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Interstitial Pneumonia with Autoimmune Features: An emerging challenge at the intersection of rheumatology and pulmonology

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Abstract

Interstitial lung disease remains a cause of significant morbidity and mortality in patients with connective tissue disease associated ILD. While some patients meet clear classification criteria for a systemic rheumatic disease, there is a subset of patients not meeting classification criteria who still benefit from immunosuppressive therapy. In 2015, the American Thoracic Society and European Respiratory Society described classification criteria for interstitial pneumonia with autoimmune features (IPAF) to identify patients with lung predominant connective tissue disease who lack sufficient features of a systemic rheumatic disease to meet classification criteria. While these criteria are imperfect, they are an important attempt to classify the undifferentiated patient for future study. Rheumatologists play a key role in the evaluation of potential IPAF patients, especially as many patients with myositis spectrum disease (e.g. non-Jo1 anti-synthetase syndrome, MDA5 disease, and Pm-Scl disease) would be classified under IPAF using the currently available inflammatory myositis criteria and would benefit from rheumatologic co-management. This review aims to describe the historical context that led to the development of these criteria, limitations of the current criteria, diagnostic challenges, treatment options, and strategies for disease monitoring.

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Introduction

Interstitial lung disease (ILD) remains a significant challenge to both the rheumatology and pulmonary communities. While the causes of pulmonary fibrosis are many, connective tissue disease associated ILD (CTD-ILD) and idiopathic pulmonary fibrosis (IPF) are two common etiologies, and rheumatologists are frequently asked to “rule out connective tissue disease” for patients with newly diagnosed pulmonary fibrosis. This is especially important as IPF and CTD-ILD are managed quite differently. Patients with CTD-ILD benefit from immunosuppression (1–3), but immunosuppression causes harm in IPF (4). Conversely, patients with IPF benefit from anti-fibrotic agents such as nintedanib (5) and pirfenidone (6), but these drugs are not approved for the use in CTD-ILD. Correctly identifying patients with CTD-ILD can be challenging if the lung is the predominant organ involved and evidence of a systemic autoimmune disease is minimal or absent. In 2015, the designation “interstitial pneumonia with autoimmune features” (IPAF) was created to describe patients with ILD who do not meet classification criteria for a defined connective tissue disease but have features of autoimmunity and might benefit from immunosuppression (7). The goal of this review is the historical context leading to the development of IPAF criteria, their limitations, and highlight the importance of the rheumatologist’s role in managing patients with IPAF.

History of treatment in idiopathic pulmonary fibrosis (IPF)

Idiopathic pulmonary fibrosis (IPF) is the most common and severe of the idiopathic interstitial lung diseases (8). Despite the lack of clear evidence supporting corticosteroid use in IPF (9), IPF was frequently treated with a combination of prednisone + immunomodulatory agent based on the hypothesis that it may be beneficial to treat any possible immune/inflammatory component. Thus, any patient with steroid-responsive disease – including CTD-ILD – would be identified through such therapeutic trials.

In 2012, however, the PANTHER-ILD trial directly compared the use of N-acetylcysteine alone, N-acetylcysteine + prednisone + azathioprine, and placebo in IPF (4). The patients enrolled in this study all had usual interstitial pneumonia (UIP), the pathologic equivalent of IPF, by biopsy or a high resolution CT (HRCT) consistent with UIP/IPF (positive predictive value of 90–100%) (10). It was recommended that patients had a negative serologic screen with RF, CCP, and ANA to exclude any defined CTD (11, 12). This multicenter clinical trial was terminated at an interim analysis due to harm; patients in the N-acetylcysteine + prednisone + azathioprine group had a marked increase in both hospitalizations and death (4). Since that study, immunosuppression in IPF has fallen out of favor (13).

Immunosuppression is beneficial in connective tissue disease associated ILD (CTD-ILD)

In contrast to IPF, the available evidence indicates that patients with CTD-ILD often benefit from immunosuppression. Two large randomized controlled studies have shown immunosuppression benefits patients with in systemic sclerosis. In 2007, the scleroderma lung study (SLS I) compared 12 months oral cyclophosphamide (goal 2 mg/kg/day as tolerated) to placebo in 145 patients with systemic sclerosis associated ILD. At the 12 month timepoint, there was an improvement in both total lung capacity (TLC) and forced vital capacity (FVC) – particularly in patients with FVC < 70% predicted (2). This benefit was

not preserved at month 24, but patients did not receive therapy between months 12–24 (3). Scleroderma lung study II (SLS II) aimed to compare 24 months of mycophenolate mofetil (MMF) to 12 months of oral cyclophosphamide. While both study groups had a significant improvement in the FVC % predicted at 24 months (2.19% and 2.88% for MMF and cyclophosphamide, respectively), patients in the cyclophosphamide group were almost twice as likely to discontinue the drug, and patients who withdrew early had a decline in FVC (3). While not controlled, several case series have reported a benefit of MMF (14) and tacrolimus (15) in inflammatory myositis associated ILD. Rituximab may also be beneficial in systemic sclerosis based on a retrospective case control study of 63 patients. Patients treated with rituximab showed a stable FVC over a 4–12 month study period while patients not treated with rituximab had a decline in FVC (absolute change in FVC% 0.8 ± 2.2 versus -4.8 ± 1.7 , $p=0.02$) (16). Combined, these studies provide evidence that the use of immunosuppression in CTD-ILD may be beneficial.

The challenge of the unclassifiable patient

Given the convincing evidence that patients with IPF and CTD-ILD respond differently to immunosuppression, the challenge remains what to do with the undifferentiated patient. There are certainly some patients with connective tissue disease and predominant lung involvement. There may also be a subset of IPF patients who would benefit from immunosuppression. One study of IPF patients demonstrated that 20% had at least one positive autoantibody. While the overall frequency of a positive serology in IPF was similar to healthy controls, seropositive IPF patients had a longer transplant-free survival in univariate analysis, but there was no difference after correction for age, gender, FVC, and DLCO (17). A second study of 668 patients with biopsy proven UIP also showed that patients with CTD-UIP had improved survival relative to IPF (18). Since patients enrolled in PANTHER-ILD were recommended to have had a negative RF, CCP, and ANA to exclude a rheumatologic disease (11, 12), there is uncertainty regarding appropriate management of this subset of IPF patients.

Evolution and development of interstitial pneumonia with autoimmune features (IPAF) criteria

Attempts to define interstitial lung disease with some features of autoimmunity began to evolve after the American Thoracic Society (ATS) and European Respiratory Society (ERS) introduced nonspecific interstitial pneumonia (NSIP) as a subset of idiopathic interstitial pneumonia with improved survival compared to IPF in 2002 (11). NSIP is a histologic diagnosis characterized by a relatively homogenous pattern of inflammation with variable degrees of fibrosis. While most patients with NSIP have a clear etiology such as drug-induced pneumonitis, resolving infection, defined CTD, or hypersensitivity pneumonitis, some patients had no etiology and were diagnosed with idiopathic NSIP (19). Soon, NSIP was recognized as the most common histopathology in patients with CTD-ILD (20, 21), which raised the possibility that idiopathic NSIP might represent a lung predominant form of undifferentiated CTD (uCTD) (11).

Between 2010 and 2012, four different research groups from various institutions attempted to develop criteria for what was then termed uCTD-ILD (Table S1) (22–25). Three groups (22, 24, 25) developed criteria based on prior classification criteria of early uCTD (26) to include additional serologies. One significant criticism of the early criteria proposed by Kinder (24) and Vij (25) were the inclusion of relatively non-specific symptoms such as weight loss and GERD. Corte and coworkers attempted to eliminate non-specific clinical symptoms in favor of Raynaud's, morning stiffness, sicca, and proximal muscle weakness (22). The 2010 Fischer criteria attempted to increase specificity for autoimmune inflammatory processes by combining radiographic, histologic, and serologic parameters. The Fischer criteria notably excluded clinical features of CTDs such as Raynaud's, proximal muscle weakness, and esophageal dysmotility as these can be affected by subjective interpretation and may be seen in other diseases (23). It remained unclear, however, whether any of these proposed criteria identified a patient population that might benefit from a different treatment approach.

In an effort to systematically study these various criteria, Assayag et al. applied the four proposed criteria to a cohort of 119 patients with ILD. Fifty-six percent of patients met at least one definition of uCTD-ILD, but only 18% met all four definitions. The overall cohort contained 28% UIP pattern based on either high-resolution CT scan or histopathology; there was no difference in the frequency of UIP in patients who met criteria for uCTD-ILD versus those who did not (27). After adjustment for disease severity using the gender-age-physiology score (28), the group identified as uCTD by the Corte criteria (but not the other criteria) had improved survival (HR 0.35, 95% CI 0.13–0.97, p 0.04) (27). This study served to highlight the need for a consensus definition that could be validated in a large cohort of patients.

In 2015, the ATS/ERS issued a consensus statement with proposed criteria for interstitial pneumonia with autoimmune feature (IPAF) (Table 1) and recommended that the term IPAF replace the prior terminology of uCTD-ILD. The proposed IPAF criteria were refined from prior proposals of uCTD to include clinical, serologic, and morphologic domains, but the included features were chosen for their specificity to connective tissue diseases. For example, the clinical features include specific features of CTDs such as Raynaud's phenomenon, palmar telangiectasia, and mechanic's hands while excluding nonspecific features such as oral ulcers, weight loss, and sicca symptoms. Serologic and laboratory criteria including low titer ANA and RF, ESR, CRP and CK were excluded in favor of more specific tests such as high titer ANA (1:320 or nucleolar/centromere pattern), anti-synthetase, anti-PM-Scl, or MDA-5 antibodies. The morphologic domain includes both high-resolution CT patterns and pathologic diagnoses that are suggestive of CTD-ILD. Examples of the various high-resolution CT scans (HRCT) are shown in Figures 1. UIP is notably excluded as a qualifying morphologic feature, but, given the predilection of CTDs to affect other thoracic compartments, pulmonary hypertension, pleural/pericardial disease, and intrinsic airway disease are included. To be diagnosed with IPAF under these criteria, the patient must have interstitial lung disease, not meet classification criteria for a defined connective tissue disease (29–34) and have at least one feature from 2 of the 3 domains (clinical, serologic, morphologic). Thus, patients with NSIP or organizing pneumonia (OP)

require only a positive serology or clinical feature to be diagnosed with IPAF; patients with UIP must have both a clinical and serologic feature of CTD to meet IPAF criteria (7).

Three large retrospective studies evaluating the IPAF criteria are summarized in Table 2. The University of Chicago pulmonary cohort showed a trend towards increased survival for IPAF relative to IPF ($p=0.07$) with a transplant free survival of 47.6%. When IPAF was stratified by the presence of UIP, non-UIP pattern IPAF behaved similarly to CTD-ILD (Figure 2) (35). A second French pulmonary cohort showed a trend towards worse survival in the first year for IPAF patients (83.6% v. 94.8%), but long-term follow-up was unavailable (36). A third IPAF cohort identified in the University of Colorado rheumatology clinic had 100% survival during follow-up, but this cohort had a higher frequency of NSIP compared to the pulmonary cohorts (91% versus 72% and 55.4%), and higher frequency of anti-synthetase antibodies (35.7% versus 17% and 0.7%) (37). The higher prevalence of anti-synthetase antibodies in the Colorado cohort may skew towards favorable outcomes as Mejia et al. reported that patients with anti-synthetase antibodies alone (e.g. classified as IPAF) had the same outcomes as patients with anti-synthetase antibodies meeting classification criteria for dermatomyositis or polymyositis (38). These retrospective cohorts indicate that the proposed IPAF criteria may identify a population of patients who would benefit from immunosuppression, but this hypothesis must be tested in prospective cohorts.

Limitations of current IPAF classification criteria

The goal of developing IPAF classification criteria is to identify patients with lung-predominant undifferentiated CTD that might benefit from immunosuppression and may not otherwise be treated with such medications. Unlike many American College of Rheumatology criteria that were created via the generation of potential criteria by expert working groups using consensus methods followed by rigorous statistical validation in large cohorts, the proposed IPAF criteria were generated from *expert opinion* of a smaller working group comprised of pulmonologists and rheumatologists. Proposed criteria did not undergo validation prior to the release of classification criteria, likely because large, high quality patient cohorts for validation did not exist. Thus, there is a clear need for the assembly of carefully phenotyped IPAF cohorts to allow for the validation and further refinement of these criteria.

As classification of IPAF requires the exclusion of a defined connective tissue disease, the reliance on *classification* rather than *diagnostic* criteria for the exclusion of rheumatologic disease is another limitation. The current ACR and/or EULAR endorsed criteria for rheumatoid arthritis (29), dermatomyositis/polymyositis (31), systemic sclerosis (34), Sjogren's syndrome (33), mixed connective tissue disease (30), and systemic lupus erythematosus (39) are classification criteria. Classification criteria are designed to ensure a homogenous population for clinical trials and research, and sensitivity is sacrificed for specificity. This issue is compounded for dermatomyositis/polymyositis as the 2015 IPAF criteria were developed using the 1975 Bohan and Peter criteria (40), which excluded patients with hypomyopathic anti-synthetase syndrome (41) and amyopathic dermatomyositis (42). New consensus criteria for idiopathic inflammatory myopathies (IIM)

were recently released and included amyopathic dermatomyositis; however, non-Jo1 anti-synthetase antibodies and other myositis-specific antibodies were again excluded (31).

The inclusion of non-Jo1 anti-synthetase and other myositis specific or associated antibodies within IPAF is perhaps the biggest issue with the current criteria. As mentioned above, only the Jo-1 (anti-histidyl tRNA synthetase) was included in the most recent myositis criteria, but clinical syndromes for other anti-synthetase and myositis specific antibodies are well described and often include ILD (Table 3). One reason for excluding these antibodies from the recent criteria is the paucity of patients with anti-synthetase antibodies and other myositis associated antibodies in the validation cohorts (43). Nonetheless, Chartrand and co-workers recently described a series of 33 patients with myositis-specific or associated antibodies and ILD who did not meet Peter and Bohan criteria for DM/PM but all of whom were felt to have an anti-synthetase syndrome or myositis spectrum disease by a multidisciplinary conference (44). While these patients may not meet the classical classification criteria for IIM, they are not as “undifferentiated” as a patient with NSIP and positive ANA alone. This point was illustrated by Scire et al, who found that 42% of patients with an anti-synthetase antibody initially meeting IPAF criteria ultimately evolved to meet formal criteria for another connective tissue disease (45). Thus, there is significant debate within the rheumatology field for the appropriateness of including these patients underneath the IPAF umbrella.

Diagnostic Challenges in IPAF

Beyond the limitations of the IPAF criteria, there are not consensus guidelines for evaluating CTD in an ILD patient. Figure 3 shows one possible approach to the diagnostic evaluation for a CTD, but there are serologic, radiographic and histologic pitfalls that must be acknowledged.

Laboratory challenges

The current IPAF criteria give substantial weight to various serologies. In the case of NSIP or organizing pneumonia, the presence of a qualifying serology alone classifies the patient as IPAF. However, serologic testing is highly variable, and challenges must be acknowledged. Given the laborious nature of indirect immunofluorescence (IIF) platforms, more commercial labs are moving to ELISA based platforms of ANA screens. While ELISA based assays are extremely reliable for identifying extractable nuclear antigens such as Sm, dsDNA, Ro/SSA, La/SSB, etc., they are unable to assess the presence of non-specific anti-nuclear antibodies – even when present at high titer (46, 47). The inability to detect non-specific antigens led to the ACR recommendation that IIF-ANAs be used for screening (48). In the case of an isolated rheumatoid factor, it is important to rule out other infectious etiologies of a positive RF, particularly hepatitis C (49).

Another significant challenge is the myositis-specific or myositis-associated antibodies (MSA). Testing for non-Jo1 antibodies is not routine. Panel composition is variable (Table S2), and patients with ILD should be evaluated with a comprehensive myositis panel. However, the use of MSA testing is limited for inpatients due to the long delay in reporting. Approximately 50% of patients with a defined anti-synthetase syndrome will be IIF-ANA

negative, but 72% of patients will have a cytoplasmic staining pattern on their IIF-ANA that may or may not be routinely reported by the testing laboratory. This portion of patients was even higher (81%) for non-Jo1 anti-synthetase patients, and patients with non-synthetase myositis syndromes rarely have anti-cytoplasmic antibodies (50). Screening for cytoplasmic antibodies, when available, may help to more rapidly identify patients with possible IPAF.

Radiologic-pathologic challenges in IPAF diagnosis

The IPAF criteria favor NSIP, OP, LIP and overlaps thereof given the relative specificity to CTD-ILD. Unfortunately, there is often discordance between histopathology at biopsy and radiographic impression. The radiographic-pathologic concordance of definite UIP is reliable based in prior reports (10, 51), but other patterns exhibit significant pathologic and radiographic disagreement. In one case series of 44 patients with probable or definite NSIP, 26 demonstrated UIP on final histology (51). Even for IPAF patients with a HRCT scan inconsistent with UIP, 50% still had UIP on biopsy (18, 52). Given that IPAF patients with pathological UIP pattern may behave clinically more like an IPF patient, tissue diagnosis has some appeal.

Lung biopsy, however, carries significant risk. Surgical lung biopsy (SLB) is currently the preferred method of histologic diagnosis and has an estimated diagnostic yield >90% (53). The reported mortality risk of SLB ranges widely from 0% in a large cohort of patients undergoing elective procedures (54) to 70% for patients with diffuse ILD and acute hypoxic respiratory failure (55). The best estimation of SLB risk comes from a recent study analyzing a national database in which over 30,000 such procedures were performed. In the elective setting, SLB was associated with overall mortality of 1.6%, and patients with presumptive CTD-ILD had 6% mortality. For non-elective procedures, SLB was associated with 16% mortality; the risk of death was unchanged for patients with presumptive CTD-ILD (56). Given the higher mortality associated with CTD-ILD, biopsies are typically not performed in the setting of a known CTD.

While conventional transbronchial biopsy (TBBx) has a low yield (20–30%) for ILD (57), transbronchial cryobiopsy represents a promising intermediary. Cryobiopsy combines flexible bronchoscopy with a cryoprobe to remove biopsy specimens >5mm in size that are sufficient for ILD diagnosis. Approximately 1500 procedures have now been reported in the literature, and two large meta-analysis indicate that cryobiopsy was sufficient for diagnosis in ~80% of cases, was associated with a shorter length of stay than surgical lung biopsy, and had mortality of 0.3–0.7% (58, 59). The limitations of cryobiopsy include limited availability and lack of standardized protocols for performing the procedure or training proceduralists (60). Nonetheless, cryobiopsy may be a viable option for patients in whom the diagnosis is unclear.

Role of the rheumatologist in the diagnosis and management of IPAF

Rheumatologists play a key role in the diagnosis and management of IPAF. Part of identifying IPAF is to rule out other CTDs. Rheumatologists have expertise in extracting the relevant clinical history. Furthermore, many objective findings for connective tissue disease such as nailfold capillary changes, mechanic's hands, and rashes can be subtle and more

readily identified by rheumatologists who have greater experience observing these physical findings. Beyond the diagnosis of CTD-ILD and IPAF, the expertise of a rheumatologist is also frequently needed for management – particularly for myositis and scleroderma spectrum disease. Many pulmonologists have limited training in the use of immunosuppressive agents and may not be experienced managing these drugs. The challenge for the rheumatologist is in disease monitoring as they may receive less training in chest CT interpretation and evaluating pulmonary function tests.

Management of IPAF

As there are no consensus guidelines for the diagnostic evaluation of CTD-ILD, there are also no management guidelines. Below are some approaches to the management of the patient with IPAF.

Pharmacologic management of IPAF

There are not currently any randomized controlled trials or case-control studies reporting the efficacy or safety of different immunosuppressive agents in IPAF as defined by the 2015 criteria. For IPAF specifically, there is only very limited case series data. One large retrospective study of 125 patients with CTD-ILD included 19 patients with IPAF. In that study, MMF was associated with an improved FVC in all patients; there was a trend towards improved FVC in IPAF (61). A large case series of rituximab in refractory interstitial lung diseases included 9 patients with IPAF, all of whom were treated with prednisone $\pm$ MMF prior to rituximab administration. Of the 5 IPAF patients with pre- and post-rituximab PFTs, 4/5 had stability or improvement post rituximab, and 1 patient treated with rituximab died (62). Thus, mycophenolate mofetil and azathioprine are likely the first-line agents based on prior experience with other CTD-ILDs (1, 3, 14, 39, 63–65). Rituximab (1, 16, 62) and calcineurin inhibitors (1, 15, 66) may play a role in refractory disease. Clearly, large prospective trials are needed in these patients to ascertain whether there is a benefit in immunosuppression and what agent is most efficacious.

Radiographic measures of stability/improvement

A recent position paper highlighted the emerging role of CT in the monitoring of ILD. Historically, thin slice (1mm) CT scans were collected at various intervals (e.g 1mm cuts at 10mm, 20mm, or 40mm intervals) to minimize radiation, which led to challenges with serial assessments and sampling error. Given new CT technologies with decreased radiation exposure, volumetric thin slice CT scan is now reasonable in most patients (67). Visual semi-quantitative comparisons estimating the degree of lung fibrosis can be performed and is predictive of mortality in studies of IPF. The challenge is that such visual estimations will have inter-reader variability (68). While not broadly available in the community at present, there is increasing interest in quantitative CT scans where a histogram of lung attenuation is plotted in an attempt to quantify the degree of inflammation and fibrosis in an automated fashion. When one such algorithm of quantitative lung fibrosis (QLF) was applied to patients enrolled in scleroderma lung study I, the QLF score correlated with changes in FVC and dyspnea scores (69). Thus, we feel that automated quantitative CT scoring will become increasingly relevant in both clinical trials and clinical care in the coming years. At present,

there is no set recommendation for the frequency of lung CT scans. A reasonable approach is to obtain an HRCT once at the time of presentation and then to repeat an HRCT only when there is confusion as to the clinical response to a treatment or sudden worsening.

Monitoring pulmonary function tests

Pulmonary function tests (PFTs) can be readily performed at most hospitals and pulmonology offices and offer high quality physiologic data when performed appropriately. Complete PFTs include spirometry to diagnose obstruction and screen for restrictive lung diseases, lung volume measurements to diagnose restrictive lung disease and assess for hyperinflation, and assessment of single-breath diffusion capacity (DLCO) in the lungs. This last value is a multifactorial parameter that integrates the intrinsic diffusion capabilities of the alveoli, the oxygen carrying capacity of the blood (hemoglobin), and pulmonary capillary blood volume. It should be noted that the measurement of DLCO is prone to error due to technical issues and has potential for significant intersession variability (70). While the ATS/ERS recommend correction for hemoglobin, they do not recommend correction for lung volume (71).

Despite the focus on histopathologic pattern, physiologic parameters are perhaps the best predictors of long-term outcome in a given patient. In studies of both UIP and NSIP, patients with a greater than 10% decrease in FVC were at significantly increased risk of death at 6 (72, 73) and 12 months (74). While DLCO has been a predictor of mortality in some studies (73, 74), this has not been a universal finding. As such, many providers obtain complete PFTs at presentation and then spirometry with DLCO every 3–6 months to monitor changes in lung function. While ATS/ERS guidelines state that the FVC and FEV1 may vary by up to 10% week to week and 15% year to year (75), the 10% threshold is often used in the ILD population to consider changes in therapy.

Remaining challenges and future work

One significant challenge in understanding and studying IPAF is the inherent heterogeneity of this entity. By definition, these patients do not meet clinical criteria of a defined CTD-entity and are therefore classified together under the rubric of IPAF. Some patients will be more myositis-like and others more systemic sclerosis-like; these clinical differences may have important outcome implications. Similarly, the various histologic and radiographic patterns likely have prognostic value beyond simply UIP being a negative prognostic indicator. Thus, careful prospective clinical and immunologic phenotyping will be imperative to identify various subsets of IPAF that may have differential response to treatment. This clinical phenotyping must include radiographic/histologic patterns, serologies, clinical features, and treatment course that can be correlated temporally to CT scans and serial pulmonary function tests.

Given the relative rarity of these patients, multi-center collaborations will be critical to studying large prospective cohorts and performing clinical trials. These studies must involve close collaborations between pulmonologists and rheumatologists to ensure proper clinical phenotyping. Additionally, the current criteria were developed by expert opinion. Future revisions will most certainly be necessary and would benefit from consensus methodology

for proposing potential criteria, and subsequent rigorous statistical validation in well phenotyped patient cohorts.

Conclusion

Given the important management and outcome differences between CTD-ILD and IPF, it is critical to develop an approach to patients who do not meet the full criteria for a defined CTD but still have some features of autoimmunity. The 2015 ATS/ERS classification criteria for IPAF provide an initial framework for evaluating these patients and determining who might receive a benefit from treatment with immunosuppressive agents. However, the inclusion of myositis specific and associated antibodies (e.g. anti-synthetase, Pm-Scl, and MDA5) is problematic, as these patients may not truly be undifferentiated. There is also no evidence to clearly demonstrate that the current IPAF criteria predict a response to immunosuppression. Collaborative studies between pulmonologists and rheumatologists are needed to (1) evaluate the benefit of immunosuppression in IPAF and (2) refine and validate these criteria using rigorous methodologies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Representative CT slices of various interstitial lung disease patterns. A. Organizing pneumonia (OP) showing scattered consolidation with areas of central lucency (reverse halo sign/Atoll sign) B. Non-specific interstitial pneumonia (NSIP) with traction bronchiectasis surrounded by ground glass in the absence of honeycombing. C. Usual interstitial pneumonia (UIP) with subpleural honeycombing and no ground glass. D. Lymphocytic interstitial pneumonia (LIP) with thin walled scattered cysts and no fibrosis.

Figure 2.

Kaplan-Meier survival curves of interstitial pneumonia with autoimmune features (IPAF), idiopathic pulmonary fibrosis (IPF), and connective tissue disease (CTD)-interstitial lung disease (ILD) cohorts. Overall, the IPAF cohort survival was significantly worse than the CTD-ILD cohort ($p < 0.001$) and marginally better than the IPF cohort ($p = 0.07$). After stratification of the IPAF cohort by the presence of usual interstitial pneumonia pattern on high-resolution computed tomography and/or surgical lung biopsy b) IPAF patients without usual interstitial pneumonia (UIP) demonstrated survival similar to those with CTD-ILD ($p = 0.45$), while those with UIP demonstrate survival similar to those with IPF ($p = 0.51$). Reproduced with permission from the ©ERS 2016. *European Respiratory Journal* Jun 2016, 47 (6) 1767–1775; DOI: [10.1183/13993003.01565-2015](https://doi.org/10.1183/13993003.01565-2015)

Figure 3.

Proposed algorithm for the diagnosis of IPAF in patients with interstitial lung disease who do not meet criteria for a defined connective tissue disease. Comprehensive serologies should include anti-nuclear antibodies by indirect immunofluorescence, rheumatoid factor (RF), anti-cyclic citrillinated peptide (CCP), and a comprehensive myositis panel.

Table 1.**ATS/ERS Classification criteria for Interstitial Pneumonia with Autoimmune Features (7)**

<p>(1) Presence of an interstitial pneumonia (by HRCT or surgical lung biopsy) <i>and</i>,</p> <p>(2) Exclusion of alternative etiologies <i>and</i>,</p> <p>(3) Does not meet criteria of a defined connective tissue disease (Table 2) <i>and</i>,</p> <p>(4) At least one feature from at least two of these domains:</p> <p style="padding-left: 20px;">A. Clinical domain</p> <p style="padding-left: 20px;">B. Serologic domain</p> <p style="padding-left: 20px;">C. Morphologic domain</p> <p>A. Clinical Domain</p> <ul style="list-style-type: none"> • Distal digital fissuring (i.e. “mechanic’s hands”) • Distal digital tip ulceration • Inflammatory arthritis <i>or</i> polyarticular morning joint stiffness ≥ 60 min • Palmar telangiectasia • Raynaud’s phenomenon • Unexplained digital edema • Unexplained fixed rash on the digital extensor surfaces (Gottron’s sign) <p>B. Serologic Domain</p> <ul style="list-style-type: none"> • ANA ≥ 1:320 titer, diffuse, speckled, homogenous patterns <i>or</i> any titer of ANA nucleolar or centromere pattern • Rheumatoid factor ≥ 2× upper limit of normal • Anti-cyclic citrullinated peptide • Extractable nuclear antigen antibodies: anti-Ro/SSA, anti-La/SSB, anti-RNP, anti-Smith, anti-dsDNA • Systemic associated antibodies: anti-topoisomerase (Scl70), anti-PM-Scl • Anti-tRNA synthetase (e.g. Jo-1, PL-7, PL-12, EJ, OJ, Ks, Zo) • Anti-MDA-5 <p>C. Morphologic Domain</p> <ul style="list-style-type: none"> • Suggestive radiology patterns by HRCT: NSIP, OP, NSIP with OP overlap, LIP • Histopathology patterns or features by surgical lung biopsy: NSIP, OP, NSIP with OP overlap, LIP, Interstitial lymphoid aggregates with germinal centers, diffuse lymphoplasmacytic infiltration (with or without lymphoid follicles) • Multi-compartment involvement (in addition to interstitial pneumonia): unexplained pleural thickening or effusion, unexplained pericardial thickening or effusion, unexplained intrinsic airway disease (such as obstruction, bronchiectasis, or bronchiolitis by PFT, imaging, or pathology), or unexplained pulmonary vasculopathy

HRCT: high-resolution computed tomography; ANA: anti-nuclear antibody; NSIP: non-specific interstitial pneumonia; OP: organizing pneumonia; LIP: lymphoid interstitial pneumonia; PFT: pulmonary function testing

Table 2.

Previously reported cohorts evaluating IPAF criteria.

	Ahmad 2017 (36)	Chartrand 2016 (37)	Oldham 2016 (35)
Location	France	Colorado, USA	Chicago, USA
Clinic type	Pulmonary clinic	Rheumatology clinic	Pulmonology clinic
N	57	56	144
% Female	49.1	71.4	52.1%
Age at dx, years (mean $\pm$ SD)	64.4 $\pm$ 14	54.6 $\pm$ 10.1	63.2 $\pm$ 11
Clinical Features	47.3%	62.5%	49.3%
Digital fissuring	7.4%	28.6%	10.4%
Digital ulceration	-	-	2.1%
Arthritis	48.1%	16.1%	17.4%
Telangiectasia	25.9%	5.4%	-
Raynaud's	74.1%	39.3%	27.8%
Digital edema	33.3%	3.6%	3.5%
Gottman's sign	11.1%	17.9%	4.9%
Serologic Features	93%	91.1%	91.7%
ANA criteria	82.4%	48.2%	77.6%
RF $\geq$ 2 $\times$ normal	7.5%	10.7%	13%
Anti-CCP	9.4%	10.7%	4.7%
Anti-dsDNA	5.7%	1.8%	7.2%
Anti-Ro (SSA)	9.4%	42.9%	16.6%
Anti-La (SSB)	1.9%	5.4%	2.9%
Anti-RNP	-	1.1%	4.9%
Anti-Sm	-	8.9%	1.5%
Anti-Scl70	5.7%	1.8%	3.0%
Anti-tRNA synthetase	17%	35.7%	0.7%
Anti-Pm/Scl	5.7%	1.8%	n.r.
Anti-MDA5	-	-	n.r.
Morphologic Criteria	78.9%	98.2%	85.4%
<i>Radiographic Criteria</i>			
NSIP on CT	42.1%	51.8%	31.9%
OP on CT	3.5%	1.8	3.5%
NSIP + OP on CT	15.8%	14.3%	7.8%
LIP	1.8%	1.8%	-
<i>Morphologic criteria on Bx</i>	29.8%	n.r.	57.6%
NSIP	8.8%	23.2%	13.1%
OP	3.5%	7.1%	9.7%
NSIP with OP overlap	1.8%	14.3%	2.1%
LIP	1.8%	1.8%	n.r.
Interstitial aggregates with germinal centers	10.5%	23.2%	7.6%
Diffuse lymphoplasmacytic infiltration	12.3%	10.7%	5.6%

	Ahmad 2017 (36)	Chartrand 2016 (37)	Oldham 2016 (35)
<i>Multi-compartment involvement</i>			
Pleural effusion/thickening	1.8%	10.7%	12.5%
Pericardial effusion/thickening	1.8%	1.8%	1.4%
Intrinsic airways disease	8.8%	12.5%	22.2%
Pulmonary hypertension	17.5%	30.4%	18.8%
Transplant-free survival	83.6%	100%	49.6%
Mean follow-up	16 months	5.5 ± 2.7 yrs	n.r.
% UIP on HRCT	28%	9%	54.6%
P value for mortality relative to IPF	0.05	n.r.	0.07
% corticosteroids	67.9%	81.8%	32.3%
% immunosuppression	28.6%	98.2%	n.r.

n.r.: not reported

Table 3.

Clinical phenotypes for select anti-synthetase and myositis associated antibodies

Cohort	n	ILD	Clinical Myositis	Joint	Raynaud's	Mechanic's hands
Anti-PL7						
<i>Hervier 2012 (39)</i>	25	20/25	11/25	14/25	8/25	5/25
<i>Labirua-Iturburu 2012 (64)</i>	18	10/18	18/18	12/18	11/18	5/18
<i>Marie 2013 (65)</i>	15	14/15	15/15	n.r.	6/15	5/15
Anti-PL12						
<i>Hervier 2012 (39)</i>	48	42/48	19/48	28/48	23/48	4/48
<i>Kalluri 2009 (76)</i>	31	29/31	11/31	18/31	20/31	5/31
Pm-Scl						
<i>Lega 2014 (77)</i>	116	38/74	n.r.	74/116	63/116	11/116
<i>De Lorenzo 2018 (78)</i>	41	25/41	38/41	19/41	32/41	33/41
<i>D/Aoust 2014 (79)</i>	26	4/26	9/26	15/26	n.r.	n.r.
<i>Muro 2015 (80)</i>	11	4/11	2/11	3/11	1/11	2/11
MDA5						
<i>Abe 2017 (66)</i>	24	24/24	n.r.	n.r.	n.r.	n.r.
<i>Chen 2012 (81)</i>	19	15/19	11/19	11/19	3/19	8/19
<i>Cao 2012 (82)</i>	15	15/15	3/15	n.r.	n.r.	n.r.

n.r.: not reported