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REVIEW

Towards a better diagnosis of idiopathic pulmonary fibrosis

D. Valeyre

ABSTRACT: Idiopathic pulmonary fibrosis (IPF) is the most common of the idiopathic interstitial pneumonias, and poses significant clinical challenges. IPF diagnosis is based on clear-cut computed tomography (CT) and histopathological criteria, in an appropriate clinical context. The diagnostic criteria include: 1) exclusion of known causes of interstitial lung disease (including connective tissue disease); 2) usual interstitial pneumonia pattern on high-resolution CT in patients not subjected to surgical lung biopsy; and 3) specific combinations of high-resolution CT with pathological patterns in case of surgical lung biopsy. Improved diagnosis of IPF may help physicians to reduce the delay before an accurate diagnosis is made and increase patient awareness and access to adequate information, follow-up and treatment.

KEYWORDS: Diagnosis, idiopathic pulmonary fibrosis

Idiopathic interstitial pneumonias (IIPs) are a group of diseases also known as interstitial lung diseases (ILDs) in the absence of any known cause and of clinical manifestations other than limited to the lung [1]. Idiopathic pulmonary fibrosis (IPF) is the most common of the IIPs, accounting for 50–60% of diagnosed cases [2] and represents both the most frequent and most severe of all ILDs. Epidemiological studies suggest that IPF is more common in males with onset usually in middle or older age (prevalence peaks at age 65–79 yrs) [2], but it has no distinct geographic distribution and does not distinguish between particular races or ethnic groups [3]. It is usually sporadic but the notion of prior familial cases can be found in 3–10% of cases. The main known risk factors that are associated with disease development include smoking (either current or past), some environmental factors, and genetic predisposition [3].

IPF is characterised by a distorted alveolar–capillary barrier architecture (several elements are involved including epithelial and endothelial cell apoptosis [4], infiltration of inflammatory cells into interstitial and alveolar spaces, fibroblast proliferation and excessive deposits of interstitial collagen) leading to an impaired gas exchange [5, 6]. The specific molecular and cellular mechanisms, cause of disease onset and disease progression are still unknown. Despite some limits, animal models of pulmonary fibrosis can be of invaluable help for evidencing some of the pathogenic processes at play in IPF [7]. IPF is now considered as a distinct entity with lesions that vary in age and location. The established view that IPF was a disease in which fibrosis was directly caused by chronic inflammation has been challenged by two main arguments: 1) clinical measurements of inflammation failed to correlate with stage or outcome, and 2) potent anti-inflammatory therapy does not improve outcome [8].

The disease course in IPF is variable. Some patients may remain stable for long periods of time but a significant proportion demonstrate slow progression and others experience acute exacerbations leading to respiratory failure and death. In some patients, pulmonary hypertension may develop as a consequence of, or disproportionate to, the underlying lung disease and may explain a clinical deterioration despite preserved pulmonary lung function [9]. As a whole, median survival is estimated at 24–36 months and a 5-yr survival is found in $\leqslant$20% of patients.

IPF diagnosis is based on clear-cut computed tomography (CT) and pathological criteria in an appropriate clinical context [10]. However, diagnosing IPF in daily practice remains very challenging. There is often a long delay between the first manifestations of the disease and its accurate diagnosis. Moreover, an accurate diagnosis with a sufficient confidence level is not achieved in some cases. However, a correct diagnosis of IPF, as early as possible, may offer patients more optimal management [1].

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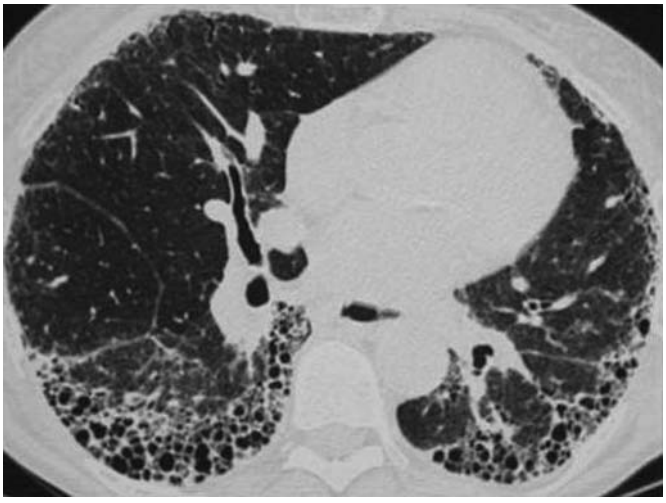

FIGURE 1. Usual interstitial pneumonia pattern on high-resolution computed tomography (M. Brauner, Dept of Radiology, Hospital Avicenne, Bobigny, France; personal communication).

DIAGNOSTIC CRITERIA FOR IPF

The first step, based on background investigation and physical examination, is to exclude known causes of ILD, *e.g.* certain drug toxicities, environmental exposures and connective tissue disease-associated ILD. Another important step based on thoracic CT and pathology consists of differentiating IPF from other IIPs, particularly nonspecific interstitial pneumonia (NSIP), but also desquamative interstitial pneumonia, respiratory bronchiolitis-associated ILD, acute interstitial pneumonia, cryptogenic organising pneumonia and lymphocytic interstitial pneumonia [1].

Findings on chest radiographs (CXR) of patients with IPF include peripheral reticular opacities that are most profuse at the lung bases [11]. However, several studies have evidenced the superior accuracy of high-resolution CT (HRCT) compared to CXR, since HRCT can identify abnormalities before they become visible on a CXR and confer more specificity [12], due to thin-section HRCT which increases spatial resolution and facilitates the visualisation of parenchymal detail to the level of the pulmonary lobules. The finding of a usual interstitial pneumonia (UIP) pattern on HRCT may be sufficient to diagnose IPF, with no need for surgical lung biopsy (SLB). A UIP pattern on HRCT relies on the following four criteria: 1) subpleural basal predominance; 2) reticular abnormality; 3) honeycombing with or without traction bronchiectasis; and 4) absence of features known to be inconsistent with the UIP pattern, *e.g.* condensations, nodules or pre-eminent ground glass (fig. 1) [13, 14]. If the observer is experienced, the accuracy of a diagnosis of IPF made according to HRCT criteria together with the clinical information is ~90% [1]. In clinical practice, HRCT scanning can provide a confident, highly specific diagnosis for half to two-thirds of IPF patients [15]. Moreover, the extent of disease observed on HRCT correlates with fibrosis and physiological impairment [16].

In the absence of a UIP pattern on HRCT, an SLB should be performed taking into consideration the patient's age, pulmonary function and absence of other specific contraindications. A typical UIP pattern at histopathology combines marked fibrosis with architectural distortion with or without honeycombing in a predominantly subpleural and paraseptal distribution, and patchy involvement of the lung parenchyma by fibroblast foci. Furthermore, the presence of small interstitial fibroblastic foci, frequently found at the periphery of remodelled areas, and the alternation of fibrosing areas and normal/subnormal parenchymal areas are two very important pathological criteria for the diagnosis. For a UIP pattern to be confirmed, features suggesting any alternative diagnosis must be lacking (fig. 2) [10]. If the patient has undergone SLB, the diagnosis will eventually rely on specific combinations of HRCT and pathological data evidencing more or less typical UIP patterns, respectively (table 1). This requires a multidisciplinary dynamic approach (pneumologist, radiologist and

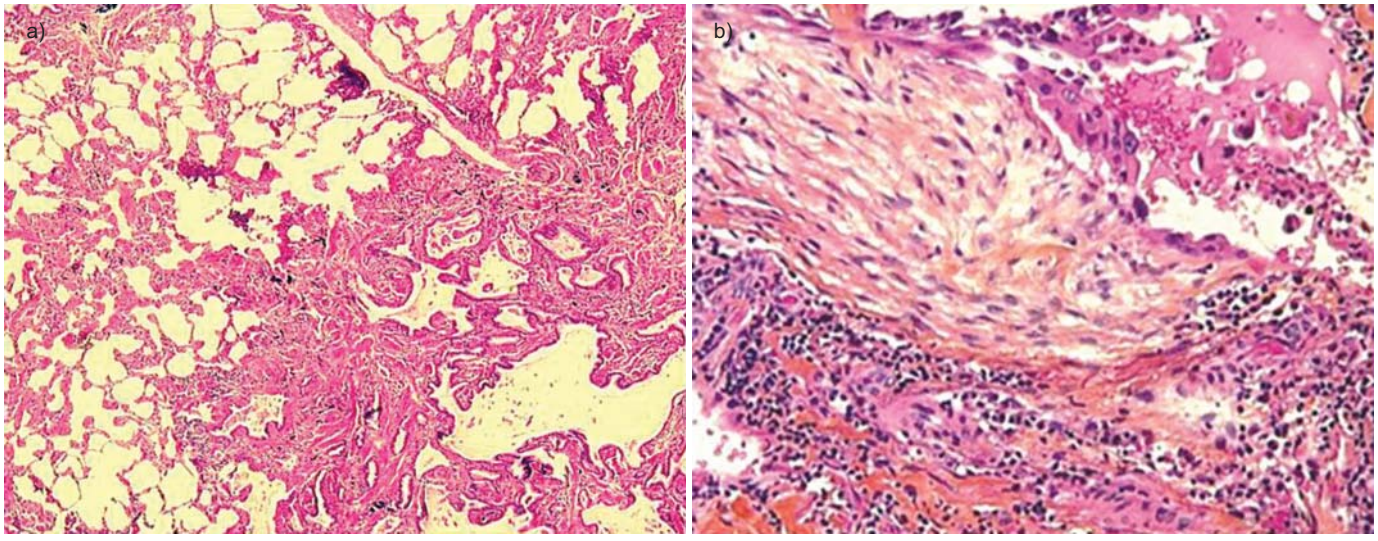

FIGURE 2. Usual interstitial pneumonia pattern on histopathology showing alternation of fibrosing areas and a) normal/subnormal parenchymal areas and b) fibroblastic foci (M. Kambouchner, Dept of Pathology, Hôpital Avicenne, Bobigny, France; personal communication).

TABLE 1 Diagnosis of idiopathic pulmonary fibrosis based on patterns discovered in high-resolution computed tomography (HRCT) and histopathology investigations

HRCT pattern	Histopathology pattern				
	UIP	Probable UIP	Possible UIP	Non-classifiable fibrosis	Not UIP
UIP	Yes	Yes	Yes	Yes	No
Possible UIP	Yes	Yes	Probable	Probable	No
Not UIP	Possible	No	No	No	No

UIP: usual interstitial pneumonia.

pathologist expert on ILD) which has been shown to improve diagnosis [17, 18].

CHALLENGES IN DIAGNOSING IPF IN DAILY PRACTICE

Delay in diagnosis

Based on informal surveys and the author's own clinical experience, some preliminary observations may be made regarding the timeliness of IPF diagnosis. Suspicion of IPF too often arises several months after the first manifestations of the disease. Typically, the first clinical features that may suggest IPF (subtle cough and/or dyspnoea) are often overlooked in the context of past or current smoking habits and/or ageing. During this phase, the physician often fails to suspect that the earlier manifestations could be due to IPF. Another important cause of delay in IPF diagnosis is secondary to the behaviour of some physicians who consider it good practice to make an approximate diagnosis of fibrosing pneumonitis, on the grounds that more differentiation among IIP will not significantly impact on the care of patients. At present, the proportion of patients with late-diagnosed IPF has not been well studied, either within or across national health systems.

The difficulty of confirming a diagnosis

Although diagnostic guidelines are available [1] they may not be consistently applied by physicians for a number of reasons. For example, the patient may not be investigated thoroughly enough to rule out alternative diagnoses. Exposure to causes of ILD simulating IPF on HRCT can be overlooked. The absence of a cautious physical examination can lead a physician to fail to recognise a connective tissue disease. For instance, without an adequate review of a patient's medical history and past documents a stage IV sarcoidosis could be overlooked, as in rare cases the CT scan can reveal honeycombing mimicking a basal and peripheral UIP pattern [19–21]. The CT and biopsy specimens may not be of a sufficient quality to confirm the diagnosis. The radiologist and/or the pathologist may be insufficiently experienced. The omission of multidisciplinary discussion [17, 18] may lead to failure to identify IPF. Finally, subjective findings of HRCT such as honeycombing may show significant inter-observer variability, making the diagnosis difficult to confirm. It is important to emphasise that radiologists with differing levels of experience and expertise may interpret radiographic images differently. A multinational European study has found that although the overall accuracy of a clinical diagnosis of IPF in expert centres is good (87.2%), the level of agreement within the expert panels that assessed the diagnoses was only fair to moderate [22]. Thus, it is essential to have a multidisciplinary discussion with a pneumologist, a radiologist and a pathologist who are familiar with ILD.

THE NEED FOR EARLY DIAGNOSIS

Early diagnosis of IPF offers benefits to patients, including adequate information, lung transplantation enrolment, avoidance of inappropriate drugs (*e.g.* steroids and immunosuppressives), and access to trials and new treatments. Healthcare providers should, therefore, be mindful of IPF as a potential diagnosis particularly in newly presenting patients who are aged >55 yrs and in patients who are smokers, ensuring that initial symptoms such as cough and dyspnoea are not considered as nonsignificant, but instead trigger the appropriate investigations. Moreover, faced with the aetiological diagnosis of ILD, IPF (the most frequent ILD) has to be considered as one of the most probable hypotheses, particularly in patients aged >55 yrs, according to Bayes' theorem.

IMPROVING DIAGNOSIS

The pillars of an improved IPF diagnosis

The guidelines (exclusion of alternate diagnosis, combination CT and histopathological evaluation, and multidisciplinary discussion) have to be strictly applied. HRCT sensitivity may also be enhanced if the scan is performed with the patient in the prone position. The availability of validated clinical diagnosis predictors could help to determine the accurate estimation of IPF diagnosis probability at an individual level, allowing a more confident diagnosis and reducing the need for pulmonary biopsy, as suggested by the very convincing study by FELL *et al.* [23]. However, confirmation of the results has to be obtained from further series before application in clinical practice.

Some technical improvements could arise from the availability of new tools, although currently there is no evidence for such a contribution. Post-processing tools could help differentiate between honeycombing and bronchiectasis when both are discussed on HRCT [24]. Computer-aided diagnosis (threshold segmentation method or texture analysis) may also be a new useful contribution for the future [25].

Even though they are no longer part of the main IPF diagnosis recommendations, both bronchoalveolar lavage (BAL) and pulmonary function testing remain interesting tools for specific conditions.

TABLE 2 Candidate biomarkers for idiopathic pulmonary fibrosis (IPF)

KL-6	A high-molecular weight glycoprotein highly expressed in tissue sections from patients with ILDs [35]. Elevated levels of serum KL-6 have been found in patients with clinically confirmed progression [33] and have been associated with increased mortality risk [36, 37].
SP-A and SP-D	C-type lectins produced mainly by alveolar epithelial type II cells. Serum levels of SP-A and SP-D are increased in IPF (but also other pulmonary diseases) [38–43] and are strongly predictive of mortality [44].
CD28	A co-stimulatory molecule normally expressed on most CD4+ T-cells. Down regulation of CD28 on peripheral CD4+ T-cells has been associated with increased risk of lung transplantation within 1 yr [45].
Circulating fibrocytes	Thought to be progenitors for fibroblasts participating in the pathogenesis of lung fibrosis [46, 47]. Circulating fibrocytes were increased in IPF, with significant further increases during acute exacerbations. A proportion of >5% of peripheral blood leukocytes was associated with increased mortality in these patients [48].
Angiogenic factors	Thought to play a role in the pathogenesis of IIPs. Elevated levels of the potent angiogenic factors VEGF and IL-8 have been associated with IPF and progressive disease [49, 50].
MMPs	Matrix degrading enzymes thought to be critically involved in the pathology of pulmonary fibrosis [51–53]. Plasma MMP1 and MMP7 levels are significantly elevated in IPF patients [54]. MMP7 levels are consistently elevated in asymptomatic *versus* symptomatic IPF, indicating that it may be a marker for early disease [55].
Oxidative stress	May be implicated in the epithelial dysfunction underlying pulmonary fibrosis [56]. Oxidant burden has been shown to be elevated in the serum [57] of IPF patients.

KL-6: Krebs von Lungen factor-6; SP: surfactant protein; MMP; matrix metalloproteinase; ILD: interstitial lung disease; IIP: idiopathic interstitial pneumonia; VEGF: vascular endothelial growth factor; IL: interleukin.

The value of BAL in excluding other disorders in the American Thoracic Society/European Respiratory Society algorithm for the diagnosis of IPF needs to be evaluated [26, 27]. However, BAL findings support the ruling out of other potential differential diagnoses, such as hypersensitivity pneumonitis, through the demonstration of a lymphocytosis >30%. In the follow-up of patients with IPF, BAL is indicated whenever new infiltrates develop suggesting infection or acute exacerbation of IPF. However, serial BAL to monitor the course of disease cannot be routinely recommended [28].

Serial changes in pulmonary function tests (PFTs) at 6 or 12 months have greater prognostic value than baseline data [1, 29–33]. "Significant decline" is defined as a reduction from baseline values of 10% for forced vital capacity and 15% for diffusing capacity of the lung for carbon monoxide ($D_{L,CO}$). "Marginal declines" (*i.e.* declines that do not meet the threshold value) may nevertheless indicate real disease progression, especially when accompanied by increased symptoms or other evidence [34]. ZAPPALA *et al.* [34] have remarked that if real disease progression could be defined in terms of marginal PFT thresholds, then this would allow increased recognition of clinically relevant disease behaviour. For example, evolution of pulmonary function as evidenced by PFTs may assist in differential diagnosis, with significant or marginal declines of forced vital capacity (>5%) and $D_{L,CO}$ (>7.5%) being significantly more common in IPF, compared to NSIP [34].

Biomarkers are a potentially valuable tool in diagnosing and treating patients with IPF. However, currently identified candidate biomarkers (table 2) present a number of drawbacks. Their specificity for a single interstitial lung disease is poor. Most have been tested only in limited numbers of patients and have not been prospectively validated. In addition, it is not yet clear whether they will provide useful information in addition to that provided by existing tests. For example, Krebs von Lungen factor-6 (KL-6) seems to be a good surrogate marker for pulmonary fibrosis, but at present cannot replace conventional diagnostic procedures [58]. Although it appears unlikely that a biomarker alone will become a valuable diagnostic tool, a combination of several biomarkers may be a promising direction for research. For example, the composite measurement of five serum proteins has been shown to correctly differentiate between IPF patients and controls, with a sensitivity of 98.6% and specificity of 98.1% [55, 58].

CONCLUSION

IPF is a severe condition with a worse prognosis than all other ILDs. The accuracy and timeliness of IPF diagnosis must be improved in order to improve treatment opportunities and outcomes. However, there is often a long delay before a diagnosis is made and today the diagnosis is too often insufficiently secure or accurate. In order to achieve this goal of a better diagnosis, a range of issues need to be addressed. The guidelines (exclusion of alternate diagnosis, optimal interpretation of CT, combination CT and histopathological evaluation with a multidisciplinary discussion implying a pulmonologist, a radiologist and a pathologist expert on ILD) have to be strictly applied. Improvements could come from the availability of more accurate and validated diagnosis predictors, new tools optimising CT efficacy and new more specific biomarkers.

STATEMENT OF INTEREST

D. Valeyre has participated as an investigator and/or member of a steering committee in several trials on idiopathic pulmonary fibrosis (INSPIRE, CAPACITY, BUILD1, BUILD3, MUSIC and BIBF).

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