An official European Respiratory Society/ American Thoracic Society research statement: interstitial pneumonia with autoimmune features

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ABSTRACT Many patients with an idiopathic interstitial pneumonia (IIP) have clinical features that suggest an underlying autoimmune process but do not meet established criteria for a connective tissue disease (CTD). Researchers have proposed differing criteria and terms to describe these patients, and lack of consensus over nomenclature and classification limits the ability to conduct prospective studies of a uniform cohort.

The "European Respiratory Society/American Thoracic Society Task Force on Undifferentiated Forms of Connective Tissue Disease-associated Interstitial Lung Disease" was formed to create consensus regarding the nomenclature and classification criteria for patients with IIP and features of autoimmunity.

The task force proposes the term "interstitial pneumonia with autoimmune features" (IPAF) and offers classification criteria organised around the presence of a combination of features from three domains: a clinical domain consisting of specific extra-thoracic features, a serologic domain consisting of specific autoantibodies, and a morphologic domain consisting of specific chest imaging, histopathologic or pulmonary physiologic features.

A designation of IPAF should be used to identify individuals with IIP and features suggestive of, but not definitive for, a CTD. With IPAF, a sound platform has been provided from which to launch the requisite future research investigations of a more uniform cohort.

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ERS/ATS task force provides nomenclature and classification criteria for patients with IIP and autoimmune features http://ow.ly/O7qao

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Introduction

This research statement summarises the efforts of the European Respiratory Society/American Thoracic Society "Task Force on Undifferentiated Forms of Connective Tissue Disease-associated Interstitial Lung Disease". The primary objective of this multidisciplinary task force was to develop consensus surrounding the nomenclature and classification of patients with suggestive forms of connective tissue disease-associated interstitial lung disease (CTD-ILD). In this statement, we propose the following: 1) a new term, "interstitial pneumonia with autoimmune features" (IPAF), to describe individuals with both ILD and combinations of other clinical, serologic, and/or pulmonary morphologic features which putatively stem from an underlying systemic autoimmune condition, but do not meet current rheumatologic criteria for a characterised CTD; and 2) a description of the proposed classification criteria for IPAF. The concepts discussed in this research statement are intended to provide a platform for the prospective study of these patients and are not intended as guidelines for clinical care.

Background

The idiopathic interstitial pneumonias (IIPs) are diffuse inflammatory and/or fibrotic lung disorders that are grouped together based on similar clinical, radiologic and histopathologic features [1–3]. The diagnosis of IIP requires the exclusion of known causes of interstitial pneumonia, such as environmental exposures, medication toxicity or CTD [2]. Identifying an underlying aetiology is important from a clinical perspective because it often impacts treatment and prognosis [4–6]. From a research perspective, accurate phenotyping informs disease epidemiology, provides insights into pathophysiologic mechanisms of disease, and facilitates the design and conduct of clinical studies.

The CTDs are a spectrum of systemic autoimmune disorders and include rheumatoid arthritis, systemic lupus erythematosus, inflammatory idiopathic myopathies, Sjögren's syndrome, systemic sclerosis and mixed connective tissue disease. Though these diseases have unique and distinguishing features, they share the common underlying mechanisms of systemic autoimmunity and immune-mediated organ damage.

One well-recognised clinical manifestation of CTD is interstitial pneumonia. Most often, interstitial pneumonia arises within the context of an established CTD, but it is not uncommon for the interstitial pneumonia to be the first, and possibly the sole, manifestation of an otherwise occult CTD [7–10]. Identifying underlying CTD in patients presenting with what is initially considered to be an IIP can be challenging [9, 11–16], as boundaries between IIPs and CTD-ILDs are not clearly defined. There is no universally accepted approach to the evaluation of such patients, however, the current international guidelines for the diagnosis of IIP recommend excluding CTD [2, 3]. Whether and how this is performed is clinician-dependent but usually involves assessing for extrathoracic features of CTD, testing for a broad array of circulating autoantibodies, and integrating specific imaging and/or histopathologic features [5, 6]. Experts argue that such evaluations can be optimised by a multidisciplinary approach, which often includes formal rheumatologic evaluation [7–9, 11, 17, 18].

A number of recent studies have shown that many patients diagnosed with an IIP have certain, often subtle, clinical features that suggest an underlying autoimmune process and yet do not meet established diagnostic criteria for any characterisable CTD [19–22]. In some patients, these features may occur in the absence of serologic abnormalities, while in others, a highly specific serum autoantibody may be present without typical systemic or extrathoracic findings. In other scenarios, radiologic or histopathologic features suggest an underlying CTD, but the absence of extrathoracic clinical or serologic findings precludes reliable classification of these patients as anything other than IIP. Such individuals have been described as having an autoimmune or rheumatologic "flavour" [20].

Researchers around the world have proposed differing, but overlapping, criteria and terms to describe these patients, including "undifferentiated CTD associated ILD" (UCTD-ILD) [19], "lung-dominant CTD" [20] or "autoimmune-featured ILD" [21]. Each term is controversial, none has been universally accepted, and because of their subtly different diagnostic criteria, each would include many of, but not all, the same patients. The lack of consensus over nomenclature and classification criteria limits the ability to conduct prospective studies needed to answer fundamental questions about these patients.

To achieve consensus around how to label and define such patients, the European Respiratory Society (ERS) and American Thoracic Society (ATS) formed the "Task Force on Undifferentiated Forms of CTD-ILD". This task force included an international, multidisciplinary panel of CTD-ILD experts, including investigators from the centres that defined the terms UCTD-ILD, lung-dominant CTD and autoimmune-featured ILD. The task force aimed to derive a uniform name and set of classification criteria for patients with IIP and an autoimmune "flavour" with the hope of developing a sound platform from which to launch future research investigations.

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Methods and process

The task force had international and multidisciplinary representation and was endorsed and supported jointly by the ERS and ATS. 13 members were pulmonologists, four were rheumatologists, and there was one thoracic radiologist and one pulmonary pathologist. The chair (A. Fischer) and vice-chairs (H.R. Collard and V. Cottin) selected the other members based on their expertise in CTD, ILD, or both.

The task force initially convened *via* teleconference calls and e-mail and held its first face-to-face meeting in Philadelphia, PA, USA in May 2013 (supplementary figure S1). Staff from the National Jewish Health medical library performed a pragmatic systematic review to identify citations limited to human studies and articles in English or in any language with English abstracts that were related to CTD-ILD and published since 2003. After extensive deliberation and collective input, a framework for the planned efforts of the task force was identified:

- *The problem.* There was unanimous agreement that some patients diagnosed with an IIP or otherwise idiopathic ILD have clinical, serologic or morphologic features that suggest the presence of a systemic autoimmune process but do not meet diagnostic criteria for a defined CTD. The lack of consensus around how to categorise these patients hinders systematic research.
- *A new term is needed.* Previously published terms describing this patient group, including broad and strict forms of UCTD-ILD, lung-dominant CTD and autoimmune-featured ILD [19–21], should be abandoned and replaced with consensus-derived nomenclature.
- *Classification criteria are needed and should be built around clinical, serologic and morphologic domains.* Extrathoracic clinical features, circulating serologic markers (*i.e.* autoantibodies), and a morphologic domain incorporating chest imaging, histopathology and pulmonary physiology, all need due consideration for inclusion in the proposed classification criteria.

After the initial face-to-face meeting, the task force communicated *via* e-mail and teleconferences. The task force was subdivided into four small multidisciplinary groups, each with a team leader (T.J. Corte, J.S. Lee, M.E. Strek and A. Fischer), to enhance group dynamics and broaden the generation of ideas revolving around its objectives. During the second face-to-face meeting (held in Barcelona, Spain in September 2013), each of the four group leaders presented their team's proposals for the nomenclature and rough framework of classification criteria. Subsequent to the second face-to-face meeting, the four group leaders, the chair and vice-chairs communicated by e-mail and teleconferences to refine the proposed classification criteria. As the criteria were being developed, they were applied retrospectively to 45 cases of interstitial pneumonia collected from five centres, which led to further modification and refinement. The task force convened for its final face-to-face meeting in San Diego, CA, USA in May 2014, and during that meeting, the group ratified the consensus nomenclature and classification criteria.

Results

Nomenclature

The task force agreed upon the term "interstitial pneumonia with autoimmune features" (IPAF). The term "connective tissue disease" was specifically avoided due to concerns that such labelling gives a false impression that these individuals have a defined CTD. The task force believed it was important to use descriptive nomenclature: an *interstitial pneumonia* is present along with certain clinical, serologic and/or pulmonary morphologic *features* suggesting the presence of an *autoimmune* process. Labelling a patient as having IPAF defines the cohort as unique; these patients do not have a classifiable CTD, yet they may be distinct from other patients diagnosed with an IIP.

Proposed classification criteria for IPAF

In the following sections we describe the proposed criteria for the classification of IPAF (table 1). The criteria reflect collective input from this multidisciplinary, international panel and were unanimously approved by the task force. The proposed criteria reflect the panel's expert opinion and will need to be validated *via* prospective research studies. We attempted to strike a balance between being too broad or non-specific *versus* being too narrow or specific.

Overall structure

The criteria state up-front several *a priori* requirements for the classification of IPAF: Individuals must have evidence of interstitial pneumonia by high-resolution computed tomography (HRCT) imaging and/or by surgical lung biopsy, a thorough clinical evaluation during which known causes for interstitial pneumonia have been excluded, and do not meet criteria for a defined CTD.

The classification criteria is organised 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

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TABLE 1 Classification criteria for "interstitial pneumonia with autoimmune features"

1. Presence of an interstitial pneumonia (by HRCT or surgical lung biopsy) *and*,
2. Exclusion of alternative aetiologies *and*,
3. Does not meet criteria of a defined connective tissue disease *and*,
4. At least one feature from at least two of these domains:
   A. Clinical domain
   B. Serologic domain
   C. Morphologic domain

A. Clinical 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 oedema
7. Unexplained fixed rash on the digital extensor surfaces (Gottron's sign)

B. Serologic domain
1. ANA ⩾1:320 titre, diffuse, speckled, homogeneous patterns *or*
   a. ANA nucleolar pattern (any titre) *or*
   b. ANA centromere pattern (any titre)
2. Rheumatoid factor ⩾2× 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

C. Morphologic domain
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 centres
   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: organising pneumonia; LIP: lymphoid interstitial pneumonia; PFT: pulmonary function testing. [#]: includes airflow obstruction, bronchiolitis or bronchiectasis.

physiologic features. To be classified as having IPAF, the individual must meet all of the *a priori* requirements and have at least one feature from at least two of the domains.

Clinical domain

In this domain, specific clinical features suggestive of an underlying CTD are included. While they are specific findings, their presence alone does not allow the diagnosis of a defined CTD. Raynaud's

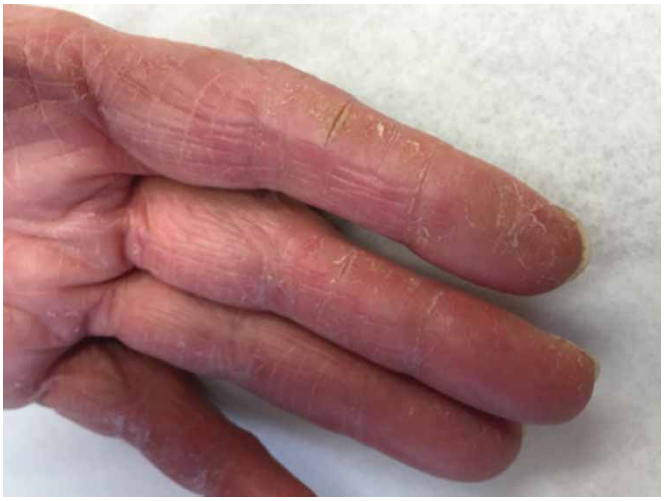

FIGURE 1 "Mechanic hands" characterised by distal digital fissuring and cracking of the skin.

phenomenon, palmar telangiectasia, distal digital tip ulceration and digital oedema are specific physical findings that are often seen in systemic sclerosis [23, 24] but rarely seen in IIP. Similarly, the features of digital fissuring ("mechanic hands") (figure 1) and a fixed rash on the digital extensor surfaces (Gottron's sign) (figure 2) are hallmarks of the anti-synthetase syndrome or systemic sclerosis-myositis overlap associated with PM-Scl antibody positivity [16, 25–32]. The use of nailfold microscopy in the evaluation of individuals with Raynaud's phenomenon is encouraged as capillary loop abnormalities can be predictive of developing a CTD such as systemic sclerosis or dermatomyositis [33–36]. Inflammatory arthropathy is included as an IPAF criterion and is characterised by symptoms or signs of peripheral joint synovitis, but joint pain alone is not included due to its lack of specificity. Other non-specific features, such as alopecia, photosensitivity, oral ulcers, weight loss, sicca symptoms, myalgia or arthralgia, are not included. Similarly, demographic profiles that may be more frequently encountered in CTD (such as younger age and female sex) are not included given their lack of specificity for CTD-ILD.

Ideally, assessment for extrathoracic features occurs through a comprehensive history and physical examination performed by clinicians including rheumatologists well-attuned to subtle extrathoracic manifestations and not based solely on self-report (*e.g.* a self-reported questionnaire).

Serologic domain

In this domain, specific circulating autoantibodies (known to be associated with CTDs) assessed as part of the evaluation of the patient with presumed IIP are included. Less specific serologic markers, such as low-titre antinuclear antibody (ANA), low-titre rheumatoid factor (RF), erythrocyte sedimentation rate, C-reactive protein or creatine phosphokinase, are not included.

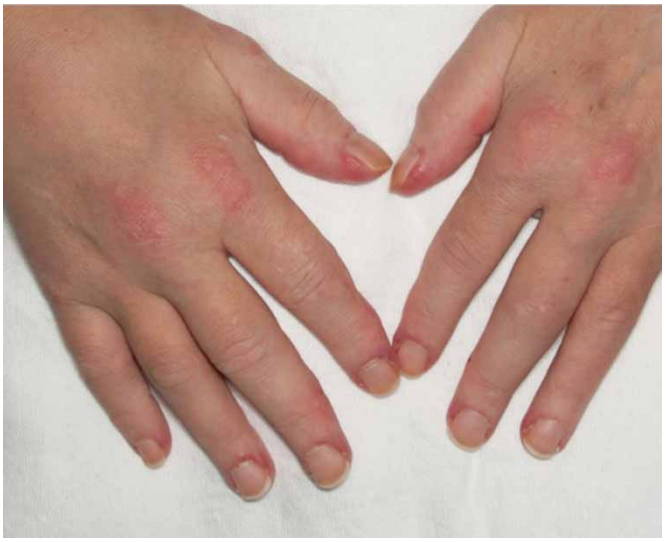

FIGURE 2 Gottron's sign characterised by fixed erythematous rash over the meta-carpal phalangeal joints. Note also the presence of periungual erythema.

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For ANA positivity with a diffuse, homogeneous or speckled staining pattern, a titre of at least 1:320 is required as this is consistent with most expert guidelines for ANA testing [36]. Low-titre ANA positivity with these staining patterns are excluded because weak ANA positivity is present in many non-rheumatic patients and even in "healthy" control populations, especially the elderly [36–39]. Regardless of titre, ANA positivity, with either a nucleolar or centromere-staining pattern, is included as an IPAF criterion. Each pattern possesses a strong association with systemic sclerosis [36, 40]; however, in the absence of other features, neither is diagnostic for systemic sclerosis.

In accordance with current guidelines for ANA testing, the preferred method for the ANA assay is by indirect immunofluorescence [41], which allows for reporting of ANA titre and staining pattern. The ELISA assay for ANA testing is less reliable [42], has been shown to be falsely negative in subsets of patients with systemic sclerosis [42], does not allow for staining pattern reporting and does not provide a titre.

Because of concerns similar to those described above for weakly reactive ANA tests, only high-titre RF values (defined as greater than or equal to twice the upper limit of normal) meet IPAF inclusion criteria. A weakly positive RF is present in many non-rheumatic patients and not infrequently in some "healthy" individuals [37–39]. For any of the other circulating autoantibodies, any value above the upper limit of normal is considered a positive serology. It is recognised that in clinical practice, serologic testing may be repeated for any variety of reasons, such as when an autoantibody titre is borderline positive. However, for the purposes of IPAF criteria, repeat serologic testing is not required if positive.

Although ANCA panel positivity has been reported with interstitial pneumonia (and usual interstitial pneumonia (UIP) pattern disease in particular) and may reflect microscopic polyangiitis or another vasculitic disease [43, 44], these autoantibodies are not included in the serologic domain because they are associated with the vasculitides, rather than the CTD-ILD spectra of disorders.

As novel autoantibodies associated with CTD are identified and become commercially available, this list may require modification.

Morphologic domain

The morphology domain consists of three sections: interstitial pneumonia patterns suggested by HRCT imaging, histopathologic features identified by surgical lung biopsy, or evidence of additional thoracic compartment involvement as determined by diagnostic imaging, histopathologic findings, right heart catheterisation (RHC) or pulmonary function testing.

Interstitial pneumonia patterns suggested by thoracic HRCT

The radiologic patterns included in the IPAF criteria are non-specific interstitial pneumonia (NSIP), organising pneumonia (OP), NSIP with OP, and lymphoid interstitial pneumonia (LIP). These patterns are commonly found in CTD-ILD, and their presence should raise the suspicion for an underlying autoimmune process [45, 46]. A radiologic pattern of UIP is seen in CTD as well (particularly in rheumatoid arthritis [47]), and as such, patients with a radiologic UIP pattern are not excluded from the IPAF definition. However, UIP was not included as a specific morphologic feature because in a patient with interstitial pneumonia, the presence of a UIP pattern alone does not increase the likelihood of having CTD. Having a radiologic UIP pattern does not exclude categorisation as IPAF, but unlike NSIP, OP or LIP patterns, there is no "credit" associated with the UIP pattern. Thus, to be considered as having IPAF, a patient with a UIP pattern on HRCT would need to have at least one feature from the other two domains (a clinical feature or a serologic feature) or another morphologic feature.

HRCT findings suggestive of NSIP are defined as basal predominant reticular abnormalities with traction bronchiectasis, peri-bronchovascular extension and subpleural sparing, frequently associated with ground-glass attenuation (figure 3) [1, 3, 48, 49]. HRCT findings suggestive of OP are defined as bilateral patchy areas of consolidation with a subpleural and lower lung zone predominance [1, 48]. NSIP with OP is defined as basal predominant consolidation, often peri-diaphragmatic, associated with features of fibrosis (*e.g.* traction bronchiectasis, reticular abnormality or lower lobe volume loss) (figure 4) [1, 48, 49]. HRCT findings suggestive of LIP are defined as predominantly peri-bronchovascular cysts, with or without ground glass opacities or reticular abnormalities (figure 5) [1, 48, 49].

Histopathologic features identified by surgical lung biopsy

The evaluation of lung parenchyma obtained by surgical lung biopsy may provide clues about whether an underlying CTD is present [50, 51]. The histopathologic features included within the morphologic domain criteria for IPAF are only those considered to be highly associated with, but not diagnostic for, the presence of CTD [50, 51]. These are the primary patterns of NSIP, OP and LIP and the secondary features

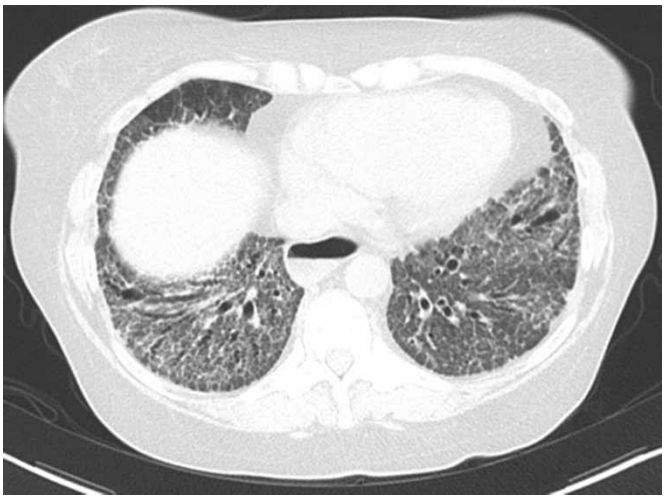

FIGURE 3 Bibasilar reticulation and traction bronchiectasis with minimal ground glass opacifications consistent with fibrotic non-specific interstitial pneumonia. Note also the presence of a dilated fluid-filled oesophagus.

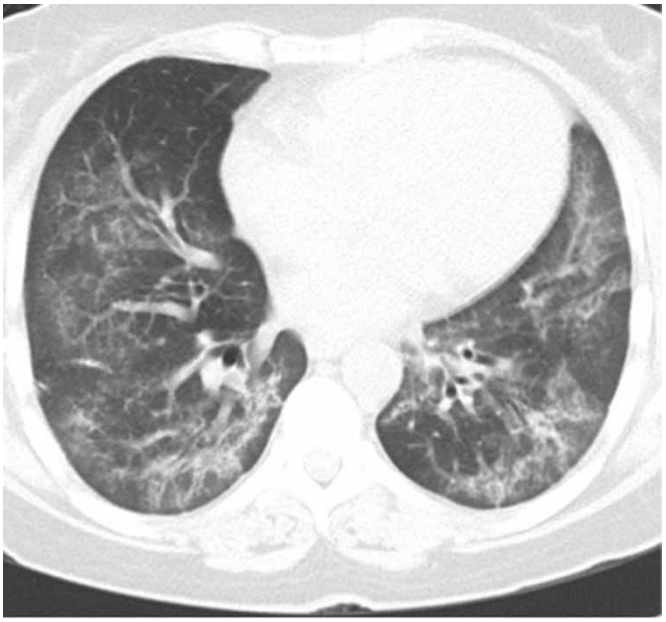

FIGURE 4 High-resolution computed tomography image suggesting non-specific interstitial pneumonia with organising pneumonia.

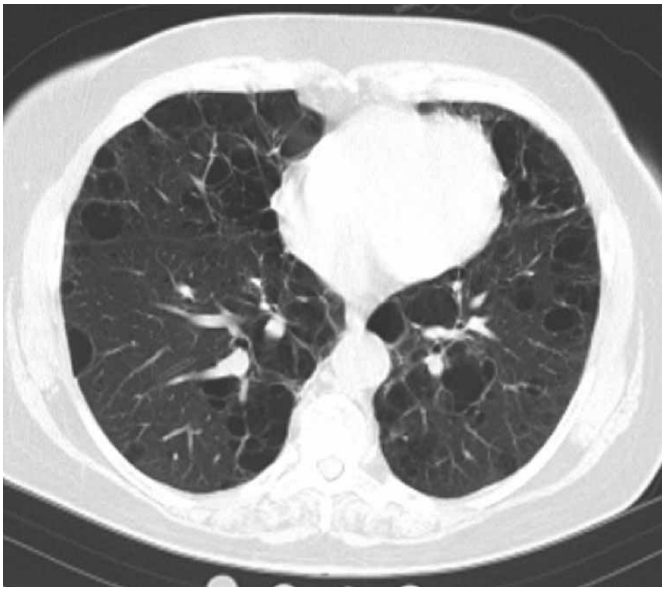

FIGURE 5 High-resolution computed tomography image suggesting lymphocytic interstitial pneumonia. Note the extensive peribronchovascular cysts.

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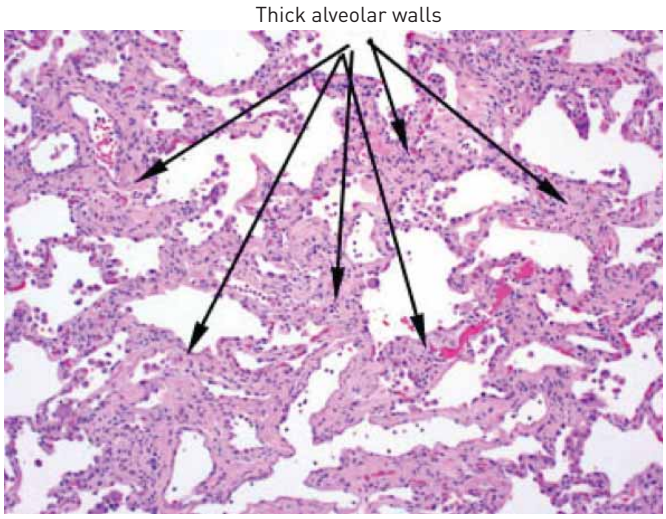

FIGURE 6 Photomicrograph of histopathology slide demonstrating fibrotic non-specific interstitial pneumonia pattern. Note the uniform thickening of all of the alveolar walls and scant chronic inflammation.

of interstitial lymphoid aggregates with germinal centres and diffuse lymphoplasmacytic infiltration with or without lymphoid follicles. The histologic features of the NSIP pattern consist of varying amounts of interstitial inflammation and alveolar wall fibrosis with a uniform appearance (figure 6) [1, 2, 49]. Cellular NSIP pattern demonstrates a mild to moderate interstitial chronic inflammatory infiltrate with little fibrosis, and fibrosing NSIP pattern consists of interstitial thickening by uniform fibrosis of the same age, usually preserving the alveolar architecture with varying amounts of cellular inflammation [1, 2, 49]. Histologically, the OP pattern is a patchy alveolar filling process characterised primarily by tufts of fibroblastic organisation involving alveolar ducts and alveoli with or without bronchiolar intraluminal polyps [1]. Other findings that may accompany an OP pattern include interstitial infiltrates of mononuclear cells, fibrinous exudates, foam cells in the airspaces and prominent type II pneumocytes. Some cases show more marked interstitial inflammation such that there is overlap with cellular NSIP [1, 3, 49]. A histologic pattern of LIP is characterised by polyclonal and inflammatory cellular infiltrates which may be diffuse and interstitial and/or which may form nodular lymphoid aggregates with or without germinal centres (figure 7) [3, 49].

Similar to the explanation for radiologic UIP, patients with a histopathologic UIP pattern are not excluded from the IPAF definition. However, histopathologic evidence of UIP was not included as a specific morphologic feature because in a patient with interstitial pneumonia, its presence alone does not increase the likelihood of having CTD. Thus, to be considered as having IPAF, a patient with a UIP pattern on histopathology also requires at least one feature from the other two domains (a clinical feature or a serologic feature), or another morphologic feature.

Multi-compartment involvement

In addition to interstitial pneumonia, the presence of several concurrent thoracic compartment manifestations is another characteristic often encountered among patients with CTD [45, 46, 51]. In this

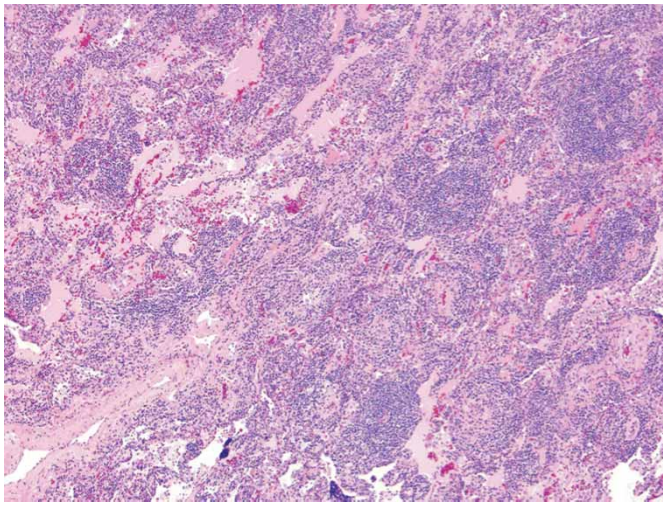

FIGURE 7 Photomicrograph of histopathology slide demonstrating lymphocytic interstitial pneumonia pattern.

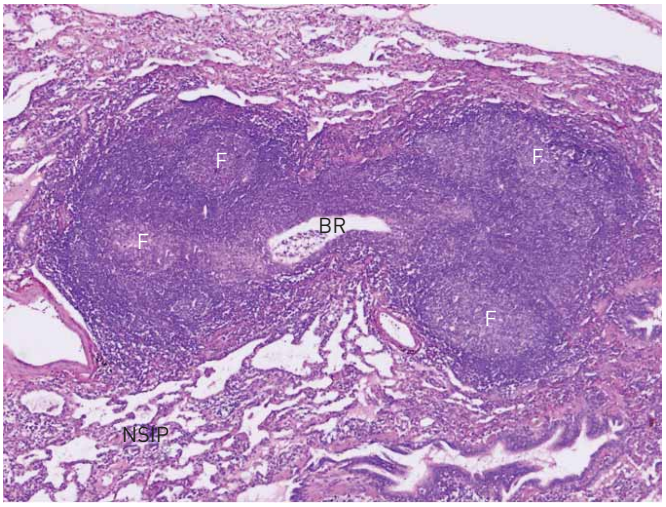

FIGURE 8 Photomicrograph of histopathology slide demonstrating follicular bronchiolitis with background pattern of non-specific interstitial pneumonia pattern. Note the large reactive lymphoid follicles (F) surrounding a bronchiole (BR).

section of the morphologic domain, we consider "multi-compartment involvement", which includes unexplained airways, vascular, pleural or pericardial abnormalities.

Unexplained intrinsic airways disease. Intrinsic airways disease (*i.e.* airflow obstruction, bronchiolitis or bronchiectasis) is a common finding in CTD patients, especially those with rheumatoid arthritis and Sjögren's syndrome, and may be seen in the setting of CTD-ILD as well [46, 52, 53]. Its presence in a patient with interstitial pneumonia may be a sign of an occult autoimmune process. Pulmonary function test findings suggestive of intrinsic airways disease include an elevated residual volume, a disproportionately reduced forced expiratory volume in 1 s (FEV_1) or low FEV_1/forced vital capacity (FVC) ratio and an elevated airways resistance. HRCT findings include a mosaic attenuation pattern, air trapping on expiratory computed tomography images, bronchial wall thickening and frank bronchiectasis [52, 53]. Peri-bronchovascular cysts may be a manifestation of follicular bronchiolitis [50, 51]. Histopathologic findings include either follicular or constrictive bronchiolitis (figure 8) [50, 51].

Unexplained pulmonary vasculopathy. Pre-capillary pulmonary hypertension (group 1 pulmonary arterial hypertension, group 1′ pulmonary veno-occlusive disease, and group 3 pulmonary hypertension due to chronic lung disease and/or hypoxia) is often associated with CTD, particularly systemic sclerosis or mixed connective tissue disease [52, 53]. Its presence is not diagnostic of CTD, as indeed, pulmonary hypertension is also frequently noted in IIP [54], but when group 1 pulmonary arterial hypertension is present along with interstitial pneumonia, or when pulmonary hypertension is severe (mean pulmonary artery pressure >35 mmHg by RHC), it does necessitate the consideration of an underlying cause, including comorbid CTD. A diagnosis of pulmonary hypertension requires cardiac haemodynamic assessment *via* RHC and is defined by the presence of a mean pulmonary pressure of $\geqslant$25 mmHg and pulmonary capillary wedge pressure $\leqslant$15 mmHg [55]. Non-invasive techniques are less reliable than RHC and include trans-thoracic Doppler echocardiography, and investigations to assess the presence of early pulmonary vascular disease such as an unexplained disproportionately low gas transfer compared to lung volumes (as seen with a disproportionately low and/or falling transfer coefficient, or high per cent FVC/per cent diffusing capacity for carbon monoxide ratio [53, 56, 57]), and marked reduced oxygen desaturation during exercise and/or sleep [53].

Unexplained pleural or pericardial effusion or thickening. Inflammation of the serosal surfaces of the lungs or heart is also seen in patients with CTD and may signal that an autoimmune process is present. Unexplained pleural or pericardial effusions or thickening on HRCT [46] or ultrasound imaging or pleuritis on lung biopsy (figure 9) would be considered as reflective of multi-compartment involvement and compatible with, though not diagnostic for, an underlying systemic autoimmune process.

Discussion

This ERS/ATS research statement proposes that the name "interstitial pneumonia with autoimmune features" (IPAF) be used to identify individuals with interstitial pneumonia and features suggestive of a CTD that do not meet established classification criteria for a characterisable CTD.

Historically, the lack of consensus on criteria has limited the ability to draw firm conclusions about this group of patients. Specifically, it is unclear whether results from a study using any one of the previously

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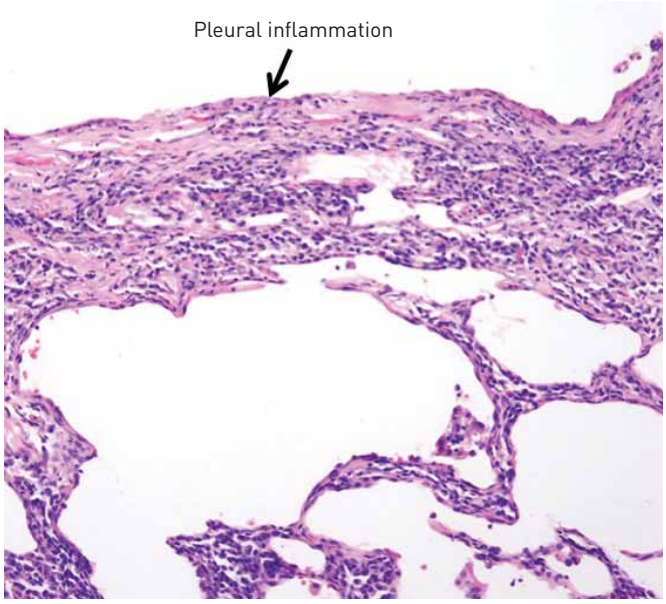

FIGURE 9 Photomicrograph of histopathology slide demonstrating chronic pleuritis overlying cellular non-specific interstitial pneumonia pattern.

published criteria [19–21] is comparable to other studies using a different set of criteria. With IPAF, uniform terminology and classification criteria for related but potentially distinct entities (UCTD-ILD, lung-dominant CTD and autoimmune-featured ILD) have been systematically developed and ratified. A strength of the IPAF nomenclature and definition is that its classification criteria were derived through international and multidisciplinary consensus.

A number of important limitations are acknowledged. Is this task force "right"? Have we excluded important features or included the wrong features? Candidly, we must accept that in the absence of data to inform decision-making, we were left to devise what this panel believes to be a reasonable *first draft* of criteria that can be readily applied by investigators who wish to study this interesting, and presently poorly defined, group of patients. We recognise that the proposed criteria must be tested and validated in future studies – revisions will be needed. We are offering these criteria as a structured framework that can be applied in a uniform manner and revisited in the future. Other CTD-ILD experts from around the world could possibly have suggested different criteria. We strove to keep the panel to a relatively small number for efficiency of communication and deliberation; of primary importance was the inclusion of investigators who developed their own criteria to classify similar patients. Essentially, we felt the need to ensure collective "buy-in" from this multidisciplinary panel that would then allow a uniform platform for further study. We also acknowledge that some patients who fulfil criteria for IPAF could be considered by certain practitioners to have partial presentations of the anti-synthetase syndrome, or systemic sclerosis spectrum of disease, or fulfil traditional definitions of UCTD [54–57]. Finally, it is likely that some individuals that initially are considered to have IPAF will evolve over time to a defined CTD.

An important clarification of this proposal, and a point of emphasis, is that the task force is not proposing guidelines or recommendations for clinical care, diagnostic testing or management of patients that meet classification criteria of IPAF. Presently, there are no data to inform any such recommendations. In the absence of data, the diagnosis (*e.g.* exclusion of CTD) and management (*e.g.* use of immunomodulatory therapies) of IPAF is left to the individual provider. There is an urgent need to prospectively study this cohort to allow for an evidence-based approach to their management. Before IPAF, the divergent classification schemes did not afford the opportunity for such prospective research.

Conclusion

In this research statement, we propose that individuals with interstitial pneumonia and certain clinical, serologic, and/or morphologic features raise suspicion for the presence of an underlying systemic autoimmune disease and should be labelled as having "interstitial pneumonia with autoimmune features" (IPAF). The classification of IPAF combines specific features from three primary domains: clinical, serologic and intrathoracic morphologic features. Adopting IPAF classification means leaving behind the previous terminologies, and allows for the future study of a more uniform cohort. Prospective studies are urgently needed to validate the proposed classification criteria and to determine the natural history and clinical implications of a classification of IPAF.

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