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Review article

# Idiopathic pulmonary fibrosis: Clinical behavior and aging associated comorbidities

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ABSTRACT

Idiopathic pulmonary fibrosis (IPF) is a progressive, irreversible and usually lethal lung disease of unknown etiology. Once considered as a relatively homogeneous, slowly progressive disease, is now recognized that the clinical behavior shows substantial heterogeneity, including an accelerated variant, and the presence of acute exacerbations. In addition, since IPF largely affects individuals over 60 years of age, the patients are at increased risk of several comorbidities that in turn have a remarkable clinical impact on the disease and increases mortality rate. Among others, combined pulmonary fibrosis and emphysema, secondary pulmonary arterial hypertension, lung cancer, and cardiovascular diseases are frequently associated with IPF and impact survival. For these reasons clinical phenotypes and comorbidities should be timely identified and managed. The aim of this review is to describe the common pulmonary and extra-pulmonary comorbidities in IPF, as well as the putative mechanisms involved.



**Contents**



## 1. Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive and deadly disease with few and modest therapeutic options and a median survival of 3–5 years following diagnosis [1,2]. The confident diagnosis of IPF is achieved by the presence of a typical pattern of usual interstitial pneumonia (UIP) either by high-resolution computed tomography (HRCT) or histology in an appropriate

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clinical setting including the absence of an identifiable etiology (Fig. 1). However, about a third of the IPF patients display atypical HRCT findings and the disease may be confused with another fibrotic lung disorder such as chronic hypersensitivity pneumonitis (cHP) or ILD secondary to autoimmune disease or diagnosed as unclassifiable interstitial lung disease [3, 4]. Moreover, there is substantial overlap in the clinical and functional behavior between IPF and non-IPF disorders and in general, virtually all the ILD patients refer progressive exertional dyspnea and dry cough, and a restrictive functional pattern with decreased forced vital capacity and compliance and hypoxemia at rest worsening with exercise.

Therefore, clinicians face two challenges for the confident diagnosis of IPF; on one hand, a patient with IPF may present atypical tomographic and/or morphologic findings and on the other, a patient with another chronic fibrotic lung disorder, e.g., cHP without identifiable causative antigen, may exhibit chest HRCT or pathological changes mimicking UIP [4]. This diagnostic uncertainty represents an important problem since the prognosis and therapeutic approach is completely different. In this context, it is recommended that patients consulting by a diffuse parenchymal lung disease be evaluated by a multidisciplinary team involving pulmonologists, radiologists, and pathologists experienced in the field of ILD, moreover, the high frequency of connective tissue disease-related ILD requires adding a rheumatologist to the team [5, 6].

Therapy represents a significant challenge in IPF. During a long time, with the notion that the disease represented an inflammatory-driven fibrosis, patients were treated with high dose of corticosteroids and immunosuppressive drugs. However, these drugs not only were unable to modify the progressive and devastating natural course of the disease, but also resulted in higher mortality [7]. From 2014, two putative antifibrotic drugs were approved for the treatment of IPF, nintedanib, an inhibitor of the Src family of tyrosine kinases, and pirfenidone, a small synthetic molecule with unknown mechanisms of action [8,9]. Both drugs reduce the loss of lung function over time and perhaps stabilize a (yet unidentified) subgroup of patients, although survival and quality of life benefits have not convincingly been established with either agent. Moreover, patients that were included in the clinical trials displayed mild or moderate pulmonary function alterations and the drugs were used for relatively short periods of time. It is not yet clear whether these drugs may show similar results in patients with more severe disease, as are usually seen in the real life, and how will be the adverse event profile with long-term (several years) of treatment. However, both drugs opened a new window in the treatment of IPF and some preliminary reports suggest that safety data did not dramatically change over time [10–12].

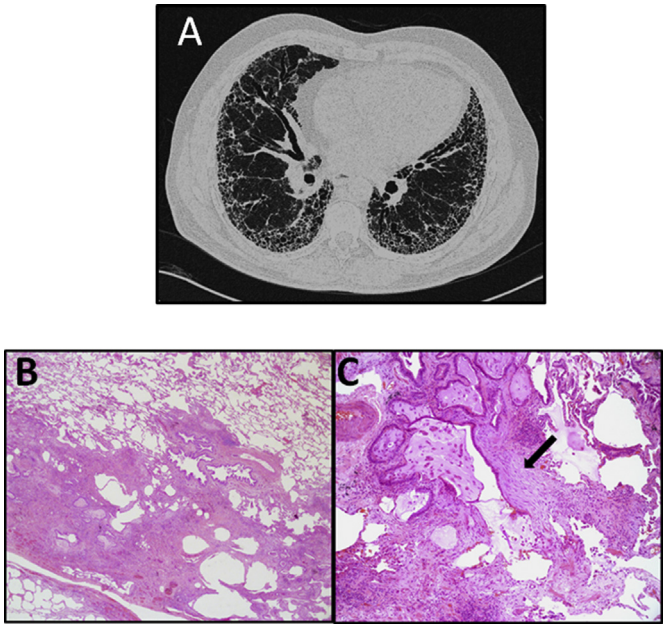


**Fig. 1. Hallmarks of usual interstitial pneumonitis A)** High-resolution computed tomography showing architectural distortion with subpleural and basal reticulation, traction bronchiectasis, and honeycombing. **B)** and **C)** Pathology of UIP pattern. **B)** Extensive subpleural fibrosis alternating with areas of mild fibrosis and others of uninvolved parenchyma in an appearance named "patchwork pattern". **C)** High magnification of an UIP lung showing architectural distortion by honeycombing and an area of active fibrosing process identified by a large subepithelial fibroblastic focus (arrow).

## 2. Clinical phenotypes and comorbidities

During a long time the natural history of IPF was considered to be characterized by a slowly progressive course. However, it is now recognized that the clinical behavior shows substantial heterogeneity and different clinical phenotypes have been defined. In addition, since IPF occurs usually in older individuals, they may present some aging-associated comorbidities which affect its clinical course and survival [2, 13]. Thus for example, the incidence and prevalence of some comorbid conditions are remarkably more frequent in patients with IPF compared with age-matched controls. Some of them, for example lung cancer, occur at least in part because they share common risk factors (smoking) and some pathogenic mechanisms (e.g., epithelial genetic instability) while others seem to be a direct consequence of IPF (pulmonary hypertension, ischemic heart disease).

To date however, the clinical course and prognosis of individual patients are difficult to predict because reliable clinical parameters or biomarkers reflecting disease progression are scanty and the studies have been usually retrospective and without verification in independent cohorts.

Most patients progress slowly with or without periods of relative stability while others experience rapid decline and die in a short time after diagnosis [14, 15]. IPF may also be complicated by an acute exacerbation characterized by an acute worsening of dyspnea and lung function that severely worsens survival [16,17].

### *2.1. Acute exacerbations*

A subset of IPF patients, more often those with advanced disease and never smokers, presents episodes of acute clinical deterioration that precede and possibly initiate the terminal phase of the disease [16, 17]. Actually, acute exacerbations result in high in-hospital mortality. The incidence is difficult to estimate but a recent meta-analysis involving six randomized-controlled clinical trials in patients with IPF revealed a weighted average of around 40 acute exacerbations per 1000 patient-years [18].

The acute episode may be "idiopathic" when it is not associated with an identifiable cause, and it is assumed that represent sudden acceleration of the underlying disease process, or secondary when it is trigger by a recognizable cause such as infection, pulmonary embolism, or heart failure among others [17, 19]. Acute exacerbations are characterized by rapid progression of dyspnea within the previous 30 days, with the presence of new bilateral ground-glass opacities or consolidation by radiography/HRCT without pneumothorax or pleural effusion, and a marked decrease in the PaO2 (Fig. 2). When performed, lung biopsy demonstrates diffuse alveolar damage superimposed to a background of UIP with or without concurrent organizing pneumonia [16, 20]. However, differentiate idiopathic from non-idiopathic acute respiratory worsening in the clinical arena is challenging, since for example, exclusion of