



Editorial

 Interstitial Pneumonia With Autoimmune Features: An Update[☆]

Actualización en neumonía intersticial con características autoinmunes

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Several diffuse interstitial lung diseases (ILD) may be related with varying frequency and severity to connective tissue diseases (CTD). Currently, there are 3 possible scenarios: ILD in patients with a definitive diagnosis of CTD; CTD initially presenting as ILD; and ILD with subtle manifestations that suggest a possible diagnosis of CTD but for which a diagnosis cannot be established with certainty.¹ In recent years, patients who did not meet the diagnostic criteria for characterized CTD, but who showed characteristics suggestive of an underlying autoimmune process have been classified using different terms, such as “undifferentiated connective tissue disease-associated interstitial lung disease (UCTD-ILD)”, “lung-dominant CTD”, and “autoimmune-featured ILD”, often with some overlap among the criteria. The lack of clear uniformity has prevented this group from being categorically accepted as an entity and from being considered as a uniform cohort for resolving key issues regarding these patients.² Identifying CTD in a patient under study for an ILD that is in principle considered “idiopathic” is always a challenging but essential step, considering the prognostic and therapeutic implications of an accurate diagnosis.^{3,4}

The clear need to unify the nomenclature and criteria used to define this group of patients and to promote research prompted a working group of the American Thoracic Society (ATS) and the European Respiratory Society (ERS) to propose the term “Interstitial Pneumonia with Autoimmune Features (IPAF)”.² The diagnostic criteria proposed were: the presence of interstitial lung disease (on chest high-resolution computed tomography [HRCT] or surgical lung biopsy); the exclusion of an alternative etiology and absence of criteria for a characterized CTD; and the coexistence of at least 2 of the following domains: clinical, serologic and morphological.²

Since this document was published in 2015, several studies have attempted to reclassify different patient series using the diagnostic criteria proposed for IPAF. Most are retrospective studies, con-

ducted mainly in patients with a diagnosis of idiopathic interstitial pneumonia (IIP) or UCTD-ILD.

Oldham et al. found that 144 of 422 patients met criteria for IPAF, and some distinct subgroups could be identified. Subjects with a pattern of usual interstitial pneumonia (UIP) had a poorer prognosis, with a survival similar to that of patients with a diagnosis of idiopathic pulmonary fibrosis (IPF) (a UIP pattern was detected in 54.6% of patients on chest HRCT and in 73.5% of the 83 patients who underwent surgical lung biopsy). The prognosis of patients with non-UIP IPAF was more favorable, similar to that of CTD-associated ILD.⁵

In another retrospective series conducted in France in 778 patients with ILD, 426 were classified as IIP, 167 as ILD associated with characterized CTD, and 57 patients were classified as IPAF (7.3%). No differences were found in 1-year survival in this cohort compared to patients with IPF. Some differences from the North American series were observed in the clinical domain. On chest HRCT, 53% presented a pattern of non-specific interstitial pneumonia (NSIP), and 20% had superimposed organizing pneumonia (OP/NSIP). Only 28% of patients had a UIP pattern on chest HRCT.⁶

A recent Japanese retrospective study analyzed 98 patients classified as IPAF to try to identify prognostic factors in subjects who fulfilled the serologic and clinical domains, according to the presence of specific autoantibodies (Ab) and radiological patterns on the chest HRCT. A radiological pattern of OP was detected in 20.4%, NSIP in 63 patients (64.3%), and an OP/NSIP superimposed pattern in 15.3%. Patients were divided into 5 groups, depending on antibodies: IPAF with systemic sclerosis-associated antibodies (SS-Ab); IPAF with positive anti-citrullinated cyclic peptide antibodies (anti-CCP); positive anti-tRNA synthetase antibodies; IPAF with positive anti-SSB antibodies; and other IPAFs (in which patients with positivity for 2 types of specific Ab were included). Patients with a radiological pattern of NSIP had significantly worse survival than those with an OP/NSIP or OP pattern, as did those with IPAF with positive SS-Ab compared with other IPAF groups with other antibodies. After a mean follow-up of 4.5 years, 12.2% (12 patients) were diagnosed with characterized CTD.⁷

In our opinion, the inclusion of this cohort of patients with evidence of an underlying autoimmune process under the term IPAF represents a significant step forward. Indeed, emerging

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studies that have used these criteria show that there is significant heterogeneity among this group, suggesting the existence of different “IPAF phenotypes” with different prognosis and management. The best management strategy for “IPAF” patients is still unclear, and the tendency is to fall back on the use of corticosteroids and immunosuppressants on the basis of the patient’s “autoimmunity”. However, if “more fibrosing phenotypes” that do not respond to this standard therapeutic approach are identified, the role of antifibrotics in this subgroup of patients will have to be explored. Two placebo-controlled clinical trials are currently ongoing in non-IPF fibrosing ILD to evaluate the efficacy and safety of pirfenidone (clinicaltrials.gov/ct2/show/NCT03099187) and nintedanib,⁸ in which patients classified as IPAF may be included.

IPAF may be regarded nowadays more as a working diagnosis than a fully defined entity, and as follow-up progresses it may ultimately form part of 2 large groups: characterized CTD and IPAF with similar features and prognosis as IPF. This topic must be studied in more depth and the current criteria must be redefined to make this classification even more homogeneous. If it is used appropriately and in consensus, we will be able to monitor our patients correctly and find answers in the near future to all outstanding issues. In clinical research, it will help us classify our patients better for more homogeneous inclusion in clinical trials of new and more efficient therapeutic strategies.

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