Unclassified or unclassifiable interstitial lung disease: confusing or helpful disease category?

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Unclassified or unclassifiable interstitial lung disease http://ow.ly/mtj0i

Since the seminal report by Averill A. Liebow in 1968 [1] of the first classification of idiopathic interstitial pneumonias (IIPs), consisting of five entities including "usual or classical interstitial pneumonia" (UIP), a secure diagnosis has, until recently, required histopathological evaluation. A histologically based classification might appear paradoxical, as a biopsy is performed in only a minority of the cases in most centres. Nevertheless, this approach has provided essential guidance for clinicians with regard to: 1) possible aetiology (*e.g.* a pattern of nonspecific interstitial pneumonia (NSIP) is not necessarily idiopathic but may be related to connective tissue disease (CTD), exposure to drugs, or antigens); 2) prognostic evaluation, largely based on the distinction between idiopathic pulmonary fibrosis (IPF) and the clinical entities associated with other histological patterns; and 3) management, with a strategic choice between anti-inflammatory/immunosuppressive therapy, and, in IPF, an anti-fibrotic approach, with pirfenidone currently the only commercially available agent with an established treatment effect.

Until recently, major changes to the Liebow classification have been confined to: 1) the removal of giant cell interstitial pneumonitis (which results from exposure to hard metals, especially cobalt and tungsten carbide, and is no longer considered to be idiopathic) [2]; 2) a clearer definition of IPF, which was something of an umbrella term in early series [3], prior to the American Thoracic Society (ATS) redefinition of IPF in 2000 [4]; 3) the recognition of bronchiolitis obliterans organising pneumonia as a clinical pathological entity [5], later to become organising pneumonia [6], and its distinction from diffuse alveolar damage; and 4) the identification of respiratory bronchiolitis associated with interstitial lung disease (ILD) [7] and of NSIP [8]. The 2002 ATS/European Respiratory Society (ERS) international multidisciplinary consensus classification of the IIPs [6] has recently been revised [9], with the most important changes in the update being the distinction between the major IIPs and rare entities (lymphocytic interstitial pneumonia and a new disease, idiopathic pleuroparenchymal fibroelastosis), and the proposal of a "disease behaviour classification", with particular reference to cases that are difficult to classify.

The problem of unclassifiable idiopathic ILD was acknowledged in 2002 [6] but was not formally individualised. With the passage of time, it has become increasingly apparent that a significant minority of ILD cases cannot be readily classified, despite the advent of multidisciplinary diagnosis (which has supplanted surgical biopsy as the diagnostic gold standard) [10]. This realisation underpinned the recognition of unclassifiable ILD as a formal entity in the revision of the ATS/ERS international classification of the IIPs [9]. By definition, no formal database exists for unclassifiable disease, justifying the

Received: June 24 2013 | Accepted: June 24 2013

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proposed disease behaviour classification as a means of achieving pragmatic management based on broad principles, in the absence of a secure histospecific diagnosis.

The report of the first series of patients with unclassifiable ILD by RYERSON *et al.* [11] in this issue of the *European Respiratory Journal* is a welcome addition to the medical literature. A total of 132 (10%) cases were identified from a longitudinal ILD cohort of 1370 patients over a 10-year period at a single centre. Interestingly, patients with unclassifiable ILD had demographic and physiological features intermediate between those of patients with IPF and those with other IIPs, as well as intermediate survival between these groups, although with a heterogeneous clinical course. The imaging pattern was found to be that of UIP in only 17% of cases and of possible UIP in 50%. The difference in outcome from IPF indicates that patients with unclassifiable ILD are not synonymous with the group of IPF patients with atypical imaging features, and corroborates the essential role of multidisciplinary evaluation (clinical, imaging and pathology) in the characterisation of unclassifiable disease [12].

The valuable observations of RYERSON *et al.* [11] should not obscure the fact that no consensus exists on the exact definition of unclassifiable disease. If strictly confined to patients with no logical first choice diagnosis following multidisciplinary evaluation, unclassifiable disease is likely to be relatively rare, based on accumulated clinical experience. However, a much larger patient subset exists in which features are intermediate between individual IIPs and, in many other cases, a tentative first choice diagnosis can be made without diagnostic confidence or a coherent differential diagnosis. These demi-semi diagnoses cause major management uncertainty and can be plausibly included in a broader definition of unclassifiable disease, in so far as accurate longer term management will depend upon the careful observation of ongoing disease behaviour.

An important caveat should be acknowledged with regard to the findings of RYERSON *et al.* [11]. This retrospective series included a great many patients in whom diagnoses were made prior to the multidisciplinary era, at a time when histological evaluation was the diagnostic gold standard. By and large, during this era, the accurate classification of disease was viewed as synonymous with the performance of a diagnostic surgical biopsy. It is hardly surprising that in the series of RYERSON *et al.* [11], failure to classify disease was dominated by the nonperformance of a video-thoracic lung biopsy (table 1). Patients who underwent lung biopsy but could not be classified into one of the existing entities may have been underrepresented. Out of 132 patients with ILD that could not be classified, 78 did not have a biopsy, and a further 11 patients had a biopsy but insufficient tissue for analysis, with only 36 patients (27% of this series and only 2.6% of the prospective ILD cohort) in whom the disease remained unclassifiable despite a biopsy performed with appropriate material available. It might be supposed that the application of high-resolution computed tomography (HRCT) expertise to multidisciplinary diagnosis might further reduce difficulties in classifying this group of patients. However, the reality is quite otherwise. Those engaged in the multidisciplinary evaluation of IIP are acutely aware of the significant prevalence of discordance between HRCT and biopsy features. One need only consider the important patient subgroup in whom a histological pattern of UIP is associated with HRCT appearances considered incompatible with the diagnosis of IPF [13]. The difficulty of integrating atypical HRCT appearances with histological findings applies equally to cases in which patterns other than UIP are disclosed by biopsy.

Thus, although the 10% prevalence documented by RYERSON *et al.* [11] underscores that unclassifiable disease is not a trivial issue, the true frequency may in fact be significantly higher. It can be anticipated that the prevalence of unclassifiable ILD will be subject to great variation depending on diagnostic expertise and may be substantially higher in less expert centres. Furthermore, the proportion of patients with unclassifiable ILD might also be expected to vary with the experience [14] and personality of thoracic radiologists and lung pathologists participating in the multidisciplinary approach process, a process driven by the eccentricities of human interaction. These considerations highlight the importance of future prospective studies of unclassifiable disease, based on multidisciplinary evaluation.

The unclassifiable cases in whom a lung biopsy was contraindicated by comorbidities, age or patient preferences can be regarded as a patient group with "unclassifiable clinical/radiological conditions" (table 1), not evaluated by multidisciplinary discussion (in the absence of histological data). It could be argued that only cases with available histology but with overlapping histological features or discrepant clinical/radiological/pathological features should be considered as truly unclassifiable, although this distinction is, perhaps, academic. However, novel approaches to obtain histological information, including lung biopsy using cryoprobes [15], are currently under evaluation, and might reduce the frequency of difficult ILD cases not amenable to histological sampling. Furthermore, although ILD should not be considered unclassifiable if an aetiology is identified, some cases in the present series of unclassifiable "idiopathic" ILD were difficult to distinguish from CTD-ILD or hypersensitivity pneumonitis. Recent studies have indeed emphasised that a number of patients may present with limited extrathoracic

TABLE 1 Main reasons for interstitial lung disease being unclassified in the series of RYERSON *et al.* [11]

Reasons	Examples
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, endstage lung)
Overlapping histological features (unclassifiable histology)	Nonspecific 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 pneumonitis

manifestations and/or autoantibodies but do not fit with established criteria for the diagnosis of CTD according to international criteria [16]. Such cases, increasingly termed ''undifferentiated CTD'' or ''lung-dominant CTD'', may eventually be regarded as classifiable with the formulation of diagnostic criteria. Although not discussed as such in the literature, it is likely that a similar grey zone may exist in the spectrum between hypersensitivity pneumonitis and IPF or idiopathic NSIP, with patients presenting with unidentified antigenic exposure or incomplete histological criteria for hypersensitivity pneumonitis.

RYERSON *et al.* [11] have identified radiological fibrosis score and baseline carbon monoxide diffusing capacity at baseline as independent predictors of survival in patients with unclassifiable ILD, therefore validating the use of these parameters (which together with histopathology and longitudinal behaviour have previously been validated in the setting of IPF) in the unexplored field of unclassifiable ILD. The authors hereby justify the empirical decision to include disease severity and an evaluation of the irreversibility of disease on HRCT as key components of the proposed disease behaviour classification in the revised ATS/ERS classification of the IIPs [9]. Briefly, the classification of disease as self-limited, reversible, stable, or progressive and irreversible (with and without the potential for long-term stabilisation with therapy) may help to adapt treatment goals and the monitoring strategy. This may prove especially valuable in difficult cases in which histospecific classification remains elusive with the passage of time. Developed for IIPs, the disease behaviour classification may eventually prove to be useful in a variety of ILDs. In the absence of a clear disease category on which to base treatment decisions, empirical management may be best based on observed progression of disease and initial responses to pragmatic therapy. The study by RYERSON *et al.* [11], by providing robust information about ILD patients that cannot be classified into one of the existing entities, paves the way for a novel pragmatic approach to the management of patients with the most complex forms of ILD.

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DOI: 10.1183/09031936.00107713

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