

Interstitial Pneumonia with Autoimmune Features



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Abstract

Interstitial pneumonia with autoimmune features (IPAF) is a research classification proposed by the European Respiratory Society/American Thoracic Society Task Force on Undifferentiated Forms of Connective Tissue Disease-associated Interstitial Lung Disease as an initial step to uniformly define, identify, and study patients with interstitial lung disease (ILD) who have features of autoimmunity, yet fall short of a characterizable connective tissue disease. Since its publication in July 2015, there has been substantial interest in IPAF. Centers from around the world have published their findings of retrospectively identified cohorts of patients who fulfill IPAF criteria, suggestions for modification of the criteria have been offered, and patients who fulfill IPAF criteria are being included as a subset in the ongoing phase II multicenter unclassifiable ILD treatment trial with pirfenidone. The

IPAF designation represents an important first step toward studying and furthering our understanding of the natural history of this cohort of patients with ILD using uniform nomenclature and a standardized set of criteria. Prospective evaluations and, ideally, interdisciplinary and multicenter collaborations will inform best practices for treatment and management and will guide future refinement to the IPAF criteria. This review focuses on the relevant background that led to the development of IPAF, summarizes the proposed criteria, discusses cohort studies of patients with IPAF published to date and what they have taught us about the IPAF phenotype, and offers insights into future directions in this arena.

Clinical trial registered with www.clinicaltrials.gov (NCT03099187).

Keywords: idiopathic interstitial pneumonias; connective tissue diseases; interstitial lung diseases; pulmonary fibrosis

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Interstitial lung disease (ILD) refers to a heterogeneous group of diffuse parenchymal lung disorders characterized by varying degrees of inflammation and/or fibrosis of the pulmonary interstitium, ultimately resulting in parenchymal damage. The ILDs are classified by specific patterns of clinical, radiographic, and histopathologic features and are broadly grouped into those considered idiopathic and those with an identifiable etiology. The most commonly identified causes of ILD are environmental or occupational exposures to organic or inorganic dusts, connective tissue disease (CTD), and drug- or radiation-induced lung injury (Figure 1).

The diagnosis of an idiopathic interstitial pneumonia (IIP), of which idiopathic pulmonary fibrosis (IPF) is the most common, requires the exclusion of known causes of ILD. As per international guidelines (1), patients newly diagnosed with ILD should undergo evaluation including clinical history and examination, pulmonary function testing (PFT), high-resolution computed tomography (HRCT) scan, surgical lung biopsy if indicated, and multidisciplinary discussion between experienced clinicians, radiologists, and pathologists to provide the most accurate diagnosis and distinguish an IIP from ILD with an identifiable etiology.

One of the most common underlying causes of ILD is CTD, which is identified in up to 30% of new ILD diagnoses (2). Because of the high prevalence of CTD in patients with newly diagnosed ILD, current guidelines recommend excluding the presence of an underlying CTD (1). Distinguishing CTD-associated ILD (CTD-ILD) from an IIP, particularly IPF, is important, because CTD-ILD has a more favorable prognosis, and the available therapeutic options differ significantly (3–5). Despite current recommendations and the importance of an accurate diagnosis to guide treatment decisions and inform patients of their prognosis, there is no standardized approach to assess for CTD.

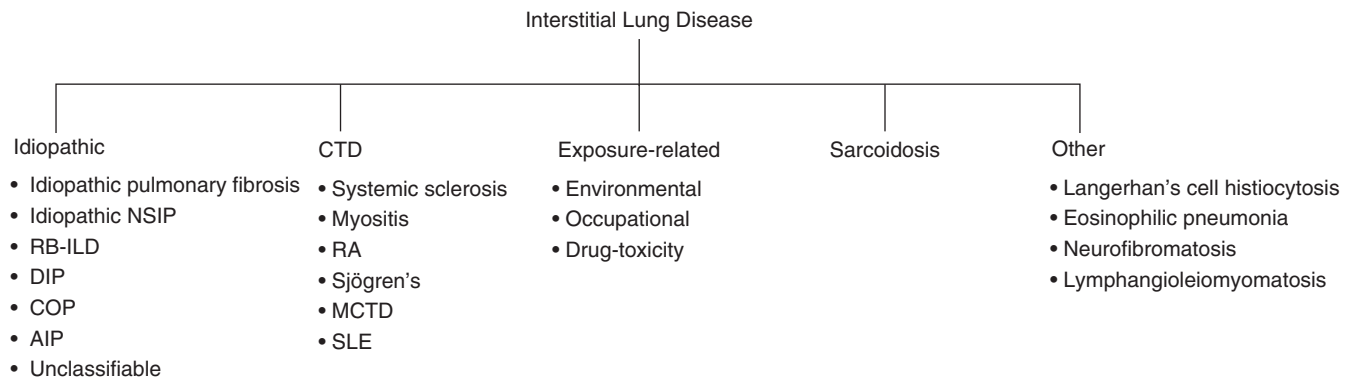


Figure 1. Classification of interstitial lung diseases. AIP = acute interstitial pneumonia; COP = cryptogenic organizing pneumonia; CTD = connective tissue disease; DIP = desquamative interstitial pneumonia; MCTD = mixed connective tissue disease; NSIP = nonspecific interstitial pneumonia; RA = rheumatoid arthritis; RB-ILD = respiratory bronchiolitis-associated interstitial lung disease; SLE = systemic lupus erythematosus. Adapted by permission from Reference 52.

Moreover, the type and extent of evaluation varies by center, is often practitioner dependent, and is impacted by the composition of the multidisciplinary team—particularly regarding rheumatologic engagement.

Practically speaking, despite extensive efforts to identify occult CTD in patients with IIP, in many instances features suggesting background autoimmunity are identified, yet the patient may not have a characterizable CTD. Take, for example, a 45-year-old woman with a pattern of usual interstitial pneumonia (UIP) by HRCT that is confirmed by surgical lung biopsy. There are no extrathoracic symptoms or signs of a CTD. Serologically, there is an isolated positive anti-SS-A antibody, and further review of her lung histopathology reveals lymphoid follicles with germinal center formation. This clinical scenario appears to represent an “autoimmune ILD” on the basis of the integration of clinical and pathologic data, yet on rheumatologic assessment she is not found to have any characterizable CTD. How should this patient be classified—and, more importantly, how does such classification impact the therapeutic approach to her ILD? Should she be considered as having IPF and treated with an antifibrotic medication or as CTD-ILD and treated with immunosuppression?

It is not uncommon to have discord among specialists around how to classify such patients, and these differences can translate to disagreements over therapeutic strategy. To some extent, this scenario highlights the ongoing interdisciplinary

divide that exists between pulmonary medicine and rheumatology, with the latter group often taking the lead on developing CTD classification criteria. Indeed, other than for systemic sclerosis, the presence of ILD is not a feature in any of the classification schemes for other CTDs. As a result, because a patient lacks the extrathoracic “autoimmune” features that, in aggregate, meet current diagnostic criteria for a specific CTD, she is not considered to have CTD by rheumatologic standards.

Though reliable determinants of prevalence are lacking, there is recognition that it is common to encounter patients with IIP who have subtle features suggestive of an autoimmune etiology and yet do not have a characterizable CTD (6). The terms “undifferentiated CTD” (UCTD), “lung-dominant CTD,” or “autoimmune-featured ILD” have all been used to describe such individuals, and each term has been associated with unique and differing sets of criteria (7–9). These sets of criteria are different enough that research studies using one set of criteria are not likely to be applicable to cohorts from centers using other sets of criteria. Assayag and colleagues (10) applied the differing criteria of UCTD (a broader form proposed by Kinder and colleagues [8] and a narrower form proposed by Corte and colleagues [3]), lung-dominant CTD, and autoimmune-featured ILD to a cohort of 119 patients with IIP evaluated in a tertiary ILD referral program and found that 56% of patients fulfilled criteria for at least one of these designations, but only 18% fulfilled all sets. Application of the broadest, least-specific

criteria (8) captured 41% of the cohort, but the narrowest, most specific (3) of the four only encompassed 21% (10). This study convincingly illustrated that a uniform definition and nomenclature was needed to study patients with suggestive forms of autoimmune ILD, particularly given the fact that these patients are often shared among specialties.

In an effort to build consensus and interdisciplinary collaboration, the American Thoracic Society and the European Respiratory Society supported an international working group on undifferentiated forms of CTD-ILD, consisting of an international, multidisciplinary panel including investigators from the centers that had put forth the previous criteria and terminology of suggestive forms of CTD-ILD (3, 7–9). The primary objective of this task force was to develop consensus surrounding the nomenclature and classification of patients with IIP and features of autoimmunity without a characterizable CTD (Figure 2). The task force published a research statement (11) outlining the “interstitial pneumonia with autoimmune features” (IPAF) concept and nomenclature along with a set of classification criteria (Table 1) to serve as a platform for future research of this IIP subset.

Review of the IPAF Criteria

The term “interstitial pneumonia with autoimmune features” was chosen to highlight the distinct nature of this subset of

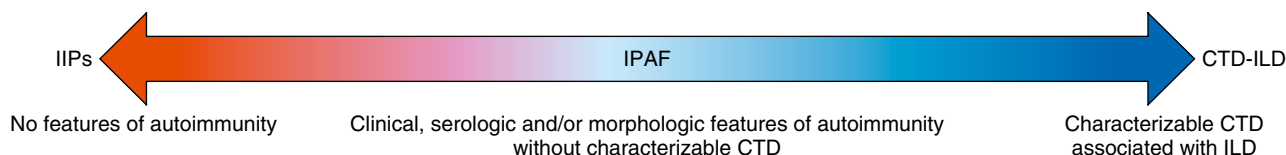


Figure 2. Continuum on which interstitial pneumonia with autoimmune features (IPAF) sits between the idiopathic interstitial pneumonias and defined connective tissue disease–related interstitial lung diseases (CTD-ILDs). IIP = idiopathic interstitial pneumonia.

ILD. The term “connective tissue disease” was specifically avoided, because of concerns that such labeling gives a false impression that these individuals are predetermined as having a CTD. Several *a priori* requirements must be fulfilled for the classification of IPAF: individuals must have evidence of interstitial pneumonia by HRCT imaging and/or by surgical lung biopsy, known causes for interstitial pneumonia must have been excluded after a thorough clinical evaluation, and patients do not meet criteria for a characterizable CTD. The classification criteria are then organized around three central domains: 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 pulmonary physiologic features. To be classified as IPAF, the individual must meet all of the *a priori* requirements and have at least one feature from at least two of the three domains (11).

Clinical Domain

The clinical domain consists of extrathoracic features that suggest an underlying CTD, but, on their own, none are diagnostic of a specific CTD. The features include distal digital fissuring (“mechanic hands”), digital tip ulceration, inflammatory arthritis or polyarticular morning joint stiffness lasting more than 60 minutes, palmar telangiectasia, Raynaud phenomenon, unexplained digital edema, and unexplained fixed rash on the digital extensor surfaces (Gottron’s sign). Less-specific features that were included in prior classification schemes (e.g., joint pain, myalgias, weight loss, photosensitivity, and sicca symptoms) were not included. The task force suggested that, ideally, the presence of clinical features should be assessed on physical examination by experienced practitioners and that self-reported symptoms should not be

used alone to identify clinical domain features.

Serologic Domain

The serologic domain consists of autoantibodies that are strongly associated with CTD and exclude nonspecific markers of inflammation, such as erythrocyte sedimentation rate or C-reactive protein. For the less-specific antibodies—antinuclear antibody (ANA) and rheumatoid factor—sufficiently high titers are required to fulfill the serologic domain criteria. ANA positivity with a diffuse homogeneous or speckled pattern at low titer can be found in healthy control subjects, healthy elderly patients (12), and patients with IPF (13), thus prompting a higher titer threshold to meet criteria. ANA of any titer with nucleolar or centromere staining pattern meets the serologic domain criteria, as these patterns are strongly associated with systemic autoimmune disease. ANA should be measured by indirect immunofluorescence for accurate results.

Morphologic Domain

The morphologic domain consists of three subdomains: radiographic patterns by HRCT, histopathologic features from surgical lung biopsy, and multicompartment features (i.e., additional thoracic involvement). If any one item from the three subdomains is present, the criteria for the morphologic domain are fulfilled.

The radiographic subdomain describes patterns from HRCT that include nonspecific interstitial pneumonia (NSIP), organizing pneumonia (OP), NSIP with OP overlap, and lymphocytic interstitial pneumonia (LIP). NSIP is the most common pattern on HRCT in patients with CTD-ILD (14), and the presence of NSIP, OP, or LIP patterns on HRCT poses additional consideration of an underlying autoimmune process. Although UIP pattern on HRCT is the most common pattern in rheumatoid arthritis–associated ILD (15)

and is also encountered in other CTD-ILDs (16), it was not given the same weight as the other IIP patterns because it is less specific for CTD.

The histopathologic pattern on surgical lung biopsy is the second subdomain within the morphologic domain. The features included in this subdomain—NSIP, OP, NSIP with OP, and LIP—are highly associated with the presence of a CTD (17). In addition to the overall histopathologic pattern on surgical lung biopsy, secondary features of interstitial lymphoid aggregates with germinal centers and diffuse lymphoplasmacytic infiltration are included in this subdomain.

Despite shared nomenclature, HRCT patterns do not correlate well with histopathologic patterns on surgical lung biopsy, with the exception of UIP (18–22). This lack of correlation for NSIP and OP patterns between HRCT and histopathology informs the rationale for including separate HRCT and histopathologic subdomains within the morphologic domain. Similar to the radiographic subdomain, UIP pattern on surgical lung biopsy was not included in the criteria because of its lack of association with an increased likelihood of CTD.

It is worth emphasizing that the presence of a radiologic or histopathologic UIP pattern does not exclude an IPAF designation but, unlike NSIP, OP, or LIP patterns, there is no morphological “credit” given to the UIP pattern. Thus, a patient with UIP pattern on HRCT or surgical lung biopsy still meets the IPAF definition by the same criterion: meeting all *a priori* requirements and having at least one feature from two of the three domains: clinical, serologic, or morphologic.

The final subdomain of the morphologic domain is the multicompartment designation, which includes unexplained pleural or pericardial thickening or effusions,

Table 1. Classification criteria for interstitial pneumonia with autoimmune features

1. Presence of an interstitial pneumonia by HRCT or SLB *and*
2. Exclusion of alternative etiologies *and*
3. Does not meet criteria for a defined CTD *and*
4. At least one feature from at least two of the following domains:

<p>A. Clinical domain</p> <ol style="list-style-type: none"> 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 phenomenon 6. Unexplained digital edema 7. Unexplained fixed rash on the digital extensor surfaces (Gottron sign) 	<p>B. Serologic domain</p> <ol style="list-style-type: none"> 1. ANA $\geq 1:320$ titer, diffuse, speckled, homogeneous patterns <i>or</i> <ol style="list-style-type: none"> a. ANA nucleolar pattern (any titer) <i>or</i> 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 (SS-A) 6. Anti-La (SS-B) 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 	<p>C. Morphologic domain</p> <ol style="list-style-type: none"> 1. Suggestive radiology patterns by HRCT: <ol style="list-style-type: none"> a. NSIP b. OP c. NSIP with OP overlap d. LIP 2. Histopathology patterns or features by surgical lung biopsy: <ol style="list-style-type: none"> 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. Multicompartment involvement (in addition to interstitial pneumonia): <ol style="list-style-type: none"> 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
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Definition of abbreviations: ANA = antinuclear antibody; CTD = connective tissue disease; HRCT = high-resolution computed tomography; LIP = lymphocytic interstitial pneumonia; NSIP = nonspecific interstitial pneumonia; OP = organizing pneumonia; PFT = pulmonary function testing; SLB = surgical lung biopsy. *Includes airflow obstruction, bronchiolitis or bronchiectasis. Adapted by permission from Reference 11.

intrinsic airways disease, or pulmonary vasculopathy. Patients with CTD often demonstrate involvement of other pulmonary structures, including airways, pulmonary vasculature, and the pleura with varying degrees of frequency with respect to the underlying disease (Table 2) (4, 23). The current research statement does not provide definitions for determining the presence

of “unexplained” multicompartment involvement with respect to airways, pleural, or vascular disease, or guidelines to interpret the presence of “diffuse” lymphoplasmacytic infiltration or lymphoid aggregates with germinal centers on biopsy. Therefore, identifying features of the multicompartment subdomain are left to the discretion of the individual clinician or investigator.

Retrospectively Identified Cohorts with IPAF

Since publication of the European Respiratory Society/American Thoracic Society IPAF research statement, a number of studies have retrospectively identified and described cohorts of patients with ILD who fulfill IPAF criteria (Table 3). It is important to note that each of these cohorts was identified retrospectively and is impacted by the methodologic limitations of cohort identification and selection.

Oldham and colleagues (24) identified 422 patients with either IIP or UCTD from their ILD database, and 144 (34%) met IPAF criteria. The mean age of the IPAF group was 63.2 years, with a majority being female (52%) and former smokers (55%). The most common clinical feature was Raynaud phenomenon (27.8%), and the most common serologic feature was ANA positivity (77.6%). Although the most common morphologic domain feature was NSIP pattern by HRCT (31.9%), the majority of the cohort demonstrated a UIP

Table 2. Connective tissue disease-associated pulmonary manifestations

	SSc	PM/DM	RA	Primary Sjögren	MCTD	SLE
ILD	+++	+++	++	++	++	+
Airways	—	—	++	++	+	+
Pleural	—	—	++	+	+	+++
Vascular	+++	+	—	+	++	+
DAH	—	—	—	—	—	++

Definition of abbreviations: DAH = diffuse alveolar hemorrhage; ILD = interstitial lung disease; MCTD = mixed connective tissue disease; PM/DM = polymyositis/dermatomyositis; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus; SSc = systemic sclerosis. The number of + signs indicates relative prevalence of each manifestation. Adapted by permission from Reference 4.

Table 3. Comparison of retrospectively identified interstitial pneumonia with autoimmune features cohorts

	Oldham <i>et al.</i> (24)	Chartrand <i>et al.</i> (27)	Ahmad <i>et al.</i> (29)	Ito <i>et al.</i> (31)	Dai <i>et al.</i> (32)	Yoshimura <i>et al.</i> (34)	Kelly and Moua (35)
Patients, <i>n</i>	144	56	57	98	177	32	101
Age, yr, mean ± SD	63.2 ± 11	54.6 ± 10.3	64.4 ± 14	67.5 ± 9	67.6 ± 8.6	63.4 ± 12.6	56.9 ± 14.2
Female	52.1	71.4	49.1	58.2	55.9	40.6	39
Ever-smoker	54.9	32.1	34	38.8	19.2	56.2	31
Clinical	49.3	62.5	47.3	NR	20.3	53.1	NR
Serologic	91.7	91.1	93	100*	92.1	71.9	NR
Morphologic	85.4	98.2	78.9	100†	95.5	96.9	NR
Clinical and serologic	14.6	2	NR	NR	NR	3.1	4
Clinical and morphologic	8.3	9	NR	NR	NR	28.1	14
Serologic and morphologic	50.7	37.5	NR	100	NR	46.9	26
All three domains	26.4	52	NR	NR	NR	21.9	56
UIP by HRCT	54.6	8.9	28	0	4.5	NR	NR
Underwent SLB, <i>n</i> (%)	83 (57.6)	36 (64.3)	16 (28.1)	17 (17.3)	0‡	22 (68.8)	51 (50.5)
UIP on SLB, <i>n</i> (%)	61 (73.5)	8 (22.2)	3 (18.8)	3 (17.6)	—	—	12 (23.5)
Treatment							
Corticosteroids	32.2	81.8	67.9	17.3	72.3	59.4	NR
Antifibrotic	NR	NR	5.4	2	NR	25	NR
Outcome							
Death	39.6	0	12.3	27.6	19.8	NR	28
Lung transplant	10.8	NR	NR	NR	NR	NR	NR

Definition of abbreviations: HRCT = high-resolution computed tomography; NR = not reported; NSIP = nonspecific interstitial pneumonia; OP = organizing pneumonia; SD = standard deviation; SLB = surgical lung biopsy; UIP = usual interstitial pneumonia pattern.

Data presented as percentage unless otherwise stated.

*Based on study design, inclusion criterion was positive serological evaluation.

†Based on reported HRCT findings of NSIP, OP, or NSIP + OP in 98 of 98 subjects.

‡All histopathology from transbronchial biopsies.

pattern on HRCT (54.6%) and on surgical lung biopsy (61 of 83 patients biopsied, 73.5%). Twenty-six percent of patients met criteria in all three domains.

Survival analysis of the Oldham cohort demonstrated that those meeting IPAF criteria had slightly better outcomes than IPF but worse than those with CTD-ILD (24). After stratifying for the presence of UIP pattern on HRCT or surgical lung biopsy, non-UIP-IPAF had similar survival to CTD-ILD ($P = 0.45$), whereas UIP-IPAF demonstrated similar survival to IPF ($P = 0.51$). Predictors of increased mortality after multivariate analysis included age and diffusing capacity of the lung for carbon monoxide (DL_{CO}), leading the authors to conclude that the Gender, Age, Physiology (GAP) scoring system (25), validated for mortality prediction in IPF, may be useful in IPAF as well. In a follow-up study of this cohort, Chung and colleagues focused on imaging predictors of survival and identified worse survival for subjects with IPAF when concomitant honeycombing or pulmonary artery enlargement is present (26).

Chartrand and colleagues (27) characterized a cohort of 56 patients meeting IPAF criteria. The cohort was identified from a group of patients who were all determined by the treating physician to have an autoimmune basis for their ILD, but without a characterizable CTD or alternative identifiable etiology. This cohort was slightly younger than that in the study by Oldham and colleagues (24), with a mean age of 55 years, and had a greater predominance of females (71%) and never-smokers (68%) (27). Similar to the Oldham cohort, Raynaud phenomenon (39%) and ANA positivity (48%) were the most common clinical and serologic domain features, respectively. Fifty-five of the 56 patients (98%) fulfilled IPAF morphologic criteria, as compared with 85% in the Oldham cohort. By HRCT, the predominant pattern was NSIP (57%), followed by the combination of NSIP and OP (18%). Of the 36 patients who underwent surgical lung biopsy, 12 (33%) had NSIP and 8 (22%) had UIP.

A majority of patients (52%) in the Chartrand cohort met criteria in all three domains. This was likely driven by the greater number of patients with identified

clinical features as compared with the Oldham cohort (62.5% in the Chartrand cohort vs. 49.3% in the Oldham cohort). Each patient in the Chartrand cohort was primarily under the care of a rheumatologist, which may explain the increase in identified clinical features. Furthermore, 36% of the cohort had a positive tRNA synthetase antibody, and the authors acknowledged that although the patients lacked other features of myositis spectrum, some could consider these individuals to have partial presentation of the antisynthetase syndrome (28).

Ahmad and colleagues (29) published data from a European cohort, comparing those with IPAF to those with IPF. Patients were identified consecutively over 3 years from a hospital discharge database searching for those with IIP or CTD-ILD. Of 778 patients screened, 156 (20.1%) had IPF, 167 (21.5%) had CTD-ILD, and 57 (7.3%) met criteria for IPAF. Similar to the Oldham cohort, patients had a mean age of 64 years but with very slight male predominance (50.9%). Raynaud phenomenon (74%) and ANA positivity (82%) were again the most common clinical and serologic features.

Clinical features, similar to the Oldham cohort, were identified in 47% of patients. Morphologically, 53% had NSIP pattern and 28% had UIP pattern on HRCT. Sixteen patients of the IPAF group underwent surgical lung biopsy; NSIP pattern was identified in five (31%) and UIP pattern in three (19%).

Overall survival at 1 year was not different between those with IPAF (83.6%) and IPF (94.8%) ($P = 0.05$), and among the IPAF cohort, UIP pattern on HRCT was not associated with worse survival. One critique of this cohort was that some of the patients ($n = 13$, 23%) had abnormal nailfold capillaroscopy demonstrating giant capillaries. On the basis of this finding, some would consider this subset to have an early form of systemic sclerosis (30), which would exclude them from an IPAF designation.

Ahmad and colleagues proposed a novel “IPAF score” indicating the total number of IPAF criteria that were met in any of the three domains. In their cohort, the mean score was 3.5, with a maximum score of 9 in one patient. Although the IPAF score was not associated with survival in this study, hypothetically, a higher “IPAF score” may be associated with progression to a defined CTD.

Ito and colleagues (31) retrospectively identified a cohort of 98 patients who fulfilled IPAF criteria. The primary aim of this study was to determine prognostic factors of the serologic and morphologic IPAF domains. Therefore, the cohort was derived by screening a database of 1,057 subjects with IIP first for positive serologies ($n = 332$); after excluding subjects for incomplete data or failure to meet the *a priori* IPAF requirements, the group was narrowed to those meeting the morphologic domain by HRCT pattern. This search strategy derived the final cohort of 98 patients who were subsequently analyzed to identify prognostic factors.

The cohort had a mean age of 67.5 years and was predominantly female (58.2%) and never-smokers (61.2%). Some 64.3% of patients had NSIP pattern on HRCT. Their analysis demonstrated that increasing age and NSIP pattern on HRCT, as compared with NSIP with OP overlap or OP alone, were associated with shortened survival. A limitation to this cohort is that the search strategy used could plausibly miss patients with IIP who would have otherwise met IPAF criteria.

Dai and colleagues (32) retrospectively identified a Chinese cohort of 177 patients from an ILD database who fulfilled criteria for IPAF and compared them to a group of 1,252 patients with ILD who did not fulfill IPAF criteria. The IPAF cohort had a mean age of 60.2 years and was 55.9% female and 80.8% never-smokers. Raynaud phenomenon (12.9%), ANA positivity (49.2%), and NSIP on HRCT (61.6%) were the most common features from the three domains. Interestingly, only 20.3% of the cohort had an identified clinical feature. Eight patients (4.5%) had UIP pattern on HRCT. No patients underwent surgical lung biopsy. Multivariate analysis demonstrated age, smoking history, anti-RNP positivity, and OP pattern on HRCT as predictors for worsened survival.

Focusing on a subset of patients with chronic fibrotic interstitial pneumonia, Yoshimura and colleagues retrospectively applied the IPAF criteria to a cohort of 194 patients from their center, of whom 163 (84%) had a clinical diagnosis of IPF (33). Thirty-two patients (16.5%) met the criteria for IPAF. Patients with IPAF were significantly younger and included a higher proportion of women, never-smokers, and patients with NSIP compared with those without IPAF. Fulfilment of the IPAF criteria was an independent predictor of overall survival (95% confidence interval, 0.017–0.952; $P = 0.045$) and incidence of acute exacerbations (95% confidence interval, 0.054–0.937; $P = 0.040$) (33).

Finally, Kelly and Moua reviewed the charts of 101 patients whom they had defined as having UCTD-ILD and noted that the vast majority (91%) also met criteria for IPAF (34). They too highlighted frequent clinical findings of Raynaud phenomenon, a positive ANA, and HRCT features suggestive of NSIP (34).

Lessons Learned from Retrospective IPAF Cohorts

The cohort studies described reflect the retrospective application of the IPAF criteria from single centers around the world. Each study is limited by referral bias, by methodologic limitations of cohort identification, and by how specifics of the IPAF criteria—in particular the morphologic domain—were applied. Despite these differences, several themes emerge: 1) Similar to ILD in general, and in particular the spectrum of CTD-ILD, there appears to be significant heterogeneity

within the IPAF phenotype, which may have prognostic implications. Just like there is an appreciation for diverse lung injury patterns in characterizable CTD-ILD—and that fibrotic patterns may portend worse prognosis (35)—there may be similar heterogeneity among those who fulfill IPAF criteria. Furthermore, it is plausible to consider that, similar to IIPs (36), an underlying pattern of UIP among those who fulfill IPAF criteria may be associated with worse survival. Recognition of heterogeneity and identifying the important factors determining prognosis may prove valuable for patient education and management decisions. 2) Determination of clinical features is likely to be more reliably detected in prospective assessments geared toward their specific detection rather than by retrospective review or by patient report and may be optimized by direct rheumatologic engagement in the evaluation of these patients. 3) Revisions to the IPAF criteria are needed, particularly with respect to the morphologic domain. Because the IPAF criteria do not rigorously define how to characterize aspects of the morphology domain, individual providers, investigators, and studies define them and identify them differently.

One major advantage of IPAF is that uniform nomenclature has been adopted, prospective research studies from diverse programs are using similar classification criteria, data are being gathered to allow for anticipated refinement of the criteria in an evidence-based manner, and there is far more interdisciplinary engagement around this intersection of pulmonary and rheumatologic medicine.

Future Directions

The IPAF proposal represents an initial consensus classification scheme put forth by a relatively small panel of multidisciplinary international experts in the field. The task force acknowledged that the proposed classification scheme was a “first draft” and anticipated that revisions to the proposal would be needed when informed by data. The designation has spurred healthy interdisciplinary dialogue, and it has become clear that modifications are needed to refine the original classification scheme. Indeed, as acknowledged in a recent expert commentary, the IPAF criteria have an intrinsically changing structure and perhaps

“the most important effect of these criteria is the identification of a gray zone of not well-defined rheumatology conditions” (37).

Numerous questions exist about the individual items within each domain. With respect to the clinical domain, a common question is if esophageal dysmotility should be included, given that this feature is common in patients with CTD. If included, how would this be defined—by esophageal manometry and/or degree of dilation by HRCT and/or barium esophagram? What about calls to broaden the clinical criteria in general by including nonspecific variables such as keratoconjunctivitis sicca or arthralgias? Should rheumatologic consultation be required to specifically assess for musculoskeletal features, particularly given the increased number of clinical features identified with specific rheumatologic involvement (27)? Should dermatologic consultation be required for cutaneous assessment? How are we to know where to start and where to stop? Undoubtedly, many of these aspects are based on collective expert opinion rather than driven by evidence *per se*. With the next iteration, other than expanding and diversifying the panel, a more systematic approach (e.g., Delphi exercise) and global input should be considered.

With respect to the serologic domain, there has been controversy around the exclusion of antineutrophil cytoplasmic antibody (ANCA) and the inclusion of anti-tRNA synthetase antibodies (38, 39). Should the serologic domain include ANCA along with proteinase-3 and myeloperoxidase antibodies? Indeed, ANCA positivity in various forms of fibrotic interstitial pneumonia has been described in patients with or without features of systemic vasculitis (40, 41). Furthermore, controversy surrounds the inclusion of anti-tRNA synthetase antibodies, as this ultimately raises the question of the definition of “antisynthetase syndrome” and if the presence of ILD with a tRNA synthetase antibody is sufficient for this classification. According to the current idiopathic inflammatory myositis scheme (42), these two features alone would not meet criteria. However, in large measure as a result of interdisciplinary interests in IPAF and the relationship to antisynthetase syndrome, there is now an international effort to develop consensus classification criteria for antisynthetase syndrome (37). Furthermore, novel autoantibodies associated with ILD will

continue to be identified and changes to the serologic domain will be needed.

The morphologic domain may remain the most challenging. Since the criteria were proposed, one common critique of the morphologic domain is the exclusion of UIP pattern on HRCT or surgical lung biopsy (43). Importantly, and as discussed above, the presence of a UIP pattern does not exclude a designation of IPAF. In the currently available IPAF literature, the frequency of UIP on HRCT and surgical lung biopsy has varied widely. Furthermore, outcomes for patients with IPAF and the presence of a UIP pattern (UIP-IPAF) have been variable in the published cohorts. In part this may be driven by how the retrospective cohorts were identified. Prospective studies will provide valuable data to inform the prevalence and outcomes of patients with UIP-IPAF.

Studies comparing CTD-ILD with UIP pattern on HRCT or surgical lung biopsy have consistently demonstrated improved survival as compared with idiopathic UIP (IPF) (36, 44–46), with the exception of rheumatoid arthritis (RA)-UIP, for which the data are conflicting (45, 47). These studies suggest that patients with an autoimmune-mediated basis to their lung disease have improved survival even with similar radiographic or histologic pattern of fibrosis, highlighting the importance of etiology in ILD natural history. As such, identifying and distinguishing between patients with truly idiopathic disease and UIP (i.e., the clinical diagnosis of IPF) from those with clinical, serologic, and/or morphologic features of autoimmune disease and UIP (i.e., UIP-IPAF) may have significant prognostic implications. Furthermore, it is likely to alter management decisions. In the current era, the use of antifibrotic therapy is limited to those with IPF because clinical trials have shown benefit in this patient population (48, 49). Data from prospective clinical trials are needed to determine whether antifibrotic therapy has a similar role in the management of other cohorts with UIP pattern of lung injury, including those with IPAF or fibrotic ILD in general.

Ambiguity exists with the current IPAF criteria regarding the extent of germinal centers or lymphoplasmacytic infiltration on histopathology required to fulfill the morphological domain. One recent study (50) designated at least three germinal centers in any one low-power field and the

presence of lymphocytes and 40 or more plasma cells in a high-power field as meeting criteria, but to date there has been no consensus on this definition.

There need to be more uniform specifications regarding how to define multicompartiment involvement in patients beyond “unexplained airways disease or unexplained pulmonary vasculopathy.” How should airways disease be defined—by PFT, imaging, and/or histopathology? And does any degree of smoking history preclude the designation of airways disease as “unexplained”? Similarly, can pulmonary vasculopathy be defined by suggestive, noninvasive tests such as PFT (i.e., disproportionately decreased D_{LCO}) or echocardiography, or is invasive testing with right-heart catheterization required? Is the presence of vasculopathy on histopathology, without clinical evidence of pulmonary vasculopathy, sufficient? How best to define the presence of pulmonary vasculopathy is a particularly interesting question, given that studies that defined it by PFT (24), imaging (26), or histopathology (50) all suggest that its presence is associated with worse outcomes.

Beyond a recognition that changes to the initial criteria are needed, more fundamental questions about the natural history and prognosis of IPAF remain unanswered. Do patients go on to develop a defined CTD, or is IPAF a distinct disease entity with pulmonary involvement as the primary manifestation? Does the interstitial pneumonia with IPAF behave like that of CTD-ILD or more like IIP? Is it the underlying lung injury pattern that predicts prognosis or treatment responsiveness, or are there specific autoimmune clinical, serologic, or morphologic features that impact prognostically and therapeutically?

Put more simply, should patients with IPAF be treated similarly to those with CTD-ILD by using immunosuppressive therapies, or should they be treated with an antifibrotic similar to IPF? Should we base such decisions on underlying lung injury patterns and/or presence of fibrosis? We await subset analysis from the phase II clinical trial with pirfenidone for unclassifiable ILD, as a subset of the enrolled subjects fulfill IPAF criteria (clinicaltrials.gov identifier: NCT03099187) (51). These and, we hope, other prospective, randomized controlled clinical trials will augment our understanding of how to manage patients with IPAF.

Finally, although intended as a research classification, we anticipate that over time there will be evolution of IPAF to a clinical diagnosis—or at least a provisional one—and perhaps IPAF will be represented in the ILD classification schema as a distinct subset residing in the intersection between IIP and CTD-ILD.

Conclusions

The construct of IPAF represents an important first step in standardizing the nomenclature and providing uniform

classification criteria that establish a platform for research of patients with IIP and features suggestive of autoimmunity. A research classification or “diagnosis” of IPAF may be provisional, as some patients may evolve to characterizable forms of CTD-ILD. Initial studies of patients identified by retrospective application of the IPAF criteria demonstrate that there is substantial heterogeneity among these cohorts, and these data highlight a need for refinement of the criteria, particularly with more structure and uniformity of how to define the morphologic domain. Future

research is needed to determine whether the natural history of IPAF is influenced by specific phenotypic clinical, serologic, or morphologic features for prognostication and to identify effective therapeutic approaches to help in the care of these patients. ■

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