulmonary lobule. The protocol for HRCT scanning of patients with suspected IPF includes a section thickness of 1-1.5 mm collimation and interval size between sections of 1-2 cm. The HRCT pattern of IPF commonly shows patchy, predominantly peripheral, subpleural, bibasal reticular abnormalities, and areas of traction bronchiolectasis with limited amount of ground glass opacity (47).

#Transthoracic echocardiography: Detects pulmonary hypertension well but has variable performance in patients with Idiopathic Pulmonary Hypertension and other Chronic Lung Disease (48).

Procedures/Techniques:

Bronchoscopy: Absence of lymphocytosis in bronchoalveolar lavage fluid may be important for the diagnosis (increased neutrophils [70-90% of patients] and eosinophils [40-60% of all patients]) (49).

Surgical lung biopsy (via open lung biopsy or video-assisted thoracoscopic surgery [VATS] [preferred]): Best sample for distinguishing usual interstitial pneumonia from other idiopathic interstitial pneumonias (50).

TREATMENT AND THERAPHY:

At present, there are no proven therapies for idiopathic pulmonary fibrosis. Given the newer insights into the pathogenesis of idiopathic pulmonary fibrosis, novel approaches must be aimed at minimizing the sequelae of repeated acute lung injury (1).

Azathioprine:
The combination of azathioprine and corticosteroids was associated with modest improvement and enhanced survival in some patients. In one prospective double blind randomized placebo controlled study with 27 patients, combination of azathioprine and prednisolone had a marginally significant survival advantage (51)

Cyclophosphamide
High dose intravenous cyclophosphamide administered every 2 to 4 weeks (dose range, 500 to 1,800 mg) has been tried in open trials of refractory IPF (52). A recent study suggested that combined corticosteroid and cyclophosphamide therapy has no impact on survival in patients with IPF (53).

Colchicines
Colchicine inhibits collagen formation and modulates the extracellular milieu and suppresses the release of alveolar macrophage-derived growth factor and fibronectin (54). However subsequent studies have failed to demonstrate any benefit of treatment with colchicine over no treatment at all (55).

Lung Transplantation
Lung transplantation has emerged as a viable option for some patients with idiopathic pulmonary fibrosis. Unfortunately, most patients are not eligible, because of older age or complicating medical conditions (1).

CONCLUSION:

Idiopathic pulmonary fibrosis is a rapidly progressive fatal disease of unknown cause characterized by sequential acute lung injury with subsequent scarring and end-stage lung disease. This disease causes a serious threat to the society along with the increased many pulmonary problems. Till today, no drug therapy has clearly been demonstrated to benefit patients with idiopathic pulmonary fibrosis, a number of novel investigational scientists hold promise for future study. The complexity of IPF study and the understanding of molecular mechanisms in the development of IPF are required for future investigation, and we hope these efforts will lead to find effective therapeutic targets for the treatment of IPF.

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