CHEST

POINT:

Does Interstitial Pneumonia With Autoimmune Features Represent a Distinct Class of Patients With Idiopathic Interstitial Pneumonia? Yes

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PODCAST

ABBREVIATIONS: anti-ARS = anti-aminoacyl-tRNA synthetase; CTD = connective tissue disease; HRCT = high-resolution CT; IIP = idiopathic interstitial pneumonia; ILD = interstitial lung disease; IPAF = interstitial pneumonia with autoimmune features; IPF = idiopathic pulmonary fibrosis; NSIP = nonspecific interstitial pneumonia; UIP = usual interstitial pneumonia

Interstitial pneumonia with autoimmune features (IPAF) defines a distinct subset of patients with an idiopathic interstitial pneumonia (IIP). The following case from our clinic supports our position and should resonate among those who routinely evaluate patients with an interstitial lung disease (ILD).

A 62-year-old man with exertional dyspnea has thoracic high-resolution CT findings of basilar-predominant reticular opacities, traction bronchiectasis, and patchy ground-glass opacities. He is a former smoker with no suspicious environmental exposures or medications, and he has no family history of pulmonary fibrosis. The connective tissue disease (CTD) review of systems is negative. Other than bibasilar crackles on chest auscultation, the physical examination is normal. Serologic results are notable for a positive antinuclear antibody at 1:80 titer, speckled pattern, and a positive anti-Ro antibody. Specialty rheumatologic consultation is undertaken, and no evidence of any CTD is identified. Surgical lung biopsy is performed for further evaluation. The histopathologic results reveal a diffuse interstitial fibrosing and chronic inflammatory pneumonitis with honeycomb changes, lymphoid hyperplasia, and patchy chronic pleuritis.

What does this patient have, and how should we classify him? Clearly, this case is not idiopathic pulmonary fibrosis or hypersensitivity pneumonitis. Because this patient does not have an underlying CTD, he is not classified as CTD-ILD. Should this patient be classified as having an IIP? The lung pathologic findings argue for this being a CTD-associated ILD; however, according to the rheumatologic evaluation and based on existing classification schemes, he does not have a characterizable CTD. To some extent, this scenario highlights the ongoing interdisciplinary divide that exists between pulmonary and the specialty that characterizes the CTDs, rheumatology. 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 this patient lacks the extrathoracic "autoimmune" features attributed to defined forms of CTD, he is not considered as having CTD according to rheumatologic standards. Arguing that this condition represents "idiopathic" nonspecific interstitial pneumonia minimizes the salient histopathologic features that argue strongly that his clinical situation is of an autoimmune nature.

The reality is that many patients with IIP have subtle features suggestive of an autoimmune etiology and yet these individuals often do not meet the classification criteria for a specific CTD.[1] Although reliable determinants of prevalence are lacking, this clinical scenario is not uncommon. The terms "undifferentiated CTD," "lung-dominant CTD," or "autoimmune-featured ILD" have all been used to describe such patients.[1-3] However, these sets of criteria are different enough that research studies being implemented in various centers using one set of criteria are not likely to be applicable to cohorts from centers using other sets of criteria. Assayag et al[4] applied the differing criteria to a

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cohort of 119 patients evaluated in a tertiary ILD referral program and found that 56% fulfilled at least one of the criteria but only 22% fulfilled all sets. Application of one criteria encompassed 41% of the cohort, but another definition only encompassed 21%, thereby illustrating that a more uniform definition to study patients with suggestive forms of autoimmune ILD was needed.

In an effort to build consensus, the American Thoracic Society and 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 of suggestive forms of CTD-ILD.[5]

The term "interstitial pneumonia with autoimmune features" was intentionally chosen by the Task Force to highlight the distinct nature of this subset of ILD. Several up-front a priori requirements must be fulfilled for the classification of IPAF: individuals must have evidence of an interstitial pneumonia according to high-resolution CT imaging and/or by surgical lung biopsy, a thorough clinical evaluation during which known causes for ILD have been excluded, and patients do not meet criteria for a defined CTD. The classification criteria are 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 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.[5]

The term "connective tissue disease" was specifically avoided due to concerns that such labeling gives a false impression that these individuals are thus predetermined to have a defined CTD. Furthermore, the Task Force explained that "considering a patient as having IPAF defines the cohort as unique."[5]

Since the initial publication of the IPAF criteria, there have been several publications from different ILD programs around the world that describe characteristics and the natural history of IPAF from their respective centers.[6-10] Each of these cohorts was identified retrospectively and influenced by referral bias and/or application of the criteria. These studies highlight that the current definition of IPAF allows for significant heterogeneity. For example, the Chicago cohort[10] had a usual interstitial pneumonia-pattern predominant cohort, and in many respects, it looked a lot like idiopathic pulmonary fibrosis, whereas the Denver cohort[9] was nonspecific interstitial pneumonia predominant, with a large number of patients with specific autoimmune serologic positivity (eg, tRNA synthetase antibodies). Differences notwithstanding, 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 refinement of the criteria in an evidence-based manner, and there is far more interdisciplinary engagement around this arena.

The original IPAF construct was just a start, and revisions to the construct will be needed. Within the current framework, some ambiguity in the definition of IPAF may allow a subset of patients with usual interstitial pneumonia pattern of disease (who may have idiopathic pulmonary fibrosis) to fulfill criteria for IPAF. Another area of concern relates to discrepancies among centers and experts around those with a positive anti-tRNA synthetase antibody and ILD. In the absence of cutaneous features of dermatomyositis or evidence of myositis, there can be disagreement around what one considers as incomplete forms of the anti-synthetase syndrome vs IPAF.[11,12]

The importance of longitudinal surveillance for evolution to CTD is essential.[13] Because ILD can be the first manifestation of underlying CTD, those who fulfill classification for IPAF are perhaps at higher risk for such evolution. We acknowledge that a patient presently classified as IPAF, while presently distinct from CTD-ILD, may evolve to a characterizable CTD, and resultant CTD-ILD.

In summary, a classification of IPAF should be considered as a distinct class within the IIP framework that encompasses a subset of patients residing in the intersection between IIP and CTD-ILD that warrants further prospective study.

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COUNTERPOINT:

Does Interstitial Pneumonia With Autoimmune Features Represent a Distinct Class of Patients With Idiopathic Interstitial Pneumonia? No

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PODCAST

What's in a name? that which we call a rose
By any other name would smell as sweet.
William Shakespeare, *Romeo and Juliet*[1]

What is in a name? The primary goal of disease classification is to stratify patients with common characteristics to optimize risk assessment and treatment approach. In patients with interstitial lung disease (ILD), a thorough history and physical examination, serologic evaluation, pulmonary function testing, and high-resolution CT (HRCT) scanning provide an etiology in the majority of cases, with connective tissue disease–associated ILD (CTD-ILD) being among the most common.[2] When an etiology cannot be established, patients are classified as having an idiopathic interstitial pneumonia (IIP). Although idiopathic pulmonary fibrosis (IPF) is known to be the most common and deadly IIP, patients with features of autoimmune disease who fail to meet established CTD criteria represent a sizeable IIP subgroup.[3] Because the natural history of IPF and CTD-ILD differ substantially, and because immunosuppressive therapy used for CTD-ILD can harm patients who have IPF,[4] correctly identifying patients with IIP due to undiagnosed CTD is critical. To address the classification of such patients, a European Respiratory Society/American Thoracic Society task force published a research statement in 2015 proposing criteria for interstitial pneumonia with autoimmune features (IPAF).[5]

To meet IPAF criteria, an individual with IIP must have one feature from two of three domains: clinical, serologic, and morphologic. The clinical domain comprises physical manifestations of CTD, such as Raynaud's phenomenon. The serologic domain includes autoantibodies common to CTD, including antinuclear antibody. The morphologic domain is separated into HRCT, histologic, and multicompartment subdomains. The HRCT and histologic subdomains include patterns commonly observed in CTD, including nonspecific interstitial pneumonia (NSIP) and organizing pneumonia. The multicompartment subdomain includes extraparenchymal manifestations of CTD.

The IPAF research statement sought to establish "a uniform name and set of classification criteria."[5] Admirable as these intentions were, the striking heterogeneity in IPAF cohorts assembled to date has yielded only one reasonable conclusion; that is, patients meeting IPAF criteria do not represent a distinct class of patients with IIP. Indeed, a recent systematic review of IPAF studies concluded much the same.[6] Three specific areas inform this conclusion: (1) the variability in ILD cohorts selected to apply IPAF criteria; (2) the inclusion of several highly specific CTD antibodies in the serologic

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