Is idiopathic pulmonary fibrosis - is environmental or genetic disease - an old wine in a new bottle of treatment

Abstract
Idiopathic Pulmonary Fibrosis is a chronic progressive (IPF) and fibrotic lung disease, where healthy lung is replaced by altered extra cellular matrix, alveolar architecture is gradually destroyed, with gradual increase of fibrosis due to deficient fibroblasts activation and proliferation and all these leads to decreased lung complaints and disrupted gas exchange, ultimately respiratory failure and death. It was previously known as most common type of Interstitial Pneumonia and treatment of choice was (before 2000) prednisolone or prednisolone with azathioprine or acetylcys teine and or warfarin with poor prognosis and median survival time was then for 2 to 4 years after diagnosis. But in less than 10 years time, the landscape of idiopathic pulmonary fibrosis’s pathophysiology, diagnostic modality, pathology and treatment had been transformed. Many people no longer consider IPF to be idiopathic rather interactions between casual factors including genetic polymorphism, aging, environmental exposures, which culminate in a malapaptine repair process.

Keywords: Idiopathic pulmonary fibrosis, muc5b gene defect, shortening of aec2 stem cell telomere length

Introduction
Idiopathic Pulmonary Fibrosis (IPF) is a chronic inflammatory lung disorder which gradually progress to establish fibrosis. This condition is found more commonly in men, but is rarer in younger than age 50 years and median age of diagnosis is about 65 years. Although the disease course is variable, unpredictable (some patients progress rapidly, other quite slowly and others have sudden worsening after periods of stability with nintedanib). The median survival time is 2-4 years after diagnosis. Though the incidence of this disease is low in India (0.5), and in the Asian countries (4.2) per 1 lack population per year, the incidence is very high in European and in north American countries, Canada etc and its incidence there is between 2-8-18 per 1 lack population per year. Anti-Inflammatory therapies with prednisolone, or prednisolone with immunosuppressive agents like azathioprine for long years did not improve the outcome rather was found putative and subsequent meta analysis with prednisolone or prednisolone with azathioprine or acetyl cysteine or warfarin or everolimus was later proved to be potentially harmful therapies. Treatment by bosenten, imatinib, mactraintan or sidenafil was also attempted since 2010-2015 but were considered potentially ineffective therapies for IPF. That are now accepted worldwide - A tyrosine kinase inhibitors (rho-rho kinase pathway inhibitors) nintedanib and anti fibrogenic agent Pirfenidone (TGFβ2 inhibitors). IPF is now generally regarded as a consequence of multiple interacting genetic and environmental risk factors with repetitive local micro injuries to aging alveolar epithelium. These micro injuries stimulate fibroblasts proliferation, produces extra cellular matrix expansions and altered matrix composition and biomechanics, induces matrix produces myofibroblast and aberrant remodeling of lung interstitium.

Pathogenesis of idiopathic pulmonary fibrosis
Environmental pollution
Particulate inhalation is responsible in initiation and progression of IPF. A history of cigarette smoking is associated with IPF in most patients. However multiple other environmental exposures including metals, stone dusts, silica dusts, fogs, agriculture, farming, viruses are also common predisposing factors for IPF to develop after age of 60 yrs.

Genetic factors
Genetic susceptibility in the development of IPF plays a significant role. Common genetic variant which accounts for 1/3rd risks for development of IPF are MUC5B, ATP11A,TOLIP(these genes are related with host defense alteration) and telomere maintains gene(TERT,TERC,OBFC)and epithelial barrier functions (DSP,DPP9). The largest genetic to all these gene variants are MUC5B and dis-regulation of AEC2 (alveolar epithelial cell) stem cells.
MUC gene

MUC5B gene defect found both in familial and sporadic IPF cases. MUC5B encodes mucin 5B precursor protein that contribute to airway mucus production and play an important role in lung host defense mechanism. Patients with IPF with MUC5B gain of function variant might have then higher rate survival than those without these variant. If these mutated and altered MUC5B in bronchiolar epithelium, there is increased protein concentration that may reduce muco cilliary clearance or impede normal lung repair process. Pathological mechanism of fibrosis, though very challenging one, it is probably due to dis regulation of type 2 alveolar cells (AEC2). These AEC2 are stem cells within lung that contribute to renewal of type 1 alveolar epithelial cell during homeostasis and after lung injury. Loss of AEC1 and abnormal AEC2 are identified in IPF with fibroblastic foci typically located adjacent to hyper plastic or apoptotic alveolar cell. 3

In IPF, premature shortening of AEC2 stem cell telomere is seen in mouse model. A study on 2016 showed that AEC2 from IPF have impaired renewal capacity consistent with AEC2 stem cell failure. Activated and abnormal AEC2 produces numerous fibrogenic growth factors and cytokines including TGFβ1, PDGF with aberrant epithelial mesenchymal cross talk driving the recruitment and activation of myofibroblasts. 4 These activated myofibroblasts deposit an increased amount of altered extracellular matrix, which again destroy alveolar architecture and interferer gas exchange. Multiple sources of myofibroblasts are proposed including residual mesenchymal cell proliferation, lung interstitium, pericytes, circulation fibrocytes, epithelial mesenchymal transition and endothelial mesenchymal cells. 5 Changes in extracellular matrix composition, altered cell behavior and interactions between fibroblast, deficient apoptosis of fibroblast and aberrant extracellular matrix, both promote fibrosis and lung stiffness. Here integrins plays a central role with mechanosensitive protein-protein interactions occurring with adhesion complex and these interaction of stimulation of TGFβ and intrinsic mechanoreduction occurs via Rho-Rho Kinase pathway which promotes myofibroblast differentiation and nintedanib acts better than Lmatinib possibly as disease modifying therapy.

Clinical presentation, sign and symptoms

Patient of IPF usually present with exertional dyspnea with or without dry cough. These presentations might initially be attributed to aging, COPD, emphysema or other cardiovascular diseases or obesity. Occasionally patients present with acute dyspnea worsening with days or weeks often accompanied by fever and influenza like symptoms. This acute exacerbation require careful diagnosis from other acute interstitial lung diseases on physical examination fine high pitched basilar inspiratory crackles are heard by stethoscope and digital clubbing is present in 30% patient.

Diagnosis

Diagnosis of Idiopathic pulmonary fibrosis is on basis of both radiological and histopathological criteria without evidence of alternative diseases. Careful attention to signs of various connective tissue disorders are essential to rule out associated diseases. In established cases pulmonary function test identify restrictive lung diseases (reduced total lung capacity) and abnormal gas exchange (reduced capacity co diffusion). Amongst differential diagnosis needs a. Known cases of Interstitial Lung Disease(ILD) b. Domestic and occupational exposures c. Connective tissue disease d. Drug toxicity e. Chronic hypersensitive pneumonia

High resolution Computed Tomography (HRCT) of chest shows reticular opacities associated with bronchiectasis and clusters of subpleural, cystic air spaces of diameter 3-10mm with honeycombing, in a predominantly bilateral, peripheral and basal distribution. These features are of typical of all types of ILD (interstitial pneumonia pattern) whereas features such as mosaic attenuation ground glass abnormality and nodules suggest IPF. When HRCT are non diagnostic true cut or open surgical open lung biopsy is advised. Every patient before going for open surgical lung biopsy, careful consideration must be done about the potential benefit of this biopsy procedure for patient younger than 65yrs only. In elder patients those are with other co morbidities or has clinically significant impairment lung function test or in acute non elective procedure the lung biopsy must be avoided and the diagnosis should rest on HRCT.

Histopathology

a. Usual interstitial pneumonia: It is characterized by
i. Interstitial fibrosis with spatial heterogeneity and patchy involvement of lung parenchyma.
ii. Areas of marked fibrosis.
b. Alveolar architecture distortion.
c. Microscopic honeycomb.
d. Cystic airspaces lined by bronchiolar epithelium filled up with mucin.
e. In IPF all these features usual interstitial pneumonia and along with aggregates of proliferating fibroblasts and myofibroblasts in the form of fibroblastic foci such fibroblastic foci are key histopathological diagnosis of IPF.

Is genetic testing necessary?

In individual with a family history of ILD suggestive of interstitial pneumonia genetic testing for mononuclear cell telomere length testing from peripheral blood will be helpful in disease course prognostification and future lung transplantation for sporadic IPF usually genetic testing is not recommended at all.

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Conflict of interest

Authors declare there is no conflict of interest.

References


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