



Interstitial Pneumonia with Autoimmune Features: What the Rheumatologist Needs to Know

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Abstract

Purpose of Review This narrative review will focus on the role of the rheumatologist in evaluating patients with interstitial lung disease (ILD) without a defined rheumatic disease and will outline the current classification criteria for interstitial pneumonia with autoimmune features (IPAF) and describe what is known regarding IPAF pathobiology, natural history, prognosis, and treatment. Lastly, knowledge gaps and opportunities for future research will be discussed.

Recent Findings IPAF is a recently defined classification of ILD patients who have features suggesting an autoimmune-mediated process, but do not fulfill current rheumatic disease criteria. The goal of the IPAF criteria is to provide a uniform case definition for the study of autoimmune ILD patients who do not currently fit within standard ILD diagnostic categories, ultimately improving diagnosis and therapy. Many of these patients are referred for rheumatologic evaluation to aid the diagnostic process.

Summary The care of the IPAF patient is complex and is multidisciplinary with pulmonology, rheumatology, pathology, radiology, physical therapy, primary care, pulmonary transplant providers all serving vital roles. The rheumatologist has several roles which include classification, disease monitoring, and management.

Keywords Interstitial pneumonia with autoimmune features · Interstitial lung disease · Rheumatologist evaluation · Pulmonary rheumatology collaboration

Introduction

Interstitial lung diseases (ILD) are a group of heterogeneous diseases affecting the lung parenchyma. These disorders are broadly classified according to suspected etiology including exposure-related (environmental, occupational, drug reactions), systemic (sarcoidosis, rheumatic disease

(RD)-associated), and idiopathic (idiopathic pulmonary fibrosis, or IPF) [1]. Patients with these disorders typically present with dyspnea on exertion and cough. In many patients, the disease can progress over time and lead to the need for supplemental oxygen, reduced quality of life, and early death.

Patients presenting with ILD undergo a broad workup including a history focused on potential exposures and extrapulmonary symptoms, detailed physical exam, serologic assessment, high-resolution computed tomography (HRCT) of the chest, and, occasionally, histopathologic evaluation of the lung tissue. The reason for the extensive workup is to identify the most likely culprit cause for their ILD, which impacts management and expected disease course.

ILD is a major contributor to disease burden in multiple RDs such as systemic sclerosis (SSc), rheumatoid arthritis (RA), Sjogren's syndrome (SS), and idiopathic inflammatory myopathies (IIM) [2]. Some patients with ILD do not meet ACR or EULAR classification criteria for various RD, yet

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their clinical features, autoantibodies, and radiographic or histopathologic findings suggest an underlying autoimmune driver of their ILD. Such patients were previously labeled with terms such as “lung dominant connective tissue disease (CTD)” [3], “undifferentiated CTD (UCTD) associated ILD” [4], and “autoimmune-featured ILD” [5]. In 2015, the European Respiratory Society (ERS) and American Thoracic Society (ATS) coined the term “interstitial pneumonia with autoimmune features” (IPAF) to describe these patients, primarily for research purposes [6••]. Up to 14% of patients with ILD seen in rheumatology clinics do not fulfill classification criteria for any of the RDs [7] yet have features suggesting the presence of IPAF, and rheumatologists frequently participate in the evaluation and management of these patients.

This review will outline the current IPAF classification criteria, describe what is known regarding IPAF pathobiology, natural history, treatment, and prognosis, and offer guidance to the rheumatologist evaluating a patient suspected of having IPAF. Future challenges and research directions will also be discussed.

IPAF Classification Criteria and Limitations

The IPAF classification includes three domains: serologic, clinical, and morphologic (Table 1). Two of the three domains must be satisfied to meet IPAF criteria [6••]. The serologic domain consists of specific autoantibodies. The clinical domain consists of signs and features seen in RDs. The morphological domain consists of radiographic and histopathologic patterns suggestive of inflammatory pulmonary lesion such as non-specific interstitial pneumonia (NSIP), organizing pneumonia (OP), or lymphocytic interstitial pneumonia (LIP) that are common in RDs. Multi-compartment involvement, defined as unexplained pleural or pericardial thickening or effusion, unexplained intrinsic airways disease, or unexplained pulmonary vasculopathy in addition to interstitial disease, is also included in the morphological domain [6••]. Usual interstitial pneumonia (UIP), the prototypical lesion of IPF, is not included as one of the morphological classification characteristics of IPAF.

Table 1 Classification criteria for “interstitial pneumonia with autoimmune features” [6]

1. Presence of an interstitial pneumonia (by HRCT or surgical lung biopsy), and 2. Exclusion of alternative etiologies, and 3. Does not meet criteria of a defined rheumatic disease, and 4. At least one feature from at least two of these domains:		
A. Clinical domain B. Serologic domain C. Morphologic domain		
Clinical domain	Serologic domain	Morphologic domain
1. Distal digital fissuring (i.e., “mechanic hands”) 2. Distal digital tip ulceration 3. Inflammatory arthritis or polyarticular morning joint stiffness ≥ 60 min 4. Palmar telangiectasia 5. Raynaud’s phenomenon 6. Unexplained digital edema 7. Unexplained fixed rash on the digital extensor surfaces (Gottron sign)	1. ANA $\geq 1:320$ titer, diffuse, speckled, homogeneous patterns or a. ANA nucleolar pattern (any titer) or b. ANA centromere pattern (any titer) 2. Rheumatoid factor $\geq 2\times$ upper limit of normal 3. Anti-CCP 4. Anti-dsDNA 5. Anti-Ro (SSA) 6. Anti-La (SSB) 7. Anti-ribonucleoprotein 8. Anti-Smith 9. Anti-topoisomerase (Scl-70) 10. Anti-tRNA synthetase (e.g., Jo-1, PL-7, PL-12; others are: EJ, OJ, KS, Zo, tRS) 11. Anti-PM-Scl 12. Anti-MDA-5	1. Suggestive radiology patterns by HRCT (see text for descriptions): a. NSIP b. OP c. NSIP with OP overlap d. LIP 2. Histopathology patterns or features by surgical lung biopsy: a. NSIP b. OP c. NSIP with OP overlap d. LIP e. Interstitial lymphoid aggregates with germinal centers f. Diffuse lymphoplasmacytic infiltration (with or without lymphoid follicles) 3. Multi-compartment involvement (in addition to interstitial pneumonia): a. Unexplained pleural effusion or thickening b. Unexplained pericardial effusion or thickening c. Unexplained intrinsic airways disease [#] (by PFT, imaging or pathology) d. Unexplained pulmonary vasculopathy

HRCT, high-resolution computed tomography; ANA, antinuclear antibody; NSIP, non-specific interstitial pneumonia; OP, organizing pneumonia; LIP, lymphoid interstitial pneumonia; PFT, pulmonary function testing. [#]includes airflow obstruction, bronchiolitis, or bronchiectasis

Adapted from: Fischer, A., et al., *An official European Respiratory Society/American Thoracic Society research statement: interstitial pneumonia with autoimmune features*. Eur Respir J, 2015. 46(4): p. 976–87

The inclusion of specific IPAF criteria within each domain continues to be critiqued. It has been suggested that ANCA antibodies should be included in the serologic domain due to an association with ILD without overt vasculitis [8]. On the other hand, removal of anti-synthetase and MDA-5 antibodies from the criteria has been proposed given that IPAF patients with myositis-specific antibodies (Jo-1, PL7, PL12, EJ, OJ, Mi-2, SRP, NXP2, TIF1 γ , SAE, and MDA-5 antibodies) behave similarly to IIM-ILD in terms of treatment response and survival [9^{*}]. In some IPAF cohorts, fever and rash were prevalent [10–14], leading to criticism that these should be added to the clinical domain [11]. Additionally, sicca and gastroesophageal reflux disease (GERD) have been suggested to be relevant clinical features of IPAF which could be included [15, 16]. In contrast, Gottron sign and digital tip ulcerations are infrequently noted in IPAF [14, 15, 17], as their presence strongly supports the definite diagnosis of IIM and SSc, respectively.

Components within the morphologic domain have also been debated. Unexplained air trapping, while included in the definition of multicompartiment involvement, is excluded in smokers in some studies [7]. Some argue that IPAF patients with a UIP pattern may merely have IPF with positive autoantibodies, as these patients had survival similar to IPF patients in some cohorts [7]. This observation led to suggestions that the presence of UIP should be an exclusion criterion for IPAF [17]. However, this trend of survival according to lung damage pattern is not uniformly found in all cohorts, with Ahmad, et al. finding that IPAF patients had better survival than IPF patients, irrespective of radiologic pattern [18]. Furthermore, the presence of autoantibodies has been shown to be a positive predictive factor for survival in IPF patients [19]. Additionally, RD patients with UIP pattern have longer survival than IPF patients and may still benefit from immunosuppression [20]. These findings highlight that the lung damage pattern might not be the key characteristic predictive of survival.

A broader issue with the existing IPAF criteria is the approach to excluding RD. Anti-synthetase syndrome, limited cutaneous SSc (formerly CREST), and UCTD may be variably diagnosed as RD-ILD or IPAF depending on the evaluating provider [21, 22]. Additionally, recent data suggests that 14% of IPAF patients eventually evolve into definable RD [22, 23]. For example, IPAF patients with rheumatoid factor and anti-CCP positivity have a high likelihood of progressing into classifiable articular rheumatoid arthritis within 5 years [24].

Given the importance of ILD classification for prognosis and treatment decisions, consultation with a rheumatologist is essential to exclude RD and to confirm findings in the IPAF clinical domain. Clinicians should also be encouraged to detail the domains that contributed to the

IPAF classification due to the inherently heterogeneous nature of this undifferentiated condition. Collaboration with our pulmonary, radiology, and pathology colleagues allows confirmation of findings within the IPAF morphologic domain. This multidisciplinary approach can significantly improve the clinical management in these patients.

IPAF Pathobiology

IPAF is assumed to have autoimmune etiology similar to RD-ILD. However, literature on the pathobiology is limited. Investigations specifically evaluating ILD patients who meet IPAF criteria have uncovered few diagnostic and prognostic biomarkers in this entity. There are also genetic and genomic associations that have been put forward to explain progression of disease in IPAF. Table 2 summarizes blood-based biomarkers studied specifically in IPAF, although their presence is not diagnostic of the underlying pathway of damage.

A recent study evaluating cytokine profiles in 39 patients with aminoacyl-tRNA-antibody positive ILD (i.e., a mix of IPAF and inflammatory myositis) found that persistent elevation of Th17 cytokine profile was associated with ILD progression [28^{*}]. Whether this is true for IPAF in the absence of anti-synthetase antibodies is unknown. A study by Liang and colleagues demonstrated that chemokine ligand 1 (CXCL1) and its receptor CXCR2 may be involved in the development of IPAF. CXCL1, via CXCR2, acts to recruit neutrophils, thus presumably exerting a damaging effect. CXCL1 levels were elevated in plasma of IPAF patients and associated with exacerbations. Additionally, CXCR2 was upregulated in the leukocytes and endothelial cells of the lungs of IPAF patients, compared to patients with idiopathic interstitial pneumonias (IIPs) [25]. Xue, et al. showed that baseline levels of markers of fibrosis, Krebs von den Lungen-6 (KL-6), and surfactant protein A (SP-A), are increased in IPAF patients who progress, that these levels increased further over time, and that these markers correlate with lung function [31].

Newton, et al. demonstrated that, similarly to IPF, shortened leukocyte telomere length (LTL) in IPAF patients is associated with progression of the disease and worse transplant-free survival. In addition, presence of the *MUC5B* promoter variant in IPAF was associated with reduced transplant-free survival [32^{*}].

Identifying reliable biomarkers that could differentiate between ILD with an autoimmune etiology from ILD subtypes driven by non-immune processes and predict lung disease progression would be clinically useful; however, additional research is needed.

Table 2 Serum biomarkers with potential diagnostic and prognostic utility in IPAF

Biomarker	Reference	Study design	IPAF sub-jects (n)	Comparison group (n)	Results
Biomarkers with diagnostic utility					
IL-4	Liang [25]	Cross-sectional	38	Non-IPAF IIP (81), COPD (36), HC (101)	<ul style="list-style-type: none"> • Significantly higher in IPAF than in non-IPAF IIP, COPD, and HC
IL-6	Liang [25]	Cross-sectional	38	Non-IPAF IIP, COPD, HC	<ul style="list-style-type: none"> • Significantly higher in IPAF than in non-IPAF IIP • Significantly higher in IPAF and non-IPAF IIP than in COPD, HC
IL-10	Kameda [26•]	Retrospective	35	IPF (51), RD-ILD (16)	• Significantly higher in RD-ILD than in IPAF
	Kameda [26•]	Retrospective	35	IPF, RD-ILD	• Significantly higher in IPAF and RD-ILD than in IPF
	Liang [25]	Cross-sectional	38	Non-IPAF IIP, COPD, HC	<ul style="list-style-type: none"> • Significantly higher in IPAF than in non-IPAF IIP • Significantly higher in IPAF and non-IPAF IIP than in COPD, HC
IL-13	Liang [25]	Cross-sectional	38	Non-IPAF IIP, COPD, HC	• Significantly higher in IPAF than in non-IPAF IIP, COPD, and HC
IL-17	Liang [25]	Cross-sectional	38	Non-IPAF IIP, COPD, HC	• Significantly higher in IPAF than in non-IPAF IIP, COPD, and HC
Biomarkers with prognostic utility					
CXCL13	Xue [27]	Retrospective	27	Non-IPAF IIP (23); IPF (19); pneumonia (20); HC (15)	<ul style="list-style-type: none"> • No significant difference between IPAF and IPF or other IIPs • Level in IIPs significantly higher than in pneumonia or HC • Inversely correlated with DLCO in IIPs • No significant difference between IPAF and IPF or other IIPs • Level in IIPs significantly higher than in pneumonia or HC • Inversely correlated with DLCO in IIPs
CCL2	Xue [27]	Retrospective	27	Non-IPAF IIP; IPF; pneumonia; HC	<ul style="list-style-type: none"> • No significant difference between IPAF and IPF or other IIPs • Level in IIPs significantly higher than in pneumonia or HC • Inversely correlated with DLCO in IIPs
Th17 cytokine profile*	Ramos-Martinez [28•]	Prospective	33	Part of a cohort of ILD patients with anti-tRNA autoantibodies (85% IPAF) (39)	<ul style="list-style-type: none"> • Levels significantly higher at follow-up in patients who progressed as compared to non-progressors at follow-up in 6 months • No baseline cytokine levels predicted disease progression at follow-up
Biomarkers with diagnostic and prognostic utility					
CXCL1	Liang [25]	Cross-sectional	38	Non-IPAF IIP, COPD, HC	<ul style="list-style-type: none"> • Significantly higher in IPAF than in non-IPAF IIP • Significantly higher in IPAF and non-IPAF IIP than in COPD and HC • Negative correlation of level with DLCO • Positive correlation with ESR and Fibmax score • Correlated with ongoing acute exacerbations or future exacerbation within the next 6 months

Table 2 (continued)

CXCL9	Kameda [26•]	Retrospective	35	IPF, RD-ILD	<ul style="list-style-type: none"> • Significantly higher in RD-ILD than in IPAF • Strong positive correlation of baseline level with treatment responsiveness (FVC during and after treatment) • Distinguished RD-ILD from IPAF and IPF with moderate accuracy • Significantly higher in RD-ILD than in IPAF • Significantly higher in IPAF than in IPF • Low accuracy in distinguishing IPAF from IPF • Weak negative correlation with FVC • Distinguished RD-ILD from IPAF and IPF with moderate accuracy • Significantly higher in RD-ILD than in IPAF • Significantly higher in IPAF than in IPF • Moderate accuracy in distinguishing RD-ILD from IPAF and IPF • Low accuracy in distinguishing IPAF from IPF • Weak negative correlation with FVC • Pre-treatment level showed strong positive correlation with treatment responsiveness (by annual FVC) • Higher level in IPAF compared to non-fibrotic lung disease • Negative correlation with DLCO • Inverse correlation with change in FVC and DLCO • In IPAF patients with progressive disease, post-treatment level was increased significantly compared to pre-treatment level • In patients with improvement, levels decreased after treatment • Baseline level higher in IPAF than non-IPAF fibrotic NSIP • Negative correlation of baseline level with DLCO • KL-6 change did not differ significantly between stable and progressive IPAF patients • Significantly higher in IPAF than in non-IPF IIP, but did not differ significantly from IPF • Level in IIP's significantly higher than in pneumonia or HC • Inversely correlated with DLCO • KL6 was higher in IPAF than in healthy controls • Significant negative correlation with FVC/DLCO • Higher baseline and follow-up (52 weeks) level in IPAF patients with disease progression compared to patients with stable/improved disease
CXCL10	Kameda [26•]	Retrospective	35	IPF, RD-ILD	
CXCL11	Kameda [26•]	Retrospective	35	IPF, RD-ILD	
KL-6	Wang [29]	Retrospective	64	Non-fibrotic lung disease (41)**	
	Yamakawa [30]	Retrospective	50	Non-IPAF fibrotic NSIP (25)	
	Xue [27]	Retrospective	27	Non-IPAF IIP; IPF; pneumonia; HC	
	Xue [31]	Prospective	65	HC (30)	

Table 2 (continued)

SP-A	Wang [29]	Retrospective	64	Non-fibrotic lung disease**	<ul style="list-style-type: none"> • Increased level in IPAF compared to in non-fibrotic lung disease • Negative correlation with DLCO • Inverse correlation with change in FVC and DLCO • In IPAF patients with progressive disease, post-treatment level was increased significantly compared to pre-treatment level • In patients with improvement, levels decreased after treatment
	Xue [27]	Retrospective	27	Non-IPAF IIP; IPF; pneumonia; HC	<ul style="list-style-type: none"> • No significant difference between IPAF and IPF or other IIPs • Level in IIPs significantly higher than in pneumonia or HC • Inversely correlated with DLCO in IIPs • Negative correlation with FVC and FEV1
	Xue [31]	Prospective	65	HC	<ul style="list-style-type: none"> • Higher in IPAF than in healthy controls • Negative correlation with DLCO • Higher baseline and follow-up (52 weeks) level in IPAF patients with disease progression compared to patients with stable/improved disease
SP-D	Yamakawa [30]	Retrospective	50	Non-IPAF fibrotic NSIP	<ul style="list-style-type: none"> • Negative correlation of baseline levels with DLCO • No significant difference between stable and progressive IPAF patients
	Xue [27]	Retrospective	27	Non-IPAF IIP; IPF; pneumonia; HC	<ul style="list-style-type: none"> • No significant difference between IPAF and IPF or other IIPs • Level in IIPs significantly higher than in pneumonia or HC

*IL-1b, IL-4, IL-6, IL-10, IL-17A, IL-18, IL-22, GM-CSF (granulocyte-macrophage colony-stimulating factor), and TNF- α (tumor necrosis factor alpha)

**COPD (chronic obstructive pulmonary disease), lung cancer, bacterial pneumonia, eosinophilic pneumonia, bronchiectasis, chronic bronchitis, emphysema, asthma, granuloma, pulmonary tuberculosis

IPAF, interstitial pneumonia with autoimmune features; IL, interleukin; COPD, chronic obstructive pulmonary disease; HC, healthy controls; IIP, idiopathic interstitial pneumonia; RD, rheumatic disease; IPF, idiopathic pulmonary fibrosis; CXCL, C-X-C motif chemokine ligand; DLCO, diffusing capacity of lung for carbon monoxide; CCL, C-C motif chemokine ligand; tRNA, transfer ribonucleic acid; ESR, erythrocyte sedimentation rate; FVC, forced vital capacity; KL-6, Krebs von den Lungen 6; NSIP, non-specific idiopathic pneumonia; SP-A, surfactant protein A; FEV1, forced expiratory volume in first second; SP-D, surfactant protein D

Evaluation and Treatment

Referral to a Rheumatologist

Patients with ILD and autoimmune features are often referred for rheumatological evaluation for the assessment of the autoimmune features and the exclusion of RD diagnoses, a critical step for the treatment algorithm of an ILD patient. Rheumatologists are instrumental in the correct classification of patients with ILD due to their unique perspective and experience with reviewing multiple systems and accurately examining the patient in accordance with ACR or EULAR criteria. In a prospective study of 60 patients, the addition of a rheumatologist to a multidisciplinary discussion of ILD patients changed the ILD diagnosis in 40% of cases. The authors thus concluded that an addition of a rheumatologist could have prevented eight unnecessary procedures (bronchoscopies and lung biopsies) as these procedures are often unwarranted in RD-ILD [33]. Another study, evaluating utility of adding a rheumatologist to multidisciplinary discussion, demonstrated that rheumatology involvement, after referral from pulmonology, led to the new diagnosis of RD-ILD or IPAF in 67% of patients with the change in therapy in 56% of these patients [34]. A comprehensive evaluation by a rheumatologist was highlighted in a study of 33 patients with initial diagnosis of IPF who were found to have myositis spectrum disease after an expanded serological and clinical rheumatologic evaluation [35]. Such a change in diagnosis clearly has critical implications for management, as immunosuppression is avoided in IPF but beneficial in RD-ILD [20]. Given the value of rheumatological evaluation, a multidisciplinary team approach that includes a rheumatologist in the evaluation of a patient with ILD has been proposed by multiple authors [36–38]. Such an approach would improve accuracy of ILD diagnosis and lead to reduced misclassification of subtypes including IPAF.

While familiarity with IPAF criteria is important, the evaluating rheumatologist must remember that IPAF can only be classified after rigorous exclusion of all RDs; thus, this should be the focus of the evaluation. Importantly, while IPAF criteria were developed for research classification purposes, in practice, they are sometimes used for diagnosis when no alternative etiology to ILD with autoimmune features can be found.

Clinical Presentation, Review of Systems, Physical Exam, and Laboratory Evaluation

If the rheumatological evaluation excludes a defined RD, the next step is to assess for the presence of autoimmune features (Table 3). Our suggested approach includes a

comprehensive clinical history to evaluate for joint pain and swelling, polyarticular morning stiffness, Raynaud's phenomenon, and other features of limited SSc, unexplained rash, and pleuritic chest pain. A family history suggesting accelerated aging such as premature graying, bone marrow failure syndromes, and lung and liver fibrosis are important questions to suggest possible genetic mutations or shortened telomeres, a potential marker of accelerated aging. The physical exam should be detailed and particularly evaluated for evidence of inflammatory arthritis, digital tip ulcerations or pitting, roughening of fingers and hands on radial surfaces ("mechanic's hands"), rash or papules on digital extensor surfaces ("Gottron sign" and "Gottron papules," respectively), palmar telangiectasias, or digital edema ("puffy fingers").

Our recommended laboratory testing, including relevant autoantibodies, is included in Table 3. We suggest evaluating for subclinical myositis by checking aldolase and creatine kinase (CK) at baseline and periodically every 6–12 months, particularly in patients with positive anti-synthetase antibodies, MDA-5 antibody, or anti-PM-Scl antibody. Elevated acute phase markers (erythrocyte sedimentation rate [ESR] or C-reactive protein [CRP]) have been shown to be prognostically relevant in various RD-ILDs [39–41] and in IPAF [25, 26].

Imaging and Pulmonary Function Testing

All ILD patients need periodic monitoring of their pulmonary parameters. Generally, pulmonary function tests (PFTs) are repeated every 3 months especially for the first 1–2 years after diagnosis or with any change in treatment. High-resolution computed tomography scan (HRCT) of the chest includes specific radiographic protocol that acquires thin cross-sectional imaging across the entire thorax in the prone and supine position, as well as during inhalation and exhalation (to assess for concomitant small airway disease or pulmonary vasculopathy). All ILD patients undergo HRCT during the initial diagnostic evaluation and is often repeated when patients experience a decline in pulmonary function or new symptoms to assess for progression of their ILD. In addition, HRCT should be repeated yearly for monitoring of lung disease progression and to exclude lung malignancy [38].

Patients presenting with ILD and autoimmune features should be screened with a transthoracic echocardiogram (TTE) for evidence of pericardial disease and pulmonary hypertension. Pulmonary arterial hypertension (PAH) is one of the classification criteria for both SSc and IPAF and is suggested on TTE by right ventricular systolic pressure > 25 mmHg, tricuspid regurgitant jet velocity > 2.8 m/sec, and right ventricular hypertrophy or dilation [42]. Such findings

Table 3 Rheumatologist approach to evaluation of patient with ILD and autoimmune features

History/review of systems*	*After excluding other RDs
<ul style="list-style-type: none"> • Joint pain, number of joints involved, duration of symptoms • Morning joint stiffness for ≥ 60 minutes • Swelling in fingers or toes • Unexplained rashes • Cold induced color changes in fingers or toes • Ulceration on tips of digits • Sharp shooting chest pain • Unexplained swelling in legs/feet or abdomen • Premature graying (≤ 30 years) • Acid reflux symptoms or difficulty swallowing • History of fluid around the heart or lungs • Family history of liver cirrhosis or pulmonary fibrosis 	
Clinical Exam**	**In addition to excluding exam features consistent with other RDs
<ul style="list-style-type: none"> • Synovitis • Objective weakness in upper and lower extremities, neck flexors, and extensors • Cracking/roughening around the edges of fingers and hands (particularly radial side) or toes/feet • Papules on extensor surfaces of extremities (Gottron papules) • Rash on extensor surfaces of extremities (Gottron sign) • Digital pitting • Digital ulceration • Palmar telangiectasias • Puffy fingers 	
Laboratory Testing***	***In addition to performing other necessary testing based on history and clinical exam
<ul style="list-style-type: none"> • CBC with differential, CMP, urinalysis • ESR, CRP • CK, aldolase • ANA by immunofluorescence (pattern and titer) • RF, CCP • SSA, SSB, Ro52, Ro60 • dsDNA, Smith • Scl-70, RNP • PM-Scl. MDA-5 • Anti-synthetase antibodies (Jo-1, PL-7, PL-12, EJ, OJ, KS) 	No need to repeat testing if already done by Pulmonary

ILD, interstitial lung disease; *RD*, rheumatic disease; *CBC*, complete blood count; *CMP*, comprehensive metabolic panel; *ESR*, erythrocyte sedimentation rate; *CRP*, c-reactive protein; *CK*, creatine kinase; *ANA*, antinuclear antibody; *RF*, rheumatoid factor; *CCP*, cyclic citrullinated peptide; *SSA*, Sjogren's-syndrome-related antigen A; *SSB*, Sjogren's-syndrome-related antigen B; *dsDNA*, double-stranded deoxyribonucleic acid; *RNP*, ribonucleoprotein; *PM-Scl*, polymyositis-scleroderma; *MDA-5*, melanoma differentiation-associated protein 5.

warrant right heart catheterization (RHC) to confirm the diagnosis of PAH.

Pulmonary Histopathology

Two types of lung biopsies can be performed: transbronchial lung biopsy (including cryobiopsy) and surgical lung biopsy. Transbronchial biopsies have lower complication rates but lower yield due to smaller sample size, while surgical lung biopsies offer greater accuracy in diagnosis but come with higher risks [43]. In general, lung biopsy is unnecessary in cases of clear RD-ILD but may be considered in cases when an ILD diagnosis remains unclear after non-invasive workup. We recently showed

that bronchoscopic evaluation did not change diagnosis in IPAF or RD-ILD [44]. In contrast, Wu, et al. described change from suspected IPAF to IPF after transbronchial lung cryobiopsy in one out of five patients [45]. Ultimately, the decision for bronchoscopy and lung biopsy should be driven by the pulmonologist.

Natural History and Prognosis

Following the publication of the IPAF criteria in 2015, several ILD and UCTD patients were re-assessed to study the natural history of IPAF. The majority of studies are

retrospective, with few prospective studies published recently.

Natural History and Prognostic Factors for Survival

There are limited and conflicting data regarding the natural history of patients with IPAF. General consensus suggests that survival in IPAF is better than in IPF, a prototypical progressive fibrotic ILD with an estimated average survival of only 3–5 years from diagnosis [46], but worse than in RD-ILD. Factors associated with longer transplant-free survival in IPAF patient cohorts include presence of the clinical domain [7], myositis-specific antibodies, particularly Jo-1 antibody [9, 13], and higher partial pressure of oxygen (paO₂) [47].

Factors associated with worse survival in IPAF include increasing age [13, 15, 48, 49], smoking history [49], lower baseline pulmonary function (forced vital capacity, or FVC, and/or diffusing capacity for carbon monoxide, or DLCO) [15, 50], pulmonary hypertension [51, 52], presence of RNP antibody [49], shorter LTL, and presence of *MUC5B* minor allele [32*]. Oldham, et al. and Kelly and Moua found that IPAF patients with UIP pattern have a similar survival to IPF [7, 17] while patients with NSIP pattern have a similar survival to RD-ILD [7]. Other studies have not confirmed these findings [18].

Evolution into Classifiable RD

It is also possible for IPAF patients to evolve into a distinct RD. In a study by Alevizos, et al., only a small proportion of patients with IPAF developed into a defined RD during follow-up, underscoring IPAF as an independent entity [23]. Other authors argue that IPAF is in fact already very similar to RD-ILD and should be treated the same way without awaiting development of a defined RD [12]. Presence of IPAF by classification criteria, treatment with immunosuppressants, and combination of female gender and having the serologic domain were found to be strong predictive factors of developing distinct RD among a cohort of ILD patients [23].

IPAF Management

Little is known about optimal medical therapy for patients meeting IPAF criteria. As the assumed underlying pathogenesis is inflammatory, the common approach is to use immunosuppressants in these patients, particularly if they demonstrate lung function decline. These treatments are extrapolated from clinical studies in RD-ILD. Accepted treatments for RD-ILD include cyclophosphamide and mycophenolate mofetil (MMF) that demonstrated efficacy

in Scleroderma Lung Trials I and II [53, 54••]. Azathioprine has been used in various RD-ILDs despite lack of randomized controlled studies. Rituximab and abatacept has shown promise in ILD, particularly in SSc [55, 56]. Recently, tocilizumab has been approved for treatment of SSc-ILD [57••]. Refractory IIM-ILD can be treated with calcineurin inhibitors and intravenous immune globulin (IVIG) [58]. Additionally, JAK inhibitors have been used for refractory cases of IIM-ILD [59] and RA-ILD [60].

Decision on Whom and When to Treat

A significant challenge in treating ILD patients in general, and IPAF in particular, is deciding when to start treatment. Indeed, a proportion of IPAF patients demonstrates long-term stability without the need for immunosuppression. On the other hand, Li, et al. found significant improvement in DLCO in treated IPAF patients and argue that early treatment is needed in IPAF based on its similarity to RD-ILD. However, the treated patient sample consisted of 12 IPAF patients, and the findings might not be generalizable to all IPAF patients [12]. The decision to initiate treatment should be weighed against the potential risks. Therapy is usually initiated if the patient experiences progressive fibrosis of the lungs (by PFT parameters or HRCT), is at high risk of progressing (such as cases of MDA-5 antibody associated disease) [61], has significant symptoms or lung function impairment at diagnosis, or if there are extrapulmonary manifestations that warrant therapy (such as debilitating arthritis).

Immunosuppressants in IPAF

Selection of therapy in IPAF is challenging because it is not known which patients will respond favorably to immunosuppression. Ito, et al. evaluated patients based on the cluster of autoantibodies and found that positivity to SSB and to SSc-associated antibodies (ANA nucleolar pattern, ANA centromere pattern, anti-ribonucleoprotein, and anti-Scl-70) predicted positive response to immunosuppression in univariate Cox regression analysis [48]. Karampeli, et al. was not able to identify significant variables predicting lung function stability in the setting of immunosuppression in his prospective study of 39 patients; however, only eight patients experienced lung function decline and thus the results were inconclusive [11].

McCoy, et al. retrospectively demonstrated that patients with IPAF treated with MMF had stabilization of lung function, particularly DLCO [62]. We recently showed that treatment with both MMF and prednisone was associated with non-progression of lung disease in patients meeting IPAF criteria. Wiertz, et al. described a case series of 13 IPAF patients with severe steroid-refractory disease who had

significant improvement in %FVC following cyclophosphamide treatment which differed from non-IPAF unclassifiable IIP patients [63]. A particular subset of IPAF associated with MSA behaves similarly to IIM-ILD [9•] and thus we should consider managing it similarly. Further research will be necessary to define other subtypes of IPAF patients who may be more responsive to other therapies.

An ongoing concern with IPAF is that IPAF-UIP behaves similarly to IPF [7, 51] and thus immunosuppression may be harmful. This notion is based on landmark PANTHER-IPF trial which showed increased mortality in IPF patients treated with a combination of azathioprine, prednisone, and N-acetylcysteine [64]. It is still unclear whether the detrimental effect is due to this combination specifically or if all immunosuppression is uniformly harmful in IPF. Furthermore, more research is needed on how to implement telomere and genetic testing in IPAF and whether short telomeres affect response to immunosuppression in IPAF.

Response to Antifibrotics

Until recently, antifibrotic therapy was restricted to patients with IPF where they effectively slow lung function decline [65••, 66]. However, the role of antifibrotic therapy in the treatment of ILD has recently expanded. Nintedanib, a multi-targeted tyrosine kinase inhibitor, has been shown to reduce rate of lung function decline patients SSc-ILD [67] and those with progressive fibrotic ILD of any etiology, including IPAF [68]. However, patients in this study were not permitted concurrent immunosuppressant therapy during the first 6 months of the trial, making it difficult to extrapolate whether either type of therapy, or a combination, is optimal in IPAF.

Referral for Lung Transplantation

The decision to refer to lung transplant is most often made by the pulmonologist and can be in collaboration with the rheumatologist, but should be done early in a patient who has declining lung function, for timely optimization of the patient for lung transplant [69].

Managing Comorbidities

Multiple comorbidities have been described in IPAF including systemic hypertension, diabetes mellitus, and ischemic heart disease [70], which could all contribute to mortality. Thus, a holistic approach and co-management of comorbidities with the primary care provider is necessary.

Furthermore, ensuring the patient is able to exercise and is referred to physical therapy/pulmonary rehabilitation early may significantly improve the patient's quality of life [71]. Notably, GERD is a frequent manifestation of ILD,

including IPAF, and has been described as a contributor to ILD development [72]. McCoy, et al. found that FVC decline occurred more in IPAF patients with GERD than those without, raising the possibility that aspiration contributes to lung disease pathogenesis in this population [62]. Identifying and treating GERD, as a comorbidity in IPAF, may prove to be an important part of management.

Gaps and Opportunities: Clinical and Research

The central hypothesis in IPAF is that the underlying pathogenesis involves inflammatory and autoimmune mechanisms. However, variable survival in IPAF cohorts challenges this notion. There is a paucity of studies regarding mechanism of damage in IPAF. It is likely that IPAF, despite the aim of the classification criteria to homogenize this population, remains a heterogeneous group which encompasses several lung diseases varying in their pathophysiology and management strategies.

Genomics

Genomic studies may allow more accurate understanding of the spectrum of this entity by separating patients into subtypes of IPAF with distinct prognostic and diagnostic biomarkers. An emerging consideration in ILD is the genetic basis for the disease, regardless of clinical classification. An example is COPA syndrome, which is an autosomal dominant disease caused by a mutation in *COPA* gene manifesting with a constellation of early onset ILD with arthritis and autoantibody presence such as ANA and rheumatoid factor; glomerulonephritis is also frequently present [73]. While usually diagnosed in childhood, late presentation/recognition may occur. It may be reasonable to consider genetic testing in a patient with IPAF whose clinical domain consists of arthritis, particularly in the setting of family history and/or concurrent glomerulonephritis.

COVID-19

A unique challenge is understanding IPAF in the context of prior COVID-19 infection. Infection with COVID-19 may induce the development of ILD [74••]. Additionally, COVID-19 virus has been linked to developing autoimmunity possibly due to the mechanism of molecular mimicry and production of autoantibodies [75, 76]. In an observational study by Mastalerz, et al., 53.5% of admitted patients with COVID pneumonia had ANA titer 1:320 or greater [77]. Patients who were infected with COVID-19 virus and who develop ILD and autoantibodies may, thus, be ultimately

classified as IPAF. However, it is still uncertain whether such classification would be appropriate and whether these patients will represent a unique subgroup of IPAF patients.

Uniform Outcome Measurement

Consensus is needed regarding most appropriate outcomes measurement in IPAF, including not only pulmonary function outcomes but also extrapulmonary morbidity (i.e., malignancy and infections) and development of additional features such as new morphological features, accrual of autoantibodies, and clinical symptoms. This will allow comparison of results across studies, with the ultimate goal of informing treatment recommendations. These goals cannot be reached without close collaboration between pulmonologists and rheumatologists. In the meantime, many of the pulmonary metrics for IPF and ILD are likely to be used for IPAF patients.

Conclusions

IPAF is a heterogeneous entity with unclear pathogenesis, prognosis, and management. The revision of the classification criteria is likely looming with further refining of our understanding of this syndrome.

The care of the IPAF patient is complex and is multidisciplinary with pulmonology, rheumatology, pathology, radiology, physical therapy, primary care, and pulmonary transplant providers, all serving vital roles. The rheumatologist has a role in (1) multidisciplinary discussion to assist in reaching this classification by excluding a defined RD and confirming the autoimmune features, (2) monitoring for emergence of a distinct RD, and (3) assistance in selection of appropriate therapeutic agents and monitoring for toxicity.

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Compliance with Ethical Standards

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