Idiopathic Pulmonary Fibrosis: Diagnosis and Prognostic Evaluation

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Key Words

Idiopathic pulmonary fibrosis · Interstitial pneumonia ·
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Abstract

Idiopathic pulmonary fibrosis (IPF) is the most common type of idiopathic interstitial pneumonia and has a dismal prognosis. Median age at IPF onset is 60–70 years and it is mainly related to cigarette smoke exposure. Its clinical profile is heterogeneous and different clinical phenotypes are now better defined: familial IPF, slow and rapid progressors, combined pulmonary fibrosis and emphysema, anti-neutrophil cytoplasmic antibodies/microscopic polyangiitis and IPF, and IPF associated with lung cancer. Acute exacerbation associated with rapid functional decline is an event that does not happen infrequently and affects survival. Diagnosis requires a typical usual interstitial pneumonia (UIP) pattern on computed tomography in the appropriate clinical setting or morphological confirmation of the UIP pattern when imaging findings are not characteristic enough. Surgical lung biopsy is the gold standard to obtain valuable information for histological analysis. However, less invasive procedures (transbronchial lung biopsy or even improved transbronchial lung biopsy by cryoprobes) are now under consideration. Prognostic indicators are mainly derived by pulmonary function tests. Recently, staging systems have been proposed.

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Introduction

Idiopathic pulmonary fibrosis (IPF) is a progressive and often fatal fibrosing interstitial pneumonia of unknown cause that is limited to the lung and associated with the histopathological and/or radiological pattern of usual interstitial pneumonia (UIP) [1]. The fibrotic process that characterizes IPF is commonly considered the result of recurrent injury to the alveolar epithelium followed by uncontrolled proliferation of bronchiolar epithelium and fibroblasts [2, 3]. The fibrosis could arise from the most mechanically stressed areas of the lung and relentlessly progresses from the peripheral basal parenchyma to the central parenchyma and upper aspects of the lung [4]. The new pathogenetic paradigm on IPF is that it is a complex process characterized by abnormal pneumocyte apoptosis and profound derangement of alveolar renewal more similar to malignant lung disease [2–5]. Indeed, epigenetic and genetic abnormalities, senescence-related processes (such as oncogene-induced senescence or senescence-associated secretory phenotypes), altered cell-to-cell communications, uncontrolled proliferation and abnormal activation of specific signal transduction pathways are biological hallmarks that characterize the pathogenesis of IPF and link this disorder to lung cancer [5, 6].

IPF accounts for ~55% of lung diseases classified as idiopathic interstitial pneumonias [1, 6]; it occurs predominantly in older adults, with an increasing incidence and a prevalence of 20.2 men per 100,000 and 13.2 women per 100,000. It has been estimated that approximately 40,000 new patients will be diagnosed with IPF each year in Europe [7–9]. Retrospective longitudinal studies suggest that the median survival of IPF patients is 3–5 years [8–11]. However, the course of IPF is variable, with some patients experiencing long periods of stability while others experience exacerbations or a rapid progressive decline. The median age at IPF onset is 60–70 years [1]. Cigarette smoke is an independent risk factor for IPF, with an odds ratio of 1.58 (95% confidence interval: 1.27–1.97) and a possible dose-response relationship between tobacco smoking and the risk of IPF [12].

Clinical Heterogeneity of IPF

IPF occurs in a sporadic form in most instances, but occasionally it can also occur in familial form; familial cases account for 0.5–3.7% of cases of IPF with up to 19% of patients reporting a family history significant for interstitial lung disease [13, 14]. In the literature, familial IPF has previously been defined with various criteria including the following: patients with clinical features compatible with IPF in combination with either compatible high-resolution computed tomography (HRCT) findings or histologic evidence of UIP found in lung biopsy specimens in 2 or more family members; in an index case with at least 2 other affected relatives, or as IPF in at least 2 first-degree relatives. While clinical features of sporadic IPF are well defined, regarding familial IPF, the clinical presentation, complications and outcome of patients are still undefined issues and it has yet to be proven whether familial forms of IPF have a particularly different natural history because of genetic influence or other factors. Some publications have compared the clinical features of familial and sporadic IPF patients and there were no distinguishing features apart from a younger mean age at diagnosis in the familial compared with the sporadic groups [15]. This may represent a true younger onset of disease in familial IPF patients, a more rapid progression to clinically overt illness or perhaps a heightened awareness with earlier diagnosis of individuals from affected families. The phenomenon which is characterized by disease onset at an earlier age or a greater disease severity status in successive generations is known as ‘genetic anticipation’ and it is a widely known characteristic of many

diseases with genetic inheritance. Genetic mutations explain part of the IPF cases. IPF in patients presenting with germline mutations in the hTERT and hTR gene associated with the telomerase complex (a ribonucleoprotein holoenzyme that protects the tips of chromosomes from ‘erosion’ during cell division) introduces criticisms about the IPF definition as in these patients the disease may not be limited to the lung but can involve other organs or structures (liver, bone marrow or hair), too [16]. Furthermore, in histological studies in familial IPF cases, different patterns (UIP, nonspecific interstitial pneumonia, desquamative interstitial pneumonia or even hypersensitivity pneumonitis) have been documented [17], reinforcing the concept that morphology per se is not a dominant element to define the disease.

Selman et al. [18] reported that a subset of sporadic IPF patients, predominantly smoking males, was characterized by a short duration of symptoms with rapid progression to end-stage disease. These patients had a different gene expression signature (rapid progressors). Brown et al. [19] recently showed that there may be a continuous spectrum of improving patient outcomes based on the duration of survival: in this study, the concept that survival begets survival appears endurable. This study is important because it emphasizes the element ‘tempo’ as an important clinical category. A CT scan may predict slow progression of the disease when honeycomb changes are not detectable, emphysema profusion is low and HRCT scoring of fibrosis is also low [20]. IPF patients with high mast cell density in surgical lung biopsy specimens seem to have a slower decline in forced vital capacity (FVC) [21]. In clinical practice, however, prediction of the rate of decline is not yet possible. Recently, Kahloon et al. [22] reported that patients with anti-heat shock protein 70 IgG autoantibodies have more near-term lung function deterioration and mortality, and CD28 downregulation on circulating CD4 T cells is associated with a poor prognosis [23].

Patients with an initial diagnosis of IPF occasionally acquire myeloperoxidase anti-neutrophil cytoplasmic antibodies (MPO-ANCA); of these, less than a quarter develop microscopic polyangiitis. The presence of eosinophils in bronchoalveolar lavage (BAL) fluid and low attenuation areas on CT might be predictive of MPO-ANCA-positive conversion [24].

Combined pulmonary fibrosis and emphysema has been recognized as another peculiar phenotype [25]: the coexistence of emphysema usually in the upper lobes and fibrosis in the lower lobes causes a slight decrease in FVC, a significant impairment in diffusing capacity of the lung

Fig. 1. Survival curve comparing IPF patients without lung cancer and IPF patients that developed lung carcinoma (data from the database of the Department of Diseases of the Thorax, Ospedale GB Morgagni, Forlì, Italy).

for carbon monoxide (DLCO), exercise hypoxemia and, in the majority of cases, pulmonary hypertension. However, a quantitative definition of emphysema and fibrosis to better define this entity is still missing. The prevalence of pulmonary fibrosis combined with emphysema is about 8% [26]. This coexistence may be explained by common pathogenetic mechanisms [6].

The incidence of lung carcinoma in IPF patients appears to be significantly increased [27]. The neoplasms are usually peripheral (nodules or masses, rarely alveolar opacification or ground glass attenuation) and reveal peculiar histological phenotypes (squamous carcinoma or adenocarcinoma-enteric type). Survival of patients with lung cancer arising from IPF is shorter than that of patients without cancer (fig. 1); it is still not clear if this depends on the progression of the neoplasm or on the fact that lung carcinoma is more frequent in rapid progressors.

The early phase of IPF is still poorly understood. Kon-doh et al. [28] identified 16 patients with IPF without pulmonary function impairment. Seven were asymptomatic. Eleven patients showed physiological disease progression. In this study, both UIP pattern (presence of bibasilar honeycombing) on HRCT and extent of honeycombing were factors associated with disease progression. Detection of the typical ‘velcro sounds’ on auscultation or accidental detection (in the context of a lung cancer screen-

ing program) of bibasilar, subpleural reticular or honey-comb changes are two modalities that could be useful for a precocious diagnosis [29, 30].

Acute exacerbation of IPF [31, 32] has become well recognized: it is a rapid deterioration of IPF during the course of the disease that is not due to a particular cause. The 1- and 3-year incidences were reported to be 14.2 and 20.7%, respectively. Nonsmoking and low FVC were recognized as significant risk factors for acute exacerbation [32]. Asymmetrical disease, concomitant emphysema, DLCO <47% of predicted, high modified Medical Research Council scale of dyspnea, high body mass index, decline in FVC at 6 months, pulmonary hypertension detected by echocardiogram and surgical pulmonary resection were reported to be other risk factors for acute exacerbation [33–38]; although right heart catheterization is the only definite method to diagnose pulmonary hypertension, increased right ventricular systolic pressure on echocardiogram is suggestive of pulmonary hypertension, and, given the obvious difficulties in performing right heart catheterization in unwell patients, echocardiography is currently the most practical method for assessing pulmonary arterial pressure [34]. Extent of involvement on HRCT and CT patterns are predictive of survival in acute exacerbation of IPF, with worse survival being associated with multifocal and peripheral HRCT patterns [38].

Table 1. Clinical classification of IPF patients

Phenotype	Characteristic hallmarks
Familial IPF	Genetic mutations (e.g. hTERT, hTERC, surfactant protein genes) Other organs may be involved
Slow progressors	Genetic signature, slow FVC decline Absence of honeycomb remodeling on CT scan
Rapid progressors	Genetic signature, anti-HSP 70 auto-antibodies; rapid FVC decline Honeycomb changes and extended disease on CT scan
CPFE	Peculiar function impairment; pulmonary hypertension; coexisting emphysema
MPO-ANCA + IPF	Autoantibodies (MPO-ANCA); BAL eosinophilia; CT: low attenuation areas
IPF-lung cancer	Peripheral nodules or masses; peculiar histologic phenotypes; emphysema
IPF-acute exacerbation	Risk factors: HRCT asymmetry, concomitant emphysema; DLCO <47%; surgery, pulmonary hypertension

CPFE = Combined pulmonary fibrosis and emphysema; HSP = heat shock protein.

Clinical phenotypes of IPF are reported in table 1. For practical purposes, the need to categorize IPF patients into different subsets with differences in clinical behavior is still unmet; however, clinicians should be aware of the heterogeneity of IPF.

Diagnostic Approach

Diagnosing IPF in daily practice may be challenging as it requires a multidisciplinary approach and there is often a significant delay between the first manifestation of the disease (typically a combination of dyspnea on exertion and dry cough) and the diagnosis [39]. An early and accurate diagnosis of IPF could be critical for a better outcome as an early therapy could reduce the decline in lung function, especially with the forthcoming advent of new specific treatment for this disease [39]. The previous guidelines [40] using major and minor criteria for the clinical (i.e. nonpathological) diagnosis of IPF have been discarded, as it is now clear that, in an appropriate clinical setting, the presence of a classical UIP pattern on the

HRCT scan is sufficient for a diagnosis of IPF to be made [1], thus obviating the need for a lung biopsy. The classical radiological UIP pattern includes: (1) the presence of subpleural abnormalities, predominantly at the lung bases; (2) reticular abnormality; (3) honeycombing with or without traction bronchiectasis, and (4) the absence of features that are inconsistent with a UIP pattern [upper or middle lobe and peribronchovascular predominance, extensive ground glass abnormality (>reticular abnormality), profuse micronodules, discrete multiple cysts distant from areas of honeycombing, diffuse mosaic attenuation/air trapping or consolidation in bronchopulmonary segment(s)/lobe(s)] [1, 41]. The UIP pattern is also characterized by the ‘temporal heterogeneity’, the alternating areas of normal lung parenchyma with patchy interstitial inflammation, fibrosis and honeycombing. This classification divides patients into different categories of ‘diagnostic uncertainty’ (definite, possible and inconsistent UIP) and for those individuals with HRCT features of possible or inconsistent types, further diagnostic evaluation (biopsy) is required [1] (table 2). However, this approach leaves a consistent ‘gray zone’. CT findings which are not typical of or even inconsistent with UIP require histological analysis [42]. Therefore, guidelines suggest a lung biopsy in these patients, even in those with an HRCT scan without honeycombing but all other UIP features, including traction bronchiectasis. Fell et al. [43] tried to address this problem and showed that increasing age and average total HRCT interstitial score of the chest may predict a biopsy confirmation of IPF. Gruden et al. [44] identified specific HRCT patterns in biopsy-proven UIP cases: classic UIP with honeycombing, fibrosis without honeycombing, minimal fibrosis and ground glass opacity. Fibrosis without honeycombing appeared to be diagnostic of UIP in the proper clinical setting; heterogeneity of the pattern contributed to its specificity.

The clinical decision to perform a surgical lung biopsy should be carefully balanced against the risks, since the risks related to this invasive diagnostic procedure are not negligible, with a 30-day mortality of about 1.9–16.7% reported in most studies [45–48]; the risk of mortality is even higher in patients with a histological UIP pattern [46]. A definitive histological diagnosis of the UIP pattern requires: (1) marked fibrosis/architectural distortion with or without honeycombing in a predominantly subpleural/paraseptal distribution; (2) patchy involvement of lung parenchyma by fibrosis, and (3) the presence of fibroblast foci; in addition, the absence of any features considered to be inconsistent with a UIP pattern is also essential [1]. The combination of CT features and histo-

Table 2. Combination of HRCT and surgical lung biopsy (SLB) for the diagnosis of IPF

IPF diagnosis	HRCT pattern	SLB pattern
Definite	Definite UIP	UIP definite, UIP probable, UIP possible, nonclassifiable fibrosis
	Possible UIP	UIP definite or UIP probable
Probable	Possible UIP	UIP possible or nonclassifiable fibrosis
Possible	Inconsistent	UIP definite

Adapted from table 6 of ATS/ERS Statement [1].

logical findings generates again different categories of clinical-radiological and anatomical subtypes: definite IPF; probable IPF; possible IPF and finally no IPF (table 2). *Probable IPF* is the scenario in which CT features are categorized as possible UIP and the histopathology report is possible UIP or nonclassifiable UIP. *Possible IPF* is when CT features are inconsistent with UIP but histopathologically a UIP pattern is found (table 2). This point is still controversial. These two categories may comprise patients with fibrosing nonspecific interstitial pneumonia or chronic hypersensitivity pneumonitis, or even patients with rarer disorders such as pleuroparenchymal fibroelastosis [49, 50] or airway-centered interstitial fibrosis [51]. The differential diagnosis between the UIP-like pattern observed in chronic hypersensitivity pneumonitis and that detected in IPF may be based on the following elements: presence of centrilobular fibrosis, bridging fibrosis and organizing pneumonia in addition to bronchiolitis, granulomas and giant cells [52]. Diagnostic clues derived from the clinical reasoning are not included in the diagnostic approach of current guidelines. Specifically idiopathic nonspecific interstitial pneumonia is an entity that mainly affects nonsmoking women in their 6th decade with an 'autoimmune background' who may develop a full-blown collagen vascular disease during follow-up [53, 54]. A typical CT scan feature, which unfortunately does not present in all cases, is sparing of the subpleural regions. Transbronchial lung biopsy is not recommended based on its low-quality evidence, but this point is controversial. Using this method, tiny specimens representing the centrilobular lung parenchyma may be obtained with a low incidence of side effects (mainly pneumothorax) [55]. A variety of morphological patterns may be detectable on these specimens, e.g. granulomas, organizing pneumonia, diffuse alveolar damage or respi-

Fig. 2. Lung sample obtained by transbronchial cryobiopsy: well-preserved lung parenchyma showing honeycomb changes (arrow), fibroblastic foci (arrowhead) and patchy fibrosis (normal lung side by side with fibrotic tissue). All these findings are diagnostic of the UIP pattern (HE; mid-power).

ratory bronchiolitis [56]. Recently, Berbesu et al. [57] suggested that transbronchial lung biopsy might be more useful than previously recognized in confirming UIP. Combinations of interstitial fibrosis in a patchwork pattern along with fibroblastic foci and/or honeycomb changes were considered diagnostic of UIP. Tomassetti et al. [58] highlighted that the UIP pattern in transbronchial biopsy specimens has a high predictive value but also has a low sensitivity (30%) and a low negative predictive value. Other minimally invasive methodologies, like cryobiopsy, could replace the actual surgical lung biopsy in the near future (although we should be very cautious). Our preliminary unpublished data indicate that the use of cryoprobes eliminates the crushing artifacts and allows to reach the periphery of the secondary pulmonary lobule (fig. 2); furthermore, the interobserver agreement between pathologists for different elementary lesions (i.e. fibroblastic foci, honeycombing or patchy fibrosis) is similar to that previously reported for surgical lung biopsy [59]. Probably in the near future, recognition of peculiar immunohistochemical profiles will increase the specificity of the UIP pattern observed in IPF patients [60]. BAL is useful in excluding other conditions, especially chronic hypersensitivity pneumonitis, which can be suspected when lymphocytosis exceeds 30% [61]. However, sensitivity and specificity of BAL for the diagnosis of IPF remains unknown, and the use of BAL is discour-

aged by current guidelines [1]. In the evaluation of suspected IPF, the guidelines recommend the multidisciplinary approach involving interstitial lung disease specialists, radiologists and pathologists [1]. This approach has been shown to improve diagnostic accuracy of IPF and other interstitial lung diseases [62].

Prognostic Evaluation

The prognosis of IPF is dire, with half of all patients progressing to death from respiratory failure within 3–5 years from initial diagnosis. Results of pulmonary function tests are routinely used as factors predicting survival of IPF patients [63]. A decline in FVC has consistently been shown to be a strong predictor of mortality [64–67] and is frequently used as an end-point in clinical trials. A decline in FVC $\geq 10\%$ within a 6-month period is associated with a nearly 5-fold increase in the risk of mortality [1, 68]. Both absolute and relative changes in FVC are currently used, but Richeldi et al. [69] recently reported that the relative change in FVC maximizes the chances in identifying a 10% decline in FVC without sacrificing prognostic accuracy. A milder decline in FVC could have prognostic significance probably when combined with other indicators such as dyspnea [70]. Therefore, agents that attenuate the decline in FVC are anticipated to play an important role in the management of patients with IPF. Other prognostic factors in clinical trials of IPF include DLCO (a decrease $\geq 15\%$ in the absolute value has been associated with an increased risk of mortality [1]) and a change in alveolar-arterial oxygen tension (a difference ≥ 15 mm Hg after 12 months has been shown to be predictive of survival) [70]. The 6-min walk test is widely

used in clinical practice. A shorter walk distance and delayed heart rate recovery after this test have been associated with an increased risk of mortality [71]. Pulmonary hypertension and brain natriuretic peptide levels are further independent predictors of survival [72–74].

An important topic in the management of IPF is the staging system. Clinical decisions concerning pharmacological and nonpharmacological treatment and inclusion in a transplant list depend on a considerate estimation of the severity of disease and also on the possibility to predict its prognosis [75], which may be based on pulmonary function tests, FVC and DLCO, for example. A recent study suggests a quite easy clinical staging system (GAP) based on gender, age, FVC (% of predicted) and DLCO (% of predicted) to predict mortality up to 3 years [76]. A risk stratification score, which was based on a Medical Research Council Dyspnea Score >3 , 6-min walking distance $\leq 72\%$ of predicted and a composite physiologic index >41 , predicted mortality with high specificity [77].

The overall extent of fibrosis on chest HRCT characterized by a honeycomb pattern and reticulation predict survival [10]. Multiple studies attempted to identify diagnostic and predictive biomarkers of IPF. Until recently, these studies were limited in size and lacked confirmation, but taken together they provided still convincing evidence that changes in blood proteins (e.g. KL-6, SP-A, MMP-7 and CCL-18) or cells (fibrocytes and T-cell subpopulations) are indicative of the presence and outcome of the disease [78–80]. More recently, larger studies have identified gene polymorphisms associated with IPF, as well as protein markers and integrated clinical and molecular prediction rules to predict outcome in patients with IPF [81].

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