SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2015; 32; Suppl. 1: 4-9

Challenges in the classification of fibrotic ILD

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Abstract. According to current international guidelines the idiopathic interstitial pneumonias (IIPs) are grouped into three categories; major, rare, and unclassifiable. Idiopathic pulmonary fibrosis (IPF) is one of the major IIPs and has been recognised as a distinct clinical entity since 2001. This has led to significant advances in our understanding and treatment of the disease and to the identification of new therapeutic targets. While multidisciplinary team assessment yields a definite diagnosis in many cases of interstitial lung disease (ILD), 15–25% of patients remain unclassifiable. This can be due to inadequate clinical, pathological, or radiological data (e.g., where a biopsy is not performed) or because results of investigations show major discrepancies, overlapping features, or mixed patterns. Patients with unclassifiable disease tend to be of similar age to those with IPF and older than those with connective tissue disorders. Survival of patients with unclassifiable disease is intermediate between IPF and non-IPF ILD. There is no single recommended treatment for patients with unclassifiable disease. However, the ILD-GAP index has recently been validated in this group and can risk-stratify patients based on four easily measurable variables. "Disease behaviour classification" (DBC) is an alternative, pragmatic approach to managing patients with unclassifiable disease. The ILD-GAP index has been shown to provide strong prognostic information in these hard-to-treat patients. In the future, new diagnostic tools such as protein biomarkers may become available to help guide therapeutic decisions. *(Sarcoidosis Vasc Diffuse Lung Dis 2015; 32; Suppl 1: 4-9)*

Key words: idiopathic interstitial pneumonia; interstitial lung diseases; idiopathic pulmonary fibrosis; classification; unclassifiable disease

Introduction

Recent years have witnessed considerable progress in the classification of idiopathic interstitial pneumonias (IIPs). These advances have improved diagnostic accuracy and better-informed treatment decisions in these difficult-to-treat conditions (1,2).

The benefits of increased specificity in classification are particularly evident when one looks at improvements that have taken place in the management of idiopathic pulmonary fibrosis (IPF), the most prevalent of the IIPs. IPF has been recognised as a distinct clinical entity since 2001 and our increased understanding of its singular clinical features has helped foster better outcomes. Pirfenidone and nintedanib have now emerged as effective agents in slowing disease progression and preserving lung function in IPF. In addition, the results of the PANTHER trials indicate that triple therapy with prednisone, azathioprine and N-acetylcysteine (NAC), while beneficial to patients with pro-inflammatory conditions such as hypersensitivity pneumonitis (HP), is actually harmful to patients with IPF and that NAC monotherapy confers no advantage (3,4).

With the participation of multi-disciplinary teams, interstitial lung disease (ILD) can now be de-

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finitively diagnosed in the majority of cases. However a sizeable proportion of IIP patients (15–25%) remain unclassifiable (5-9). This can be due to inadequate clinical, pathological, or radiological data (e.g., where a biopsy is not performed) or because results of investigations show major discrepancies, overlapping features, or mixed patterns (10).

Here, we will provide a brief historical update on IIP classification and move on to focus on what is actually known about unclassifiable IIPs. We will then review the evidence associated with a new prognostic model that is being developed to improve management in patients with unclassifiable ILD.

Update on classification of IIPs

The most recent classification of idiopathic interstitial pneumonias (IIPs) is set out in the 2013 statement from the American Thoracic Society and the European Respiratory Society (1,2). According to this scheme, IIPs are subdivided into three groups: major IIPs, such as idiopathic pulmonary fibrosis (IPF); rare IIPs such as pleuroparenchymal fibroelastosis, and unclassifiable IIPs (Table 1).

The majority of new knowledge that has accumulated over the past 15 years has been associated with IPF, the most common IIP. IPF was first recognised as a distinct clinical entity in 2001 as part of the reclassification of IIPs by the ATS/ERS multidisciplinary consensus committee (11). This document was the first to formally confine a diagnosis of IPF to individuals with the histological lesion of usual interstitial pneumonia (UIP) in the absence of any definable cause for fibrosing lung disease. Before 2001, IPF had different names in different countries and the terms typically included all of the fibrosing ILDs, without discriminating between histological subtypes. The development of a narrow definition of IPF as a disease entity has been highly beneficial in advancing understanding of the disease and its management.

We now know that all patients with IPF will inexorably progress but that the rate of disease progression varies among individuals (12). Some patients will deteriorate rapidly and die within a few months of diagnosis while others will have stable disease for many years. There are also some patients with IPF who will experience acute exacerbations, catastrophic events with a very high mortality rate.

Another advance in the field of IPF has been the growth of evidence from large, randomised clinical trials (RCTs). Prior to the 2001 guideline, approximately 200 patients had taken part in international RCTs; in the decade between 2000 and 2010, just under 3000 patients participated, worldwide, in RCTs; and in the current decade, more than 3000 patients have already been enrolled in trials. Having a more explicit definition of IPF enabled clinical trials to be conducted, which in turn has culminated in the approval of effective therapies for a condition which was hitherto untreatable.

The past decade has also seen improvements in our comprehension of the pathophysiology of IPF. While it was previously thought that IPF developed

Table 1. Revised American Thoracic Society/European Respiratory Society classification of idiopathic interstitial pneumonias: Multidisciplinary diagnoses (2)

Major idiopathic interstitial pneumonias	Rare idiopathic interstitial pneumonias	Unclassifiable idiopathic interstitial pneumonias*
• Idiopathic pulmonary fibrosis • Idiopathic non-specific interstitial pneumonia • Respiratory bronchiolitis – interstitial lung disease • Desquamative interstitial pneumonia • Cryptogenic organizing pneumonia • Acute interstitial pneumonia	• Idiopathic lymphoid interstitial pneumonia • Idiopathic pleuroparenchymal fibroelastosis	

* Causes of unclassifiable idiopathic interstitial pneumonia include (1) inadequate clinical, radiologic, or pathologic data and (2) major discordance between clinical, radiologic, and pathologic findings that may occur in the following situations, (a) previous therapy resulting in substantial alteration of radiologic or histologic findings (e.g., biopsy of desquamative interstitial pneumonia after steroid therapy, which shows only residual non-specific interstitial pneumonia; (b) new entity or unusual variant of recognised entity, not adequately characterised by the current ATS/ERS classification (e.g., variant of organising pneumonia with supervening fibrosis); and (c) multiple high-resolution computed tomography and/or pathologic patterns that may be encountered in patients with idiopathic interstitial pneumonia.

as a consequence of chronic inflammation, it is now apparent that IPF is a disease of aberrant wound healing occurring in genetically susceptible individuals (13). Instead of resolution of injury, an abnormal repair process in people with IPF leads to overexpression of cytokines and growth factors that have a proliferative profibrotic effect in the lungs. This new insight into the pathogenesis of IPF has contributed to the development of agents such as pirfenidone and nintedanib that exhibit anti-fibrotic effects, and which have been demonstrated to slow disease progression and preserve lung function in patients with IPF (14-16).

In spite of this progress, there remain unresolved challenges in the diagnosis and management of IPF. Importantly, not all cases of IPF are readily identifiable as IPF. It is possible for a patient to have an HRCT scan that does not exhibit a usual interstitial pneumonia (UIP) pattern, but for a definite UIP pattern to reveal itself in a subsequent surgical lung biopsy and follow the typical disease course of inexorable decline. In addition, UIP does not necessarily signal IPF. While the primary clinical presentation of UIP is IPF, other conditions can give rise to an appearance that is indistinguishable from IPF. These include asbestosis, rheumatoid arthritis, sarcoidosis, scleroderma, and chronic hypersensitivity pneumonitis (Figure 1).

Unclassifiable ILD

Beyond IPF, a further challenge is that a significant proportion of ILD patients have unclassifiable disease, based on current classification. While these patients present with pulmonary fibrosis, disease manifestations do not allow them to be definitively categorised. With regard to terminology, it is important to distinguish between patients who are "unclassified" because they have not yet been fully assessed and those who are "unclassifiable" following comprehensive evaluation by the MDT.

Patients with unclassifiable ILD pose a major challenge, particularly if they have severe disease. The 2013 ATS/ERS guidelines formally recognised that it is not possible to categorise all ILD patients and defines "unclassifiable ILD" as one of three subcategories of IIP, the others being "major" and "rare" IIPs (2).

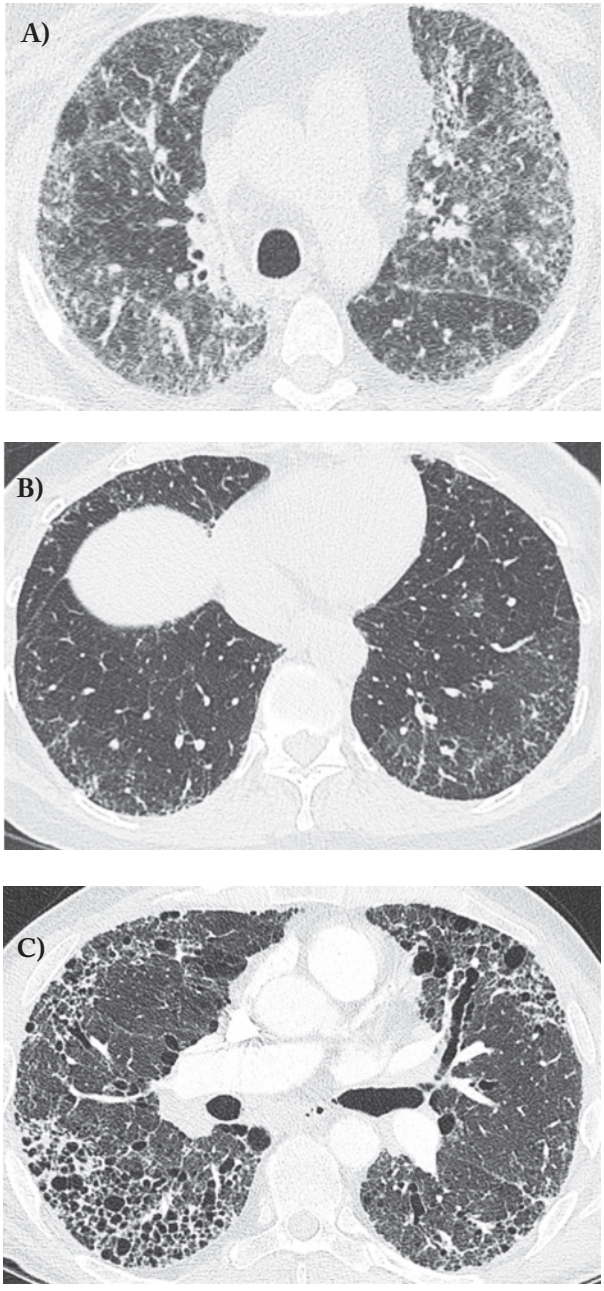

Fig. 1. Three biopsy and MDT confirmed cases of IPF demonstrating that the HRCT can in some cases be impossible to characterise (A and B) with only case C fulfilling the CT criteria outlined in the current international consensus guidelines

It is thought that prognosis in unclassifiable patients may be slightly more favourable compared to those with IPF but it is nonetheless poor (8). Importantly, individuals with unclassifiable ILD lack a definitive diagnosis despite full diagnostic evaluation

Table 2. Main reasons for interstitial lung disease being unclassified (10)

No biopsy performed or biopsy non-contributory (unclassified or unclassifiable clinical/radiological condition)
- Biopsy not proposed by physician (stable or mild disease with biopsy outweighing the anticipated benefit; other reasons)
- Contraindication or too old to biopsy
- Biopsy denied by the patient
- Sampling not contributory (insufficient tissue, inadequate site of biopsy, end-stage lung disease)

Overlapping histological features (unclassifiable histology)
- Non-specific interstitial pneumonia – usual interstitial pneumonia
- Hypersensitivity pneumonitis – usual interstitial pneumonia
- Others

Major discrepancy between clinical imaging and histological features (unclassifiable clinical/radiological/pathological condition)
- Stable disease – usual interstitial pneumonia histological pattern
- Other situations

Uncertain aetiology (unclassifiable clinical condition)
- Unclear diagnostic boundary with connective tissue disease – interstitial lung disease
- Unclear diagnostic boundary with hypersensitivity pneumonias

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with the consequence that they are denied clear information on prognosis and optimal therapy.

The prevalence of unclassifiable ILD is generally estimated at 15–25% (5-9). There are several reasons why a patient may be unclassifiable (Table 2) (10). Inadequate clinical, pathologic or radiologic data can make it impossible to sub-classify patients. For example, a biopsy may not be performed because the risk-benefit balance is not supported, such as in patients with stable or mild disease, or in very old or severely ill patients. In other cases, a biopsy may be performed, but it may not be informative due to insufficient tissue, sampling errors or the presence of end-stage fibrosis.

Other common reasons for patients being deemed unclassifiable are major discrepancies between any of clinical history, radiological appearance or histology or the presence on radiology or biopsy of overlapping features or mixed patterns, which make a confident diagnosis impossible. Previous therapy may cause substantial alterations in the radiologic or histologic findings suggestive of a new disease entity or atypical presentation of an already recognised disease. In other situations, diagnostic features may overlap with those of other diseases, such as CTD or other systemic disease.

In a study of 228 patients with ILD, 29 were considered to have "undefined ILD" (6). These patients had a mean age of 65 years, similar to patients diagnosed with IPF, and were significantly older than patients with connective tissue disorder (CTD). Men and women were approximately equally affected by undefined ILD and CTD, whereas IPF showed a strong male predominance. In a separate study, patients with unclassifiable ILD were less likely to be smokers and more likely to be female compared with patients with IPF (8). Similarly, in a Danish study, patients with unclassifiable ILD were of similar age to those with IPF but more likely to be female and less likely to be smokers (9). In all three studies, survival in patients with unclassifiable ILD was intermediate between patients with IPF and non-IPF controls, with a mean 5-year survival of 57–70% (Table 3).

Table 3. Baseline patient characteristics and 5-year survival rates from three studies of patients with unclassifiable ILD (6,8,9)

	Thomeer (6)	Ryerson (8)	Hyldgaard (9)
Age (SD)	65 (14)	68 (13)	59 (14)
Female gender, %	90	47	55
Ever smokers, %	-	63.6	71
FVC % predicted (SD)	76 (21)*	69 (22)	71 (22)
DLCO % predicted (SD)	47 (21)	48 (20)	53 (23)
5 year survival, %	69.5	69	57

* VC % predicted.

Prognostic models in unclassifiable ILD

Recently, a prognostic score was developed for predicting survival in patients with ILD. Known as the modified ILD-GAP Index, it is a simple risk-prediction model that assigns points for four variables – ILD subtype, gender, age, and lung function – to yield a total score ranging from 0 to 8 (17).

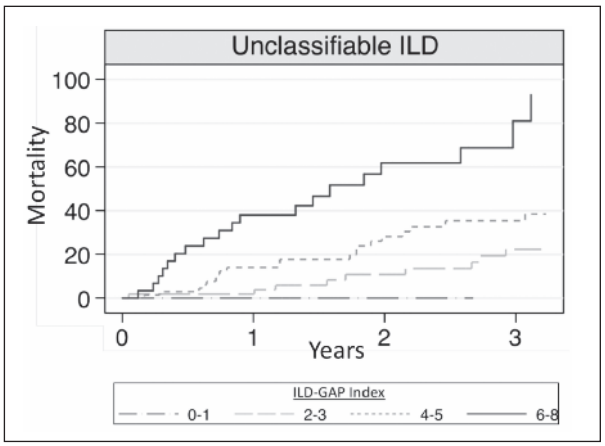

Fig. 2. Mortality in unclassifiable ILD stratified by the ILD-GAP Index (17). Abbreviations: CT-ILD, connective tissue disease-associated ILD; HP, hypersensitivity pneumonitis; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; NSIP, non-specific interstitial pneumonia.

The ILD-GAP Index has been shown to perform well in patients with all subtypes of ILD, including unclassifiable disease (Figure 2).

Among patients with unclassifiable ILD, 3-year mortality is around 80% in patients with the highest ILD-GAP score (6–8 points) versus around 20% in those with the lowest score (0–1 points) (17). The ILD-GAP model thus seems capable of risk-stratifying patients with unclassifiable disease from diverse populations based on four easily measured variables. It may prove helpful to clinicians when facing decisions about how best to manage these patients – for instance, whether to opt for lung transplantation or palliative treatment.

An alternative, pragmatic approach to clinical decision-making involves looking at the consequences of the disease and how to manage them. This strategy, known as "disease behaviour classification" (DBC), is described in the 2013 ARS/ERS guidelines (2). It classifies patients into five groups according to their clinical behaviour and for each group, outlines different treatment goals and monitoring strategies (Table 4). Managing patients according to disease behaviour essentially describes how clinicians approach patients and base decisions on all available clinical information: e.g. age, lung function, results of HRCT, bronchoalveolar lavage

Table 4. Idiopathic interstitial pneumonias: classification according to disease behaviour* (2)

Clinical Behaviour	Treatment Goal	Monitoring Strategy
Reversible and self-limited (e.g., many cases of RB-ILD)	Remove possible cause	Short-term (3–6 mo) observation to confirm disease regression
Reversible disease with risk of progression (e.g., cellular NSIP and some fibrotic NSIP, DIP, COP)	Initially achieve response and then rationalise longer term therapy	Short-term observation to confirm treatment response. Long-term observation to ensure that gains are preserved
Stable with residual disease (e.g., some fibrotic NSIP)	Maintain status	Long-term observation to assess disease course
Progressive, irreversible disease with potential for stabilisation (e.g., some fibrotic NSIP)	Stabilise	Long-term observation to assess disease course
Progressive, irreversible disease despite therapy (e.g., IPF, some fibrotic NSIP)	Slow progression	Long-term observation to assess disease course and need for transplant or effective palliation

RB-ILD, respiratory bronchiolitis-interstitial pneumonia; NSIP, non-specific interstitial pneumonia; DIP, desquamative interstitial pneumonia; COP, cryptogenic organising pneumonia.

* The distinctions in Table 4 are made by assimilating several factors: (1) A confident multidisciplinary diagnosis that often identifies the expected pattern of disease behaviour (e.g., IPF). However, in other idiopathic interstitial pneumonias (e.g., NSIP) more than one pattern of behaviour is possible; (2) disease severity, based on lung function and/or HRCT. In severe NSIP a progressive irreversible course is frequent; (3) evaluation of potentially reversible and irreversible features based on review of the HRCT and biopsy if available; and (4) short-term disease behaviour. Disease behaviour must be refined over time in individual patients considering longitudinal changes in disease severity.

(BAL) and biopsy, signs of CTD, response to previous therapy and course of disease.

The two case studies following this review were selected to shed further light on the difficulties that are still inherent in the classification of fibrotic ILD in clinical practice.

Conclusions

Despite major advances in our understanding of IIPs, unclassifiable disease is common in clinical practice and occurs most often due to the absence of lung biopsy or conflicting test results. The prognosis of patients with unclassifiable disease is intermediate between that of IPF and non–IPF ILD, at approximately 70% after 5 years. To date, we are unable to provide these patients with a confident diagnosis and treatment direction remains unclear.

However, tools such as the ILD-GAP Index, which predicts mortality based on four easily measured clinical variables, or DBC, which predicts likely disease behaviour based on all available clinical information have shown success in helping to guide treatment decisions in unclassifiable ILD patients. The modified ILD-GAP approach has been shown to have strong prognostic value and may prove helpful in managing this under-served group of patients.

Promising new diagnostic techniques may one day be able to help guide the management of patients with unclassifiable disease. We are beginning to identify protein signatures that accompany disease progression in the blood of patients with IPF and these may be able to indicate whether we should be using anti-fibrotic therapies, such as pirfenidone or nintedanib, or anti-inflammatory, immunomodulatory drugs.

Finally, a critical step forward will be to conduct clinical trials of anti-fibrotic drugs in patients with non-IPF ILDs. Patients with unclassifiable pulmonary fibrosis do not currently meet eligibility criteria for anti-fibrotic clinical trials, so it is unknown how they will respond to these agents. Given that there is a solid rationale for believing that anti-fibrotics could benefit some unclassifiable patients, it is important that we devise a means to test this hypothesis.

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This article is based on the proceedings of the Advance in IPF Research (AIR) meeting 2014 (Copenhagen, Denmark), which was sponsored by InterMune International AG, a wholly owned Roche subsidiary. Medical writing assistance was provided by professional medical writers at IntraMed International (Milan, Italy) and funded by InterMune International AG, a wholly owned Roche subsidiary