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REVIEW

Interstitial Pneumonia with Autoimmune Features: 8 Years after Nomenclature and Classification—Where are We Not and Where Are We Headed?

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Abstract

Purpose of Review The term interstitial pneumonia with autoimmune features (IPAF) was proposed by an international task force as a research classification to standardize nomenclature for patients with idiopathic interstitial pneumonia (IIP) and features of connective tissue disease (CTD). This review aims to discuss the advances made in understanding this research classification and the clinical implications of this term.

Recent Findings Multiple cohort studies have described the clinical presentation of patients meeting criteria for IPAF with heterogeneity noted particularly in the morphologic domain as compared to clinical and serologic domains. Treating these patients according to their clinical presentation and features remains the key expert opinion given the paucity of data to inform therapeutic strategies in IPAF.

Summary There are still several challenges and unresolved questions which preclude the application of IPAF as a clinical diagnosis. Whether IPAF represents a clinical diagnosis distinct from CTD-ILD or IIPs or precursor or an overlap of these conditions remains controversial and warrants further investigation.

Keywords Interstitial pneumonia with autoimmune features · Antifibrotics · Immunosuppression · Idiopathic interstitial pneumonia · Connective tissue disease

Introduction

Interstitial lung diseases (ILD) are a heterogenous group of fibroproliferative disorders of known or unknown cause. Connective tissue disease-related ILDs (CTD-ILD) are the most common among ILDs with an established pathological association and portend favorable prognosis compared to idiopathic pulmonary fibrosis (IPF) and other idiopathic interstitial pneumonias (IIP). ILD can manifest in any form of CTD but is mostly seen in scleroderma, rheumatoid arthritis, and idiopathic inflammatory myopathy. The different CTDs are defined by criteria based on clinical signs and serologies per the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria [1–3]. However, a proportion of patients newly diagnosed with ILD present with one or more features of CTD without meeting the defined criteria for a particular CTD. While terms such as undifferentiated CTD [4], lung-dominant CTD [5], or autoimmune-featured ILD [6] were deliberated to distinguish this patient population, the lack of consensus impeded further understanding of the disease course and management among these patients.

Dawn of Interstitial Pneumonia with Autoimmune Features

Eight years ago, the consensus-derived term, interstitial pneumonia with autoimmune features (IPAF) was first proposed by an international task force as a research classification to standardize nomenclature regarding patients with IIP and features of connective tissue disease [7••]. This term was meant to be applied as a research classification to be inclusive of these patients who have ILD and combinations of features suggestive of a CTD but not meeting the specific

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diagnostic criteria for CTD. The aim of this task force was to enhance an understanding of the natural history of this patient population and further develop research questions to improve outcomes through uniformity in the classification criteria [7••].

Classification of IPAF

Based on this task force recommendation, the term IPAF was organized around the clinical domain, serological domain, and most importantly, morphologic domain which differentiated this term from the multiple previous criteria [7••]. Patients with ILD who met at least one feature from at least two of these domains were classified as having IPAF.

The presence of specific features of underlying CTD such as Raynaud's phenomenon, distal digital tip ulceration, and mechanic hands, among others, is included in the clinical domain [7••]. These features are highly suggestive of an underlying autoimmune pathology and are hallmark features of some of the common autoimmune conditions [2, 3, 8], but their presence alone is insufficient for a diagnosis of a definitive CTD. Other symptoms such as sicca symptoms, weight loss, and dysphagia were considered non-specific to be included in this definition.

The serologic domain includes multiple specific autoantibodies that are known to be associated with CTDs [7••]. Low titers of the antinuclear antibody (ANA) and rheumatoid factor and markers of inflammation which may be prevalent in the general population were excluded. Of note, indirect immunofluorescence ANA assay with reporting of titer and staining patterns is preferred due to greater clinical diagnostic importance [9].

The morphologic domain, an important addition to the previously considered definitions for this patient population, is further classified into high-resolution computed tomography (HRCT) image patterns, histopathologic features on surgical lung biopsy, and/or evidence of multi-compartment involvement [7••]. The HRCT patterns specific to this classification include non-specific interstitial pneumonia (NSIP), organizing pneumonia (OP), NSIP with OP overlap, and lymphoid interstitial pneumonia (LIP), all features predominantly seen in patients with CTD-ILD. The exception here is rheumatoid arthritis, which is more commonly associated with usual interstitial pneumonia (UIP), a pattern not specifically included in this IPAF definition. The presence of UIP on HRCT does not, however, exclude the patient from having IPAF. The histopathologic features, similarly, are highly specific to an underlying autoimmune pathology and include NSIP, OP, LIP, and interstitial lymphoid aggregates with germinal centers and diffuse lymphoplasmacytic infiltration with or without lymphoid follicles [7••]. A key clinical consideration in the management of patients with CTD-ILD is the impact of extrapulmonary involvement on disease progression and quality of life. Hence, unexplained intrinsic airway disease, vascular involvement, pleural, or pericardial abnormalities are included in this domain as well.

Clinical Presentation of IPAF

Multiple cohort studies have described the characteristics and clinical presentation of patients meeting the criteria for IPAF defined by this consensus statement [10•, 11–20]. Demographically, patients are predominantly females in their fifties to sixties. The majority of the patients in most of these studies fulfilled the serologic and morphologic domains. A wide range of 25–50% of patients fulfilled criteria for all three domains [10•, 11, 12, 16]. While several features in the clinical and serologic domain are similar in these cohorts, there is considerable heterogeneity in the morphologic domain within these cohorts. Raynaud's phenomenon and inflammatory arthritis were the predominant clinical autoimmune features, followed by mechanic's hands. Positive ANA defined as > 1:320 titer, diffuse, speckled, homogenous patterns or ANA nucleolar, or centromere patterns (any titer) was universally predominant among all these cohorts. Other serologies reported in these studies were rheumatoid factor, anti-Ro (SS-A), and anti-tRNA synthetase antibodies. NSIP was the predominant pattern on HRCT as well as histopathology in most of the cohorts [10•, 12–15, 19].

Management

Currently, there are no specific therapies for IPAF since it is a research classification and not a well-defined clinical entity. There is significant heterogeneity in the therapeutic strategy for patients classified to have IPAF and is typically based on the underlying autoimmune features versus a clinical presentation more akin to IIP (Fig. 1). Treatment practices have been extrapolated from data generally available for CTD-ILD (mainly, scleroderma) and less so, other IIPs or unclassifiable ILD. Factors such as age, gender, smoking history, clinical signs, serologies, patterns on HRCT, and/or histopathology must be taken into consideration. Other patient-related factors to consider include functional status, comorbidities, concomitant medications, disease stage, extrapulmonary manifestations, and shared decision-making.

Among patients with CTD-ILD, immunosuppression remains the mainstay of treatment [21–24]. Initial randomized control trials for scleroderma-ILD focused on cyclophosphamide, particularly with FVC improvement noted in the scleroderma lung study (SLS) I [25]. With SLS II reporting non-inferiority of mycophenolate mofetil (MMF)

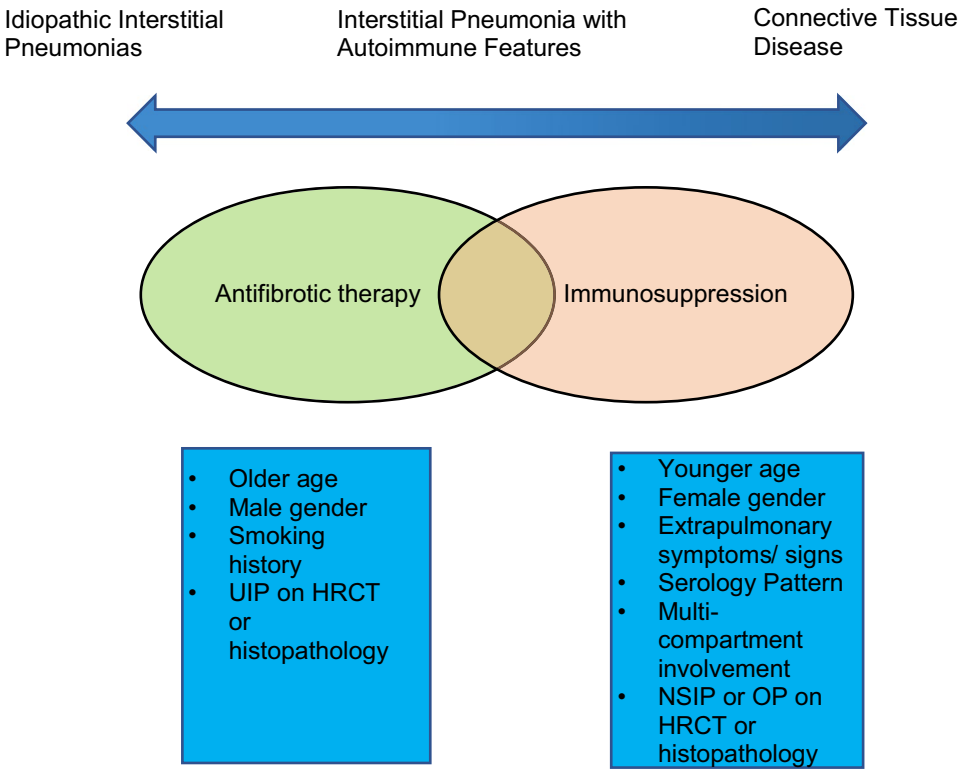

Fig. 1 Initial therapeutic strategy for interstitial pneumonia with autoimmune features. UIP, usual interstitial pneumonia; NSIP, non-specific interstitial pneumonia, OP, organizing pneumonia; HRCT: high-resolution CT scan

compared to cyclophosphamide in scleroderma ILD with better tolerance, it is considered the first line of therapy in CTD-ILD [26]. Cyclophosphamide is utilized much more frequently in acute exacerbations or life-threatening presentation of CTD-ILD. Recent data further support the use of rituximab in patients with CTD-ILD, particularly as salvage therapy [27••]. Tocilizumab can preserve lung function and has been approved for patients with scleroderma-ILD [28]. Other often used medications in CTD-ILD include azathioprine and calcineurin inhibitors. Single-center studies have reported stabilization of lung function in patients with IPAF treated with MMF and/or corticosteroids [29•] or at least an improvement in the decline of lung function after initiation of therapy with MMF [30]. Other smaller studies have reported the potential benefit of azathioprine, rituximab, and cyclophosphamide in this patient population [31–33]. Overall, whether similar efficacy of immunosuppression can be attained in IPAF remains uncertain.

Antifibrotic therapies, nintedanib and pirfenidone, are approved for the treatment of IPF [34, 35]; nintedanib is for scleroderma ILD [36]. Nintedanib has been reported to slow down disease progression in patients with non-IPF progressive pulmonary fibrosis including a small proportion of patients who met criteria for IPAF [37]. However, no background immunosuppression was allowed in the initial part of the study limiting the interpretation of this therapeutic strategy in patients who may have a greater inflammatory component to their disease. Two studies showed pirfenidone to slow the decline in lung function among patients with progressive unclassifiable ILD/progressive fibrotic ILD including patients with IPAF, and additional research has been recommended [38–40]. One small study reported better outcomes in patients with IPAF-UIP treated with immunosuppressive therapy compared to those treated with antifibrotic therapy, particularly when stratified by the pathological presence or absence of inflammatory cell infiltration [41]. Other studies have reported a smaller proportion of patients meeting IPAF criteria treated with antifibrotic therapy. Regardless of whether the clinical presentation leans towards CTD-ILD or IIP, antifibrotic therapy should be considered in patients who meet the criteria for progressive pulmonary fibrosis [40].

Like other ILDs, the supportive comprehensive care plan is an important component in the management of patients with IPAF [22, 42]. Pulmonary rehabilitation and long-term oxygen supplementation are recommended for this patient population. It is equally important to screen for and treatment comorbidities such as gastroesophageal reflux, pulmonary hypertension, and sleep-disordered breathing [43]. In patients with advanced disease, lung transplantation should be considered.

Clinical Implications and Controversies

There is substantial heterogeneity in clinical presentation, response to current therapies, and outcomes among patients who meet the diagnostic criteria for IPAF. First, we do

not have a complete understanding of the epidemiology of patients labelled to have IPAF who develop a systemic autoimmune disease in the future. There are several studies which have demonstrated the presence of autoantibodies in IPF patients [44–47] without an impact on clinical outcomes or response to antifibrotic therapies [48]. On the other hand, about 20% of patients with autoimmune diseases are present with ILD as the initial clinical presentation. Compared to patients with IPF, a greater proportion of IPAF progressed towards a specific CTD diagnosis. IPAF cohorts with short follow-up periods reported small numbers of patients who developed a systemic autoimmune disease. However, cohorts, with a longer follow-up period greater than 3 years at least, have reported 12.2% [14], 16% [49], and 26% [50], and patients developed other characteristics to fulfill criteria for an autoimmune condition, respectively. In another study, 20% of patients diagnosed with IPF, with radiologic and/or histologic UIP pattern ($n = 190$) but met criteria for one IPAF domain, were prospectively followed jointly by rheumatologists and pulmonologist; 28.9% of these patients developed a systemic autoimmune disease [51]. Data is currently insufficient to discuss on how we monitor for the potential development of CTDs, but generally, patients meeting IPAF criteria may benefit from a thorough rheumatological evaluation and routine monitoring for the development of CTD symptoms.

While the majority of the ILD community includes testing for myositis-specific antibodies in the diagnostic algorithm of ILD, the lack of specifications in the ATS/ALAT/ERS guidelines makes it challenging to standardize the testing and interpretation of these results [52]. There has been considerable debate on the inclusion of myositis-specific antibody in the criteria for IPAF given that the majority of these patients could likely be given a clinical diagnosis of CTD-ILD. One study demonstrated survival among patients with IPAF with MSA to be akin to patients with idiopathic inflammatory myopathies (IIM)-ILD [53]. Consideration to whether patients who have mechanic's hands and positive MSA are simply early ILD predominant presentation of IIM is crucial. Furthermore, patients with polymyositis/dermatomyositis-related ILD, particularly with MDA-5, often have rapidly progressive disease, and the ramifications of the diagnostic term on the management of these patients are an important consideration.

The presence of UIP on HRCT or histopathology does not exclude the patient from having IPAF; however, it is currently not specified within the classification criteria. One large study reported a greater number of patients with UIP on HRCT as well as histopathological analysis [11] compared to the predominant NSIP features from other cohorts; accordingly, this study also demonstrated higher mortality among patients with IPAF compared to those with CTD-ILD. Furthermore, patients meeting IPAF criteria with UIP on HRCT and/or histopathology had worse outcome compared to those with non-UIP IPAF and CTD-ILD but were akin to IPF [11]. Given these diagnostic and prognostic implications of UIP on HRCT and/or histopathology, this diagnostic criterion should be considered for inclusion in the morphological domain. Additional features that may differentiate UIP on HRCT and histopathology in IPAF compared to CTD or IPF further warrant investigation [54–56].

Additionally, several recent studies have demonstrated the incorporation of the Envisia genomic classifier (EGC) to increase diagnostic confidence in patients with fibrotic ILD without obtaining surgical lung biopsy [57–59]. Using machine learning, an algorithm based on genomic data from SLBs was used to identify a molecular signature for a UIP pattern, and based on this, the pattern of gene expression in lung tissue obtained by transbronchial biopsy is classified as UIP or not UIP. A positive EGC may be able to further predict disease progression in patients with fibrotic ILD [60, 61]. Further investigation into the utility of this test in the IPAF classification and whether a positive test may sway the treatment strategy towards antifibrotic therapy over immunosuppression is warranted.

Finally, several of these factors become important considerations in the treatment of these patients. While some studies have evaluated certain prognostic factors in patients with IPAF, we do not have a succinct understanding of who we should treat and when is the appropriate timing of treatment. There is further a grey zone in immunosuppression versus antifibrotic therapy, and treatment decisions currently lean on expert opinion on whether the patients might follow a clinical course like CTD-ILD or IIP. The current underlying message is to treat the patient according to the clinical presentation and features and not the research classification.

Conclusion

In 8 years into the classification of this entity, there are still several challenges and unresolved questions which preclude the application of IPAF as a clinical diagnosis. Whether IPAF represents a clinical diagnosis distinct from CTD-ILD or IIPs or a precursor to these conditions or just an overlap of these conditions remains controversial. Utilizing these criteria as a research classification to further understand the underlying pathobiological mechanism and develop targeted therapeutic strategies for these patients is essential in improving outcomes among patients meeting the criteria for IPAF. Ultimately, we need prospective research to determine if this classification system matters in real-world clinical practice, to determine if the disease progression of different subgroups meeting IPAF criteria behaves differently, and to determine when the time is right to revisit these criteria.

Compliance with Ethical Standards

Conflict of Interest TK reports speaker and consultation fees from Boehringer Ingelheim Inc. and consultation fees from United Therapeutics Corp and PureTech Lyt-100 Inc. unrelated to submitted work.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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