Idiopathic Pulmonary Fibrosis: A Systemic Disease?

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Introduction

Idiopathic pulmonary fibrosis (IPF) is a specific type of chronic progressive fibrosing interstitial pneumonia associated with a histopathologic pattern of usual interstitial pneumonia. IPF is typically considered to be a lung-limited disorder. Although the primary manifestations of IPF are pulmonary in nature, IPF is increasingly recognized as a systemic disease due to its strong association with comorbidities and complications.

Genetics of Idiopathic Pulmonary Fibrosis

The genetic etiology of IPF is in favor of considering the disease as a systemic syndrome. Early reports of cases of pulmonary fibrosis occurring in families suggested a genetic predisposition to some forms of the disease.[1] Wang *et al*.[2] identified chromosome 10q22 as an IPF-related region. Genes residing in this region include surfactant proteins A1, A2, and D. These have been identified as candidate genes. Mutations in *TERT* or *TERC* and surfactant protein C have been identified in sporadic IPF individuals.[3-5] A significantly higher proportion of patients with IPF display shorter telomeres in peripheral blood and in alveolar epithelial cells, as compared to controls.[3,4] A meta-analysis shows that the *MUC5B* promoter rs35705950 polymorphism is strongly associated with the risk of IPF,[6] the result has been confirmed by an independent analysis in two cohorts with sporadic IPF.[7]

Gastroesophageal Reflux Disease

There are so many pulmonary or extrapulmonary comorbidities and complications of IPF, which further support that IPF is a systemic disease. Architectural distortion and increased traction on mediastinal structures may lead to weakening of the lower esophageal sphincter and increased gastroesophageal reflux disease (GERD). GERD is associated with several pulmonary disorders, while IPF shows the strongest association. The incidence of GERD in patients with IPF is higher than that in the general population, and it has been reported to be 62.3%.[8] GERD also plays an important role in the development and progression of IPF, including acute exacerbations.[9] Long-term chronic suction of gastric contents, including gastric acid, pepsin, and bile acid, could damage pulmonary alveolar epithelium, resulting in abnormal tissue repair and eventually pulmonary fibrosis. Interestingly, three randomized controlled trials have shown patients with IPF taking a proton pump inhibitor/H_2 blocker (PPI/H_2B) had a significantly smaller decline in forced vital capacity at 30 weeks and fewer acute exacerbations,[10] suggesting that treating GERD may benefit IPF patients.

Coronary Artery Disease and Pulmonary Hypertension

Patients with IPF have been reported to be more vulnerable to vascular diseases. It has been reported that increased risks of acute coronary syndrome, angina, and deep-vein thrombosis proceed the diagnosis of IPF.[11] A study[12] with 460 IPF patients and 1925 controls showed that the incidence of newly diagnosed coronary artery disease (CAD) was higher in patients with IPF (6.8%)

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compared to controls (2.8%), leading to the conclusion that IPF itself is an independent risk factor for CAD after adjusting for age, hypertension, diabetes, and hypercholesterolemia. Multiple studies have reported an increased incidence of venous thromboembolism in patients with IPF compared with the general population.[11] A study of Danish population from 1980 to 2007 revealed that the incidence of IPF was higher among individuals with a history of venous thromboembolism than those without. The incidence of pulmonary hypertension (PH) in IPF patients has been reported to be 23.5% at a tertiary referral center in China.[13] IPF patients with higher systolic pulmonary artery pressure may have poorer right ventricular function. PH may worsen dyspnea, right heart dysfunction, and decrease the life quality of the patients with IPF.

Dyspnea and Depression and Lung Cancer

Dyspnea and depression influence one another: dyspnea is a primary cause of depressive symptoms, and conversely, depression exacerbates the perception of respiratory symptoms. Patients with IPF often report extremely poor sleep quality and with sleep-related breathing disorders (SRBDs). In 2001, Clark *et al.*[14] studied 48 patients with IPF through overnight oximetry and noted that nocturnal hypoxia was common and affected the quality of life. Some studies[15] suggested that patients with IPF presented poorer sleep quality and daytime sleepiness and higher apnea-hypopnea index. Patients with IPF present alterations in sleep architecture, including decreased sleep efficiency, slow wave sleep and rapid eye movement (REM) sleep, and increased sleep fragmentation. Moreover, sleep-related hypoventilation during the vulnerable REM sleep period and obstructive sleep apnea-hypopnea syndrome are frequent, but remain usually underdiagnosed. These SRBDs in IPF are associated with alterations of the sleep structure, reduction of quality of life, and increased risk of mortality. Besides, lung cancer was also identified as one of the comorbidities of IPF and the two diseases share several risk factors and pathogenic pathways and also show a similar anatomic distribution.

From what has been discussed above, we come up with the standpoint that IPF is a kind of systemic disease.

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Conflicts of interest

There are no conflicts of interest.

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