

# IPAF: *Interstitial pneumonia with autoimmune features*. A new entity?

**Eleni Bibaki<sup>1,2</sup>,  
Athina Trachalaki<sup>2</sup>,  
Eirini Vasarmidi<sup>1,2</sup>,  
Aikaterini Antoniou<sup>1,2</sup>**

<sup>1</sup>Thoracic Medicine, University Hospital,  
University of Crete, Heraklion, Greece

<sup>2</sup>Molecular and Cellular Pneumology  
Laboratory, Medical School, University of  
Crete, Heraklion, Greece

The diffuse parenchymal lung diseases, often collectively referred to as the interstitial lung diseases<sup>1</sup> (ILD), are a heterogeneous group of disorders that are classified together because of similar clinical, radiographic, physiologic, or pathologic manifestations<sup>2,3</sup> and are characterized by inflammation and/or fibrosis of the lungs. In particular, ILDs include idiopathic interstitial pneumonias (IIPs)<sup>4</sup>, and a number of variants secondary to environmental and occupational exposures, sarcoidosis, pulmonary Langherans cell histiocytosis, lymphangioliomyomatosis, connective tissue diseases (CTDs), as well as a miscellanea of less frequent forms such as ILDs associated with systemic vasculitides<sup>1,4,5</sup>.

The diagnosis of IIPs requires the exclusion of known causes of interstitial pneumonia since that has an impact on both treatment and prognosis. Patients with connective tissue diseases<sup>6</sup> associated ILD<sup>6</sup> are thought to have a more favorable clinical course when compared to those with idiopathic pulmonary fibrosis<sup>2,7</sup>. Even though ILDs have already been firmly classified, the diversion in IIPs and secondary ILDs are not efficient, since 4–15% of patients with ILD cannot be given a specific diagnosis even after thorough investigation by a multidisciplinary team<sup>8,9</sup>. Therefore, the 2002 ATS/ERS classification proposed an “unclassifiable” (uILD) category of IIP, acknowledging that a final diagnosis may not be achieved, even after lengthy multidisciplinary discussion. The uILD group is associated with clinical characteristics and a prognosis intermediate between IPF and non-IPF ILDs. The risk of disease progression or death in subjects with unclassifiable uILD aligns closely with the presence of baseline clinical and radiological features similar to IPF, in particular, radiologic diagnosis of UIP or possible UIP, HRCT fibrosis score, and presence of honeycombing<sup>10</sup>. Better characterization of this group was therefore essential.

Diagnosing a CTD in patients with ILD is highly relevant, since it is associated with a better prognosis<sup>11</sup> and has an impact on management<sup>12</sup>. Although ILD is generally found in patients already diagnosed with a given CTD, ILD can be the first manifestation of a CTD, with systemic manifestations of the underlying CTD being limited to subtle serological and clinical autoimmune abnormalities, not fulfilling the international criteria for the diagnosis of a given CTD<sup>7,13</sup>. The long-term prognosis of CTD-ILD is better than that IPF<sup>11</sup>, which is at least partly explained by the frequent pattern of

## Correspondence:

Katerina M. Antoniou  
Department of Respiratory Medicine,  
University Hospital of Heraklion, Crete, Greece,  
e-mail: kantonou@med.uoc.gr

NSIP in CTDs<sup>14</sup>, with reportedly less difference in survival between UIP-CTD and IPF<sup>15</sup>.

On these basis, a task force (of pulmonologists and rheumatologists) was formed to develop a consensus regarding patients with ILD, who demonstrate clinical or serological features suggestive of a CTD, but fails to meet established CTD diagnostic criteria<sup>7</sup>. A significant subset of such individuals have been described as having an autoimmune or rheumatologic “flavour”<sup>16</sup>. Researchers around the world have proposed differing, but overlapping, criteria and terms to describe these patients, including “undifferentiated CTD associated ILD” (UCTD-ILD)<sup>17</sup>, “lung-dominant CTD”<sup>7</sup> or “autoimmune-featured ILD”<sup>16</sup>. The task force introduced a novel entity termed *interstitial pneumonia with autoimmune features* (IPAF). This new classification system incorporates not only clinical and serological manifestations of CTD, but also morphological features suggestive of a CTD encountered on high-resolution computed tomography (HRCT), surgical lung biopsy (SLB) and pulmonary function testing (PFTs)<sup>6</sup>. To diagnose a patient with IPAF there must be evidence of interstitial pneumonia by high-resolution computed tomography (HRCT) imaging and/or by surgical lung biopsy, all known causes for interstitial pneumonia should be excluded after a thorough clinical evaluation and no criteria for a defined CTD should be met. The classification criteria is organised around three central domains (and listed comprehensively in Table 1): a clinical domain consisting of specific extrathoracic features, a serologic domain consisting of specific circulating autoantibodies, and a morphologic domain consisting of specific chest imaging features, histopathologic features or the involvement of other pulmonary compartments. Figure 3.

Although this novel nomenclature represents a big proportion of patients previously categorized as uILD, the problem still exists since the task force is not proposing guidelines or recommendations for clinical care, diagnostic testing or management instructions for patients that meet classification criteria of IPAF. Patients that fulfill classification as IPAF are managed clinically as CTD-ILD or idiopathic interstitial pneumonia, as per the discretion of their treating provider. We already know from the PANTHER trial that combination of prednisone, azathioprine, and n-acetylcysteine increased the risk of death and hospitalization in patients with IPF<sup>18</sup>, and two novel anti-fibrotic drugs are now used for the treatment of IPF. Pirfenidone, as compared with placebo, reduced disease progression, as reflected by lung function, exercise tolerance, and progression-free survival<sup>19</sup> and nintedanib

reduced the decline in FVC, which is consistent with a slowing of disease progression<sup>20</sup>. There have been no controlled clinical trials in patients with uILD or IPAF, no pharmacological treatments are approved for the treatment of this population, it is unknown whether these patients could benefit from immunosuppressant or anti-fibrotic therapy. To address this unmet need, a new clinical trial has been designed to evaluate the efficacy and safety of pirfenidone in patients with fibrosing uILD. The results are to be seen.

So far, few cohort retrospective studies regarding IPAF have been conducted with conflicting results. Ahmad et al observed that compared to IPF, patients with IPAF are more frequently females, have distinctive characteristics, have relatively frequent abnormalities at nailfold capillaroscopy, with no difference in age or in overall survival<sup>21</sup>. Instead, the Chicago study revealed that patients with IPAF had marginally better survival than patients with IPF, but worse than CTD-ILD. A NSIP pattern, or the presence of the clinical domain was associated with improved survival. Thought the subgroup analysis with regard to the presence of clinical characteristics revealed differences in survival, suggesting that more studies should be conducted for the better classification of those patients<sup>22</sup>. Finally, a clinical trial of phase II is ongoing comparing the efficacy of antifibrotic versus immunomodulatory therapy in patients with uILDs.

In conclusion, several questions still need to be answered with well-designed, prospective, multi-center studies of IPAF. Is the natural history of IPAF different from IIP? What proportion of IPAF patients will develop a CTD? Do the criteria need modifications? What impact does histopathology have on IPAF prognosis? What is the role of immunosuppression for patients with IPAF and is there a role for anti-fibrotic therapy e particularly those with the more fibrotic patterns of ILD?

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