# Interstitial Lung Disease and Other Pulmonary Manifestations in Connective Tissue Diseases

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## Abstract

Lung involvement in connective tissue diseases is associated with substantial morbidity and mortality, most commonly in the form of interstitial lung disease, and can occur in any of these disorders. Patterns of interstitial lung disease in patients with connective tissue disease are similar to those seen in idiopathic interstitial pneumonias, such as idiopathic pulmonary fibrosis. It may be difficult to distinguish between the 2 ailments, particularly when interstitial lung disease presents before extrapulmonary manifestations of the underlying connective tissue disease. There are important clinical implications in achieving this distinction. Given the complexities inherent in the management of these patients, a multidisciplinary evaluation is needed to optimize the diagnostic process and management strategies. The aim of this article was to summarize an approach to diagnosis and management based on the opinion of experts on this topic.

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Interstitial lung diseases (ILDs) comprise a group of diffuse parenchymal infiltrative lung disorders classified according to etiologic, clinical, radiologic, and histopathologic features. Some of the most common forms of ILD, such as idiopathic pulmonary fibrosis (IPF), are of unknown origin; however, some have identifiable causes, including environmental exposures, drugs, tobacco smoke, genetic disorders, and autoimmune diseases. The latter group includes connective tissue diseases (CTDs), which are characterized by immune-mediated tissue injury that can involve the lungs.[1-3]

The features of CTD-related ILD (CTD-ILD) usually present in patients already diagnosed as having CTD. However, ILD may be the presenting feature, sometimes accompanied by findings suggestive of an underlying autoimmune process but not sufficient for a definitive CTD diagnosis.[3,4] Under such circumstances, the diagnosis and clinical implications thereof often remain unclear.[5,6] In patients with CTDs, ILD is associated with substantial morbidity and mortality. For example, the 5-year mortality rate is 3-fold higher in patients with rheumatoid arthritis (RA) and scleroderma who have ILD.[7,8] However, compared with those with idiopathic interstitial pneumonias (IIPs), patients with CTD-ILD are more likely to respond to immunosuppressive therapy and have a better prognosis.[3,5,6,9]

Because of the challenges in diagnosis and management of patients with CTD-ILDs, a multidisciplinary approach involving relevant specialties, including pulmonology, rheumatology, radiology, and pathology, is vital for optimal care. In November 2017, a multidisciplinary symposium on pulmonary manifestations of CTDs took place at Amelia Island, Florida, organized by the Divisions of Rheumatology and Pulmonary, Allergy, and Sleep Medicine of Mayo Clinic in Florida. This article summarizes the proceedings of this conference.

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- Interstitial lung disease is present in approximately 40% of patients with connective tissue disorders, contributing to increased morbidity and mortality.
- Interstitial lung disease in association with connective tissue disorder has a better prognosis than idiopathic counterparts.
- Characteristic patterns on chest computed tomography help distinguish the various interstitial lung disease manifestations in patients with connective tissue disorders.
- Treatment options have expanded and may offer improved outcomes.

## CLINICAL APPROACH TO CTD-ILD

Interstitial lung disease complicating CTD typically, but not always, occurs after an established diagnosis of a CTD.[1] Because CTD-ILDs share radiologic, physiologic, and even histopathologic features with IIPs and other ILDs, close collaboration between rheumatology, pulmonology, radiology, and pathology is important in achieving an appropriate diagnosis and guiding management.

Dyspnea and cough are unlikely to be differentiating symptoms between CTD-ILD and other ILDs,[10] and the clinician must probe for extrapulmonary symptoms with a careful systems review for clues toward an underlying CTD. Similarly, the respiratory examination will be less revealing than findings outside the lung in helping to identify an underlying systemic inflammatory disorder as the basis of the patient's ILD.

After a thorough history and physical examination, the pulmonary function test is instrumental for diagnosing and tracking ILD. Typically, ILDs will be characterized by a restrictive ventilatory defect (ie, reduced total lung capacity, normal forced expiratory volume in 1 second/forced vital capacity [FVC] ratio) with reduced diffusing capacity of the lung for carbon monoxide (DLCO); however, the spirometry can be normal in mild disease or mixed obstructive-restrictive disorders (eg, coexisting emphysema).[11] It is also important to remember that DLCO can be reduced by both

pulmonary hypertension (PH) and emphysema. For serial monitoring, the FVC and DLCO are most commonly used, along with oximetry, which is used to monitor for hypoxemia requiring oxygen supplementation and as a potential indicator for lung transplant evaluation.[9,11]

High-resolution computed tomography (HRCT) is essential in the initial evaluation of any suspected ILD. There is a good correlation between the extent of ILD assessed by HRCT and the degree of pulmonary impairment measured by FVC and DLCO.[12,13] In addition to the pattern of ILD, HRCT provides information on the airways, pulmonary artery, pleura, coexisting emphysema or cancer, and extrapulmonary structures that may be relevant in the management of the patient. The HRCT can be diagnostic of usual interstitial pneumonia (UIP), the histologic pattern seen in patients with IPF. However, UIP can be seen with CTD-ILD (particularly RA), as well as others (eg, chronic hypersensitivity pneumonitis).[14-16] Thus, the clinical context and correlation remain essential.

In established CTD, the role of a surgical lung biopsy remains uncertain. It may provide prognostic information,[17] but whether it would alter management remains unclear. However, when there is uncertainty about an underlying CTD, a lung biopsy may be important to distinguish from other interstitial pneumonias, particularly IPF. Surgical lung biopsy has the highest yield, but bronchoscopic cryobiopsy, which provides larger biopsy specimens compared with traditional forceps biopsy, may find an increasing role in this regard.[18] Bronchoalveolar lavage is neither diagnostic nor specific but may be used to rule out other processes, such as infection or hemorrhage. Distinguishing IPF-UIP from a CTD-ILD whenever possible has significant therapeutic implications. Antifibrotic agents such as pirfenidone and nintedanib have been shown in clinical trials to slow the loss of lung function in IPF; but in contrast, immunomodulators (eg, azathioprine and prednisone) that are typically used for CTD-ILD may potentially be more harmful in IPF.[19]

## PATHOLOGY OF CTD-ILD

As already noted, lung biopsy may be obtained for evaluation of ILD in some patients without a clear diagnosis of CTD or atypical features on clinical or radiologic presentation. In such patients, pathologic diagnosis of CTD-ILD can be challenging. Connective tissue disease—related ILDs may show all major patterns seen in IIPs, including nonspecific interstitial pneumonia (NSIP), UIP, lymphoid interstitial pneumonia (LIP), organizing pneumonia (OP), acute interstitial pneumonia/diffuse alveolar damage (DAD), and, in rare cases, desquamative interstitial pneumonia.[20,21] Of note, NSIP is more commonly seen than is UIP in the setting of CTD-ILD (except in RA), whereas UIP is the most common pattern in patients with IIPs.[22] The distribution of histopathologic patterns varies depending on the type of CTD, but there is no specific association between any ILD pattern and a particular CTD.

The histologic differences between CTD-UIP and IPF-UIP have not been clearly defined. Cipriani et al[23] proposed histologic criteria to differentiate CTD-UIP from IPF-UIP by a quantitative pathologic study using fibroblastic foci, lymphoid aggregates, and presence of an NSIP pattern as the parameters (Figure 1). They concluded that CTD-UIP had fewer and smaller fibroblast foci than did IPF-UIP. Of patients with CTD-UIP, those with RA-UIP had more and larger lymphoid aggregates than did patients with IPF-UIP. Their study also showed that the coexistence of UIP and NSIP patterns was one of the most salient features in distinguishing CTD-UIP from IPF-UIP.[23] The histologic variability in different lobes has also been demonstrated in patients with IIPs.[24] Surgical lung biopsies from multiple lobes of 109 patients with IIP were reviewed by 3 expert pulmonary pathologists, who assigned a diagnosis of UIP vs NSIP in each lobe. In 26% of 109 patients with IIP, there was interlobar histologic variability (ie, a UIP pattern in ≥1 lobe and an NSIP pattern in ≥1 lobe).

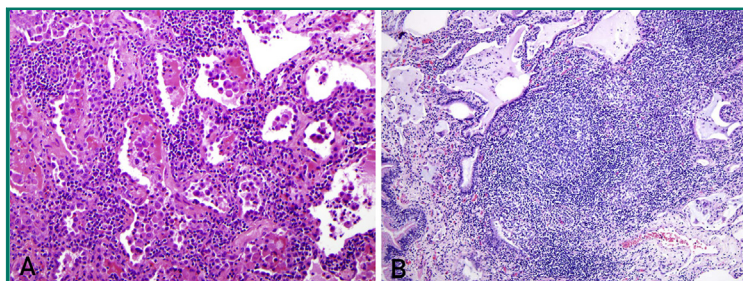It has been recognized that many patients thought to have IIP after lung biopsy



**FIGURE 1.** Histopathologic features suggestive of connective tissue disease—related interstitial lung disease. A, Heavy lymphoplasmacytic infiltrates in the alveolar interstitial septa, diagnostic for lymphocytic interstitial pneumonia (hematoxylin-eosin, original magnification ×200). B, Lymphoid follicle with prominent germinal center is seen in a background of interstitial fibrosis in a patient with rheumatoid arthritis (hematoxylin-eosin, original magnification ×100).

manifest clinical or serologic features suggestive of an underlying autoimmune process without meeting the established criteria for a CTD.[3,4] The European Respiratory Society and the American Thoracic Society (ATS) Task Force proposed the term *interstitial pneumonia with autoimmune features* (IPAF), which is elaborated on in more detail later herein.[4]

## IMAGING ASPECTS OF CTD-ILD

Various thoracic imaging abnormalities may be encountered in patients with CTDs (Table 1),[25,26] but the pattern associated with the greatest morbidity and mortality is ILD. Therefore, when HRCT is performed for patients with CTDs, assessment of the presence and pattern of ILD is important and is typically approached using the ATS consensus criteria used for IIPs.[26,27] These imaging patterns for ILD correlate with those described for histopathologic patterns.[26]

The UIP pattern on HRCT is characterized by reticulation associated with fibrotic features, including architectural distortion, traction bronchiectasis, and possibly honeycombing.[21,27] These findings are peripheral and basal predominant, although some upper lobe abnormality is typically present. Findings considered inconsistent with the UIP pattern include an upper or middle lung or peribronchovascular predominance,

**TABLE 1. Relative Frequencies of Computed Tomography Imaging Patterns Among CTDs[a]**

| CTD | UIP | NSIP | OP | LIP | DAD | Hemorrhage | Airway[b] | Nodules[c] | Serositis[d] |
|-----|-----|------|-----|-----|-----|-----------|-----------|------------|--------------|
| RA | +++ | ++ | ++ | + | + | − | +++ | +++ | +++ |
| SSc | + | +++ | + | − | + | − | − | − | − |
| PM/DM | + | +++ | +++ | − | ++ | − | − | − | − |
| SjS | + | ++ | − | ++ | + | − | + | + | − |
| SLE | + | ++ | + | ++ | ++ | +++ | − | − | +++ |
| MCTD | + | ++ | + | − | − | − | − | − | + |

[a]− = absence of finding; + = lowest and +++ = highest; CTD = connective tissue disease; DAD = diffuse alveolar damage pattern; LIP = lymphocytic interstitial pneumonia pattern; MCTD = mixed connective tissue disease; NSIP = nonspecific interstitial pneumonia pattern; OP = organizing pneumonia pattern; PM/DM = polymyositis/dermatomyositis; RA = rheumatoid arthritis; SjS = Sjögren syndrome; SLE = systemic lupus erythematosus; SSc = systemic sclerosis; UIP = usual interstitial pneumonia pattern.
[b]Bronchiectasis, bronchial wall thickening, small centrilobular nodules (that may reflect follicular bronchiolitis), and constrictive bronchiolitis.
[c]Typically ≥1 cm (not centrilobular).
[d]Pleural or pericardial fluid or thickening.

extensive ground-glass opacity, micronodules, discrete cysts, significant mosaic perfusion and air trapping, and consolidation.[27]

The NSIP pattern consists of bilateral, basal-predominant ground-glass opacity and reticulation associated with traction bronchiectasis. The presence of fibrotic abnormalities varies from minimal, in patients with cellular NSIP, to pronounced, possibly with honeycombing resembling UIP, in patients with fibrotic NSIP. The pattern of lesser lung involvement adjacent to the pleura (subpleural sparing) suggests NSIP.[28]

The OP pattern consists of patchy, peripheral, often frankly subpleural, and peribronchiolar consolidation that may migrate. Perilobular opacities and the reversed ground-glass halo sign may occur. The LIP pattern is often nonspecific at HRCT, but one manifestation—multiple, thin-walled cysts—may be recognized.[29]

The imaging appearances of the various IIP patterns are generally indistinguishable from their CTD-associated counterparts,[25] but several clues to a CTD-associated etiology may be recognized:

- Combined NSIP-OP pattern. When a basal-predominant fibrotic abnormality shows a superimposed OP pattern (Figure 2), CTD, especially idiopathic inflammatory myopathies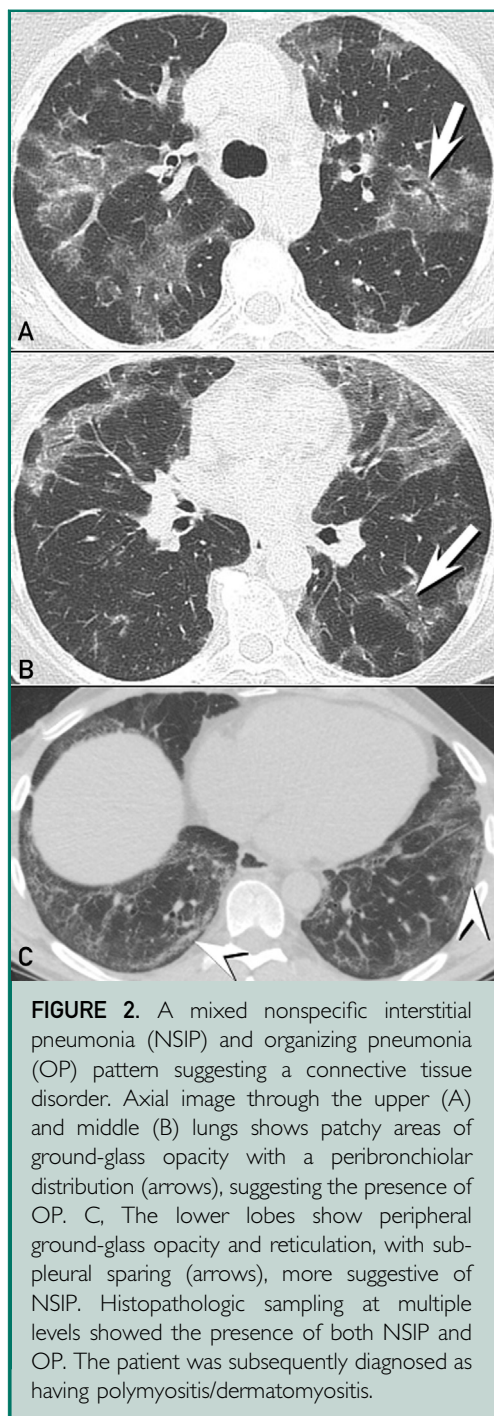 (IIMs) or antisynthetase syndrome (AS), should be suspected.[21,30] Occasionally, AS presents with acute respiratory failure and DAD superimposed on a basal-predominant IIP pattern.[25,31]
- Unclassifiable interstitial pneumonia may result from atypical or mixed imaging findings,[27] including a peribronchovascular distribution, or when DAD is superimposed on another IIP pattern, potentially indicating the presence of CTD.[25]
- Clues favoring CTD-UIP over IPF-UIP include straight-edge sign (fairly straight and abrupt interface between fibrotic and normal lung), exuberant honeycombing sign (extensive honeycomb cyst formation constituting >70% of fibrotic-appearing lung), and anterior upper lobe sign (reticulation and honeycombing concentrated in the anterior upper lobes) (Figure 3).[32]
- Other thoracic imaging findings suggesting CTD.[25] Other clues to the presence of CTD and their relative prevalence, most commonly affecting the thorax, are detailed in Table 1.

## Radiology Report in CTDs: Essential Elements

Several elements should be included when reporting HRCT results in patients with CTD:

- Presence of pulmonary parenchymal abnormalities and the pattern of any

**FIGURE 2.** A mixed nonspecific interstitial pneumonia (NSIP) and organizing pneumonia (OP) pattern suggesting a connective tissue disorder. Axial image through the upper (A) and middle (B) lungs shows patchy areas of ground-glass opacity with a peribronchiolar distribution (arrows), suggesting the presence of OP. C, The lower lobes show peripheral ground-glass opacity and reticulation, with subpleural sparing (arrows), more suggestive of NSIP. Histopathologic sampling at multiple levels showed the presence of both NSIP and OP. The patient was subsequently diagnosed as having polymyositis/dermatomyositis.

interstitial pneumonia using the ATS reporting scheme[27]

- Large main pulmonary artery size (>2.9 mm or the main pulmonary artery larger than the ascending aorta considered abnormal), which may indicate the presence of PH

- Findings that may indicate the etiology of the CTD (Table 1), such as serositis, airway disease, cysts, etc
- Findings that may indicate a complication, such as pneumonia or nodules measuring 1 cm or larger, which can herald the development of lymphoma, particularly in the setting of Sjögren syndrome (SjS)

For patients with systemic sclerosis (SSc), semiquantitative HRCT assessment of pulmonary disease severity as limited or extensive combined with FVC assessment may segregate patients into low- and high-risk categories, potentially identifying patients requiring treatment.[33] The optimal HRCT threshold varies among studies evaluating this approach but clusters around 20% of total lung volume.[33,34]

## SCLERODERMA

Scleroderma is a chronic autoimmune rheumatic disease characterized by small-vessel vasculopathy and fibrosis of the skin and internal organs. Immune-mediated mechanisms seem to be central to endothelial cell injury accompanied by fibroblast recruitment and activation, which result in accumulation of extracellular matrix and fibrosis.[35]

Among the CTDs, scleroderma carries the highest case-based mortality, with median survival after diagnosis estimated to be 11 years.[36] Approximately 50% to 55% of deaths are due to scleroderma itself.[37,38] Systemic sclerosis is diagnosed when the characteristic skin abnormality is associated with internal organ involvement.

Pulmonary involvement occurs in more than 80% of patients with scleroderma and includes ILD (most common), pulmonary arterial hypertension (PAH), pleural effusion, constrictive bronchiolitis, respiratory muscle weakness, and aspiration pneumonia (related to esophageal dysfunction).[37,39] In recent years, ILD and PAH have become the main causes of scleroderma-related deaths, surpassing renal crisis.[37,38,40]

Patients with SSc-ILD typically present with exertional dyspnea or cough but may sometimes be asymptomatic.[41-43] Inspiratory
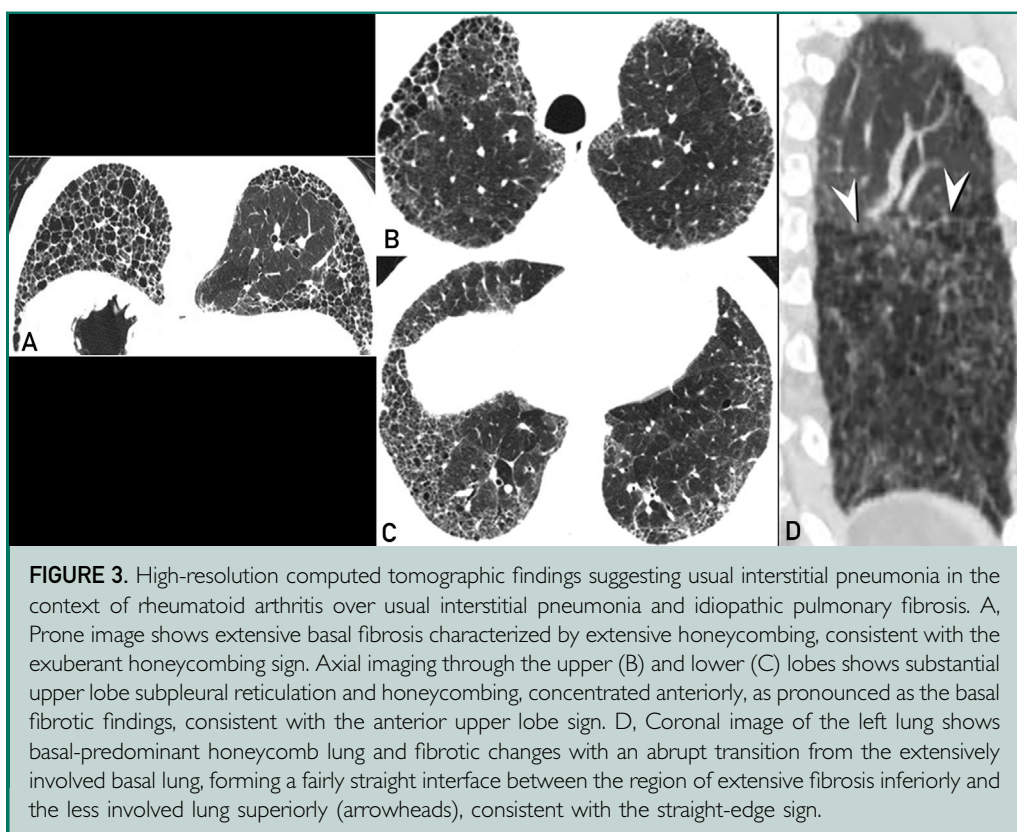
**FIGURE 3.** High-resolution computed tomographic findings suggesting usual interstitial pneumonia in the context of rheumatoid arthritis over usual interstitial pneumonia and idiopathic pulmonary fibrosis. A, Prone image shows extensive basal fibrosis characterized by extensive honeycombing, consistent with the exuberant honeycombing sign. Axial imaging through the upper (B) and lower (C) lobes shows substantial upper lobe subpleural reticulation and honeycombing, concentrated anteriorly, as pronounced as the basal fibrotic findings, consistent with the anterior upper lobe sign. D, Coronal image of the left lung shows basal-predominant honeycomb lung and fibrotic changes with an abrupt transition from the extensively involved basal lung, forming a fairly straight interface between the region of extensive fibrosis inferiorly and the less involved lung superiorly (arrowheads), consistent with the straight-edge sign.

crackles are usually present, but digital clubbing is rare. Occasionally, a restrictive pattern on pulmonary function results may relate to diffuse thoracic cutaneous sclerosis or respiratory muscle weakness[41-43]; DLCO that is reduced out of proportion to the FVC in the absence of coexisting emphysema should raise suspicion for the presence of PH.[44] Parenchymal abnormalities seen on HRCT most commonly reflect an NSIP pattern[14]; less commonly, a UIP pattern is seen. Other HRCT findings may include pulmonary artery enlargement suggestive of PH and esophageal dilatation.

Diagnosis of SSc-ILD is generally achieved in the presence of an NSIP or UIP pattern on HRCT of the chest and does not require histopathologic confirmation. Unexpected findings on imaging or atypical clinical features suggestive of other processes, including drug toxicity and infection, may necessitate further diagnostic evaluation, such as bronchoscopy and lung biopsy.

Most patients with SSc-ILD experience gradual progression reflected in increasing fibrotic changes on imaging and decline in pulmonary function.[34] Acute exacerbation of ILD may occur, as seen in other chronic fibrotic ILDs, and likely shortens survival. Predictors of mortality in patients with SSc-ILD include age, FVC, DLCO, HRCT fibrosis severity, bronchoalveolar lavage fluid neutrophilia, and presence of PH.[45] Mortality risk prediction models that may assist in prognostication for individual patients are available.[34,46,47]

Pharmacologic therapy with mycophenolate mofetil or cyclophosphamide provides modest benefit for patients with SSc-ILD. A 12-month clinical trial comparing oral cyclophosphamide with placebo showed a slightly reduced rate of decline in FVC (expressed as percentage of predicted) favoring cyclophosphamide therapy (mean ± SD, $-1.0 \pm 0.92$ vs $-2.6 \pm 0.9$, respectively; $P < .03$).[48] There were also slight differences in physiologic and symptom outcomes

favoring the cyclophosphamide group. In a subsequent clinical trial, mycophenolate mofetil therapy was shown to provide similar benefits compared with oral cyclophosphamide but with less drug-related toxicity.[49] Based on these results, other studies of an observational nature, and clinical experience, mycophenolate mofetil therapy is currently favored in the treatment of patients with SSc-ILD.[50] However, the decisions regarding who to treat and when to initiate therapy remain difficult because the benefits of pharmacologic therapy are modest and the downsides, including drug-related toxicities, are significant. Although low-dose prednisone has been used, the role of corticosteroids is limited in patients with SSc-ILD because the risk of renal crisis is associated with prednisone dose greater than 15 mg/d.[51] The potential therapeutic roles of antifibrotic agents (ie, pirfenidone and nintedanib), biologic targeted therapies (eg, rituximab, tocilizumab, and fresolimumab), and autologous stem cell transplant remain to be clarified and continue to be investigated.

## RHEUMATOID ARTHRITIS

The most common lung manifestation of RA is ILD, coming to clinical attention in approximately 10% of the RA population.[52] An additional 30% of patients with RA have subclinical lung disease. Although the incidence of some extra-articular disease involvement, such as vasculitis, has been diminishing in recent years with the advent of more effective therapies for RA, there is no evidence that the prevalence of RA-ILD has decreased.[53] Lung disease may precede the development of joint disease in up to 20% of patients who have RA-ILD.

Middle-aged men; those with a smoking history of greater than 25 pack-years, who are positive for rheumatoid factor or anticitrullinated peptide antibodies; those with other extra-articular disease manifestations; and those with the human leukocyte antigen—antigen D—related double-shared epitope are at particular risk for the development of RA-ILD.[52,54]

The most common pattern of RA-ILD is UIP in most series of patients in Western countries. However, a study from China reported that 58% of 237 patients with RA-ILD had an NSIP pattern on HRCT.[54]

Histopathologic evaluation of RA-ILD has revealed an increased presence of citrullinated proteins compared with patients with ILD without RA.[55] An increase in CD20- and CD168-positive lymphocytes has been reported in patients with RA-NSIP and RA-UIP compared with patients with idiopathic NSIP or UIP. These and other findings have led to consideration of the lung as being ground zero for the generation of autoimmunity in RA, with aberrant antigen presentation in the lung, particularly in patients who are smokers.[56]

Rheumatoid arthritis ILD progresses at a variable rate. Five years after ILD diagnosis, 20% of patients will progress to an FVC of less than 50%, and 40% will progress to a DLCO of less than 40%.[16] The 1-year mortality is reported to be 14% in patients with RA-ILD compared with 4% in patients with non-ILD RA, and 10-year mortality was 60% and 35%, respectively.[57] The risk of death for individuals with RA-ILD is approximately 3-fold higher than that for patients with RA without ILD. Median survival after the diagnosis of RA-ILD is approximately 2.6 years, and it is responsible for 10% to 20% of all RA-related mortality.[52,53,58]

To date, no immunosuppressive or immunomodulatory therapies have been consistently shown to stabilize or improve RA-ILD. Indeed, especially elderly patients with RA given high doses of glucocorticosteroids and chemotherapy are at high infection risk, and, in general, the evidence for efficacy of this therapy for RA-ILD is very limited.[59] Of the biologicals having potential utility for the treatment of RA and other CTD-ILD, rituximab has had the most interest, but with mixed results. Note that virtually all nonbiological and biological disease-modifying antirheumatic drugs have been associated with pulmonary toxicity, although, in general, this risk is low.[59] Antifibrotic therapy may also be a promising approach to the management of RA-ILD.

Currently, a randomized clinical trial is underway examining pirfenidone.[60]

## SYSTEMIC LUPUS ERYTHEMATOSUS

Lung involvement in systemic lupus erythematosus (SLE) is common and can affect any compartment, with pleurisy being most common, although more severe disease manifestations can rarely occur. Lupus pneumonitis is a feared complication of SLE, characterized on histology by acute lung injury. It can present with rapidly progressive dyspnea, fever, unilateral or bilateral infiltrates, and, occasionally, hemoptysis, and may be seen as part of the presenting features of SLE. Pathology may show deposits of immune complexes composed of DNA, anti-DNA antibody, and complement and deposits of DNA−anti-DNA immune complexes.[61] Progression to respiratory failure is common and results in high mortality. Diffuse alveolar hemorrhage (DAH) can occur in this syndrome, although DAH may occur for other reasons related to SLE, including antiphospholipid syndrome, and distinguishing these entities can be challenging.[62]

Patterns of ILD such as UIP, NSIP, and LIP have been described in SLE[63] but are less common than in scleroderma, IIM, or RA.

Shrinking lung syndrome is rarely seen in SLE, is characterized by dyspnea, and is often accompanied by pleurisy (>60%). Typically, FVC and DLCO are reduced, although DLCO corrected for alveolar volume is usually normal. Shrinking lung syndrome is suspected in patients with SLE who have dyspnea with normal lung parenchyma on HRCT (ie, no evidence of ILD) and no evidence of PH but abnormal pulmonary function test results. The etiology may be related to pleural changes, pain, and subtle changes in lung density that affect compliance, and, thus, limit normal inspiration. Esophageal balloon manometry may be helpful to assess lung compliance and chest wall and pleural dynamics.[64] If inflammation around the lung is suspected, it should be treated; if pain is the predominant feature, then treatment of the pain may be helpful to limit compliance changes and preserve functional capacity.

In SLE with antiphospholipid syndrome, thromboembolic disease leading to PH, capillaritis with or without overt hemoptysis, or DAH and acute respiratory distress syndrome can develop.[65] In those cases, high-dose glucocorticoids combined with cytotoxic therapy, B-cell−deleting therapy, and plasmapheresis may be necessary.[66]

## SJÖGREN SYNDROME

Sjögren syndrome is characterized by CD4 T-cell infiltration of lacrimal and salivary glands, increased interferon-γ and interleukin-2 production, and abnormal B-cell activation, resulting in autoantibody production, hypergammaglobulinemia, and increased risk of lymphoma. Xerotrachea, pleuritis, and airway and parenchymal lung disease have all been described in patients with SjS.

All forms of ILD, including NSIP, UIP, and LIP, have been described in SjS, and they can be progressive.[63] Clinical presentations of ILD may be obscured due to the presence of cough in patients with SjS, related to xerotrachea or small airways disease such as constrictive or follicular bronchiolitis as a manifestation of LIP, where lymphoplasmacytic infiltrates can involve airways and result in obstruction.[67] Male smokers are at the highest risk for ILD.[63]

In cases in which new nodules are noted, the possible development of lymphoma and amyloidosis must be considered.[68,69] The risk of lymphoma in SjS is 3% to 5% greater than that in the general population and can include mucosa-associated lymphoid tissue, diffuse B-cell, and follicular lymphomas. Risk factors for the development of lymphoma include extraglandular features, such as cutaneous vasculitis, neuropathy, rheumatoid factor positivity, and the presence of cryoglobulins.[70]

## IIMS AND AS

The IIMs include a group of disorders characterized by muscle inflammation from an autoimmune attack, leading to muscle

weakness. Although the main manifestation is myositis, as the name implies, extramuscular involvement is common and can be more clinically significant than myositis itself. For example, swallowing abnormalities, cardiac involvement, and pulmonary disease are all frequently found. Among these manifestations, ILD has a prevalence of 30% to 40% and is associated with an estimated mortality of 40%.[71] Recognition of autoantibodies has led to consideration of humoral immune etiology as an explanation for all manifestations, but particularly in ILD, because more than 75% of patients who are serologically positive (eg, antisynthetase antibodies) develop ILD.[72-75]

Antibodies against melanoma differentiation—associated gene 5 are associated with amyopathic dermatomyositis and the development of acute and rapidly progressive ILD.[75] Myositis-associated and myositis-specific antibodies are detectable in the sera of 50% of patients with polymyositis/dermatomyositis. Myositis-associated antibodies are not specific to polymyositis/dermatomyositis and are found in a variety of autoimmune diseases. In contrast, myositis-specific antibodies seem to define specific clinical phenotypes. Myositis-associated antibodies are classified by their target into 4 groups; the most relevant are those targeted against ribonucleoproteins involved in protein synthesis (anti—aminoacyl-tRNA synthetase [ARS] antibodies, also known as antisynthetase antibodies).[76] Jo1 is the most common ARS antibody, but 7 more have been discovered to date (PL7, PL12, OJ, EJ, KS, Zo, and Ha).

Antisynthetase syndrome corresponds to the combination of an inflammatory myopathy and the presence of antisynthetase antibody. It is characterized by the association with other features, such as mechanic's hands, Raynaud phenomenon, fever, and, more importantly, ILD.[77-80] Different phenotypes of AS have been recognized based on it, with more muscle involvement seen in anti-Jo1, anti-EJ, and anti-PL7.[79,80]

The prevailing pathologic patterns are OP, UIP, NSIP, and DAD, which coincide with the described HRCT findings.[80-82]

Interestingly, HRCT features of NSIP pattern combined with subpleural and peribronchovascular areas of consolidation, resembling OP, seem to be relatively common in AS.[83]

Because AS was first identified in patient cohorts with IIM (ie, dermatomyositis or polymyositis), it has usually been treated by protocols primarily designed for myositis, most often with high-dose corticosteroids as the mainstay drug; however, the available data so far indicate that the major determinant of morbidity and mortality in this entity is the presence of ILD, and in many cases, there is corticosteroid resistance that necessitates the use of other immunosuppressive medications, such as mycophenolate, which is supported by only retrospective data.[50]

Other options, such as calcineurin inhibitors (tacrolimus or cyclosporine), have been evaluated in the refractory form of the disease.[84,85] There has been growing enthusiasm for the use of rituximab, a monoclonal antibody against the CD20 B-cell surface marker, in the treatment of this entity.[86]

## VASCULITIS

Systemic vasculitis typically has been associated with non-ILD pulmonary manifestations, such as lung nodules or DAH.[87] Recently, however, ILD has been recognized in patients with antineutrophil cytoplasmic antibody (ANCA)—associated vasculitis, particularly if they are positive for antimyeloperoxidase antibodies.[88,89]

A few small series, mostly retrospective, have identified specific features of patients with positive antimyeloperoxidase antibodies and pulmonary fibrosis. The most common radiographic and pathologic pattern is UIP, and less commonly NSIP[90]; it seen more often in men and at an older age compared with other CTDs, with a mean age at onset typically in the late 60s.[89,91,92] Interstitial lung disease either precedes or occurs concomitantly with the onset of vasculitic features.[88-92] As mentioned previously herein, the clinical picture and demographic characteristics could be very similar to those of patients with IPF; however, increased attenuation around areas of honeycombing and cystic

lesions are seen more often. On histology, patients with ANCA-ILD had more prominent inflammatory cell infiltration, germinal centers, lymphoid follicles, and cellular bronchiolitis compared with patients with IPF.[93]

Most patients with ANCA-ILD reported in the literature have been positive for p-ANCA and antimyeloperoxidase antibody[88-93]; however, data from our group found that approximately one-third of the patients with ANCA-associated vasculitis and ILD were c-ANCA/proteinase-3 positive, a higher percentage than previously reported.[94]

The mortality rate of patients with ANCA-ILD seems to be higher compared with that of patients with CTD-ILDs, and more similar to patients with IPF[89,91,95]; however, a small study reported that immunosuppressive treatment tended to be more effective in patients with ANCA-UIP compared with patients with IPF.[93]

## INTERSTITIAL PNEUMONIA WITH AUTOIMMUNE FEATURES

As previously mentioned, many patients with IIP have subtle features suggestive of an autoimmune etiology, and these individuals quite often do not meet the classification criteria for a specific CTD.[1,96] It has even been suggested that idiopathic NSIP is an autoimmune disease or the lung manifestation of undifferentiated CTD.[97,98] With generally improved outcomes associated with CTD-ILD,[9] and because different treatment approaches are often implemented in these patients,[99] determining whether suggestive forms of autoimmune ILD represent a spectrum of CTD-ILD, rather than IIP, is important.

The terms *undifferentiated CTD*,[98,100] *lung-dominant CTD*,[2] and *autoimmune-featured ILD*[101] have all been used to describe patients with suggestive forms of CTD-ILD. Each of these categories has a unique set of proposed criteria and represents the ideas of investigative teams from distinct ILD referral centers. These sets of criteria are different enough that research studies being implemented in various centers using one set of criteria may not be applicable to cohorts from centers using other sets of criteria. In an effort to build consensus, a European Respiratory Society and ATS Task Force, "An International Working Group on Undifferentiated Forms of CTD-ILD," was formed to develop consensus regarding nomenclature and criteria for classification of suggestive forms of autoimmune ILD.[4] The term *interstitial pneumonia with autoimmune features* was proposed by this Task Force.[4] The term *connective tissue disease* was specifically avoided due to concerns that such labeling gives a false impression that these individuals have a defined CTD.

### Classification Criteria for IPAF

There are several a priori requirements for the classification of IPAF. Individuals must have evidence of interstitial pneumonia by HRCT or surgical lung biopsy and a thorough clinical evaluation during which known causes for interstitial pneumonia have been excluded, and they must not meet the criteria for a defined CTD. The classification criteria are then organized around 3 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 and histopathologic or pulmonary physiologic features. To be classified as having IPAF, the individual must meet all of the a priori requirements and have at least 1 feature from at least 2 of the domains (Table 2).[4]

Historically, the lack of consensus on criteria limited the ability to draw firm conclusions about this group of patients.[102] With IPAF, uniform terminology and classification criteria for related but potentially distinct entities (undifferentiated CTD-ILD, lung-dominant CTD, and autoimmune-featured ILD) has been systematically developed and ratified. A strength of the IPAF nomenclature and definition is that its classification criteria were derived based on international and multidisciplinary consensus, although a variety of important limitations were acknowledged.[4]

**TABLE 2. Classification Criteria for Interstitial Pneumonia With Autoimmune Features[a]**

1. Presence of an interstitial pneumonia (by HRCT or surgical lung biopsy)

2. Exclusion of alternative etiologies

3. Does not meet the criteria of a defined CTD

4. At least 1 feature from ≥2 of these domains:
    A. Clinical domain
    B. Serologic domain
    C. Morphologic domain

A. Clinical domain
    1. Distal digital fissuring (ie, "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)

B. Serologic domain
    1. ANA ≥1:320 titer, diffuse, speckled, homogeneous patterns or
        a. ANA nucleolar pattern (any titer) or
        b. ANA centromere pattern (any titer)
    2. RF ≥2 × ULN
    3. Anti-CCP
    4. Anti-dsDNA
    5. Anti-Ro (SS-A)
    6. Anti-La (SS-B)
    7. Antiribonucleoprotein
    8. Anti-Smith
    9. Antitopoisomerase (Scl-70)
    10. Anti-tRNA synthetase (eg, 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 centers
        f. Diffuse lymphoplasmacytic infiltration (with or without lymphoid follicles)
    3. Multicompartment involvement (in addition to IP):
        a. Unexplained pleural effusion or thickening
        b. Unexplained pericardial effusion or thickening
        c. Unexplained intrinsic airways disease[b] (by pulmonary function tests, imaging, or pathology)
        d. Unexplained pulmonary vasculopathy

[a]ANA = antinuclear antibody; CTD = connective tissue disease; HRCT = high-resolution computed tomography; IP = interstitial pneumonia; LIP = lymphoid interstitial pneumonia; NSIP = nonspecific interstitial pneumonia; OP = organizing pneumonia; RF = rheumatoid factor; SS-A = Sjögren syndrome—related antigen A; SS-B, Sjögren syndrome—related antigen B; ULN = upper limit of normal.
[b]Includes airflow obstruction, bronchiolitis, or bronchiectasis.

Since the initial publication of IPAF, several publications from diverse ILD programs describe characteristics and the natural history of IPAF from their respective centers around the world.[103-107] Each of the cohorts was retrospectively formed and affected by referral bias and/or how IPAF criteria were applied. It has become clear that as devised, the current definition of IPAF has been noted to allow for significant heterogeneity. For example, the Chicago cohort[107] had a UIP pattern-predominant cohort and looked a lot like IPF, and the Denver cohort[106] was NSIP predominant, with a large number of patients with specific autoimmune serologic positivity (eg, anti-ARS antibodies). Within the current framework, some ambiguity in the definition of IPAF may allow a subset of patients with a UIP pattern of disease (who may have IPF) to fulfill the criteria for IPAF. Another area of concern relates to discrepancies among centers and experts around those with a positive anti-ARS antibody and ILD. In the absence of cutaneous features of dermatomyositis or evidence of myositis there can be disagreement regarding what one considers to be incomplete forms of the AS vs IPAF.[108,109] As the heterogeneity is acknowledged, one advantage of IPAF is that uniform nomenclature has been adopted, prospective research studies from diverse programs are using similar classification criteria, and data are being gathered to allow for refinement of the criteria. Furthermore, there is now more interdisciplinary involvement in this arena.

It is recognized that the IPAF criteria must be tested and validated in future prospective studies, and modifications highlighting the importance of longitudinal surveillance of affected patients will be needed.[4,110] Adopting IPAF means leaving behind the previous terminologies and allows for future study of a more uniform cohort. Prospective studies are urgently needed to refine the first draft of the proposed classification criteria and to determine the natural history and clinical implications of a classification of IPAF.

## PH IN CTD

Connective tissue disease, particularly scleroderma, is associated with all diagnostic groups of PH. For example, the pulmonary artery vasculature can narrow as a consequence of CTD, producing increasing pulmonary vascular resistance and group 1 PAH. Indeed, CTD is the second most common cause of group 1 PAH.[111] Conversely, group 1 PAH develops in approximately 10% of patients with scleroderma.[112] In addition, left heart disease, such as heart failure with preserved ejection fraction, is not uncommon due to systemic hypertension, resulting in group 2 pulmonary venous hypertension. Last, associated ILD and hypoxemia can produce group 3 PH in connection with lung disease.

It is important to maintain a high index of suspicion for PH as a potential cause in patients with CTD with new-onset dyspnea. Indeed, approximately 25% of group 1 PAH is due to CTD. Screening with echocardiography can be helpful, particularly in patients with scleroderma and risk factors for PAH, such as positive anticentromere antibody and telangiectasias. Multiple screening strategies have proved successful in increasing diagnostic yield (sensitivity of 96%-100%).[113] Conversely, use of antinuclear antibody testing to screen for CTD in patients with PAH is recommended.[114] Confirmation of diagnosis requires right heart catheterization and subspecialty evaluation, preferably in an accredited pulmonary vascular center.[115]

Unfortunately, treatment tailored to controlling the underlying CTD does not seem to have much effect on the associated PAH. Exceptions may include SLE and active systemic vasculitis. In addition, there is little to suggest that treatments targeting ILD have any ameliorating effect on PAH.[116] Nonetheless, there is clear evidence in support of PAH-specific therapies to lessen symptom burden and reduce clinically meaningful events, such as hospitalization (risk reduction, 57%).[117] Hospitalization represents a major risk in patients with group 1 PAH,[118] and combination

PAH-specific therapy reduced all-cause hospitalization from 15% to 5% compared with single-drug treatment regimens.[117] Current treatment guidelines advocate oral PAH therapy with strong consideration for combination treatment in New York Heart Association functional classes II and III, and infusion prostanoid therapy for functional class IV patients.[119] Unfortunately, PAH-specific treatment may not be as effective in CTD-PAH based on a review of 11 randomized controlled trials comparing 827 patients with CTD-PAH with 1935 patients with idiopathic PAH, with less benefit in 6-minute walk distance and reduction in clinical worsening.[120] Of note, randomized prospective trials of PAH-specific therapy in group 3 PH patients with ILD have universally failed to prove benefit.[121-123]

Prognosis is generally worse for PAH-CTD compared with other group 1 subgroups (83% vs 93% at 1-year survival; $P<.001$).[124] It seems that patients with PAH-SLE may be the exception, with 5-year survival of 84%; anti-U1 ribonucleoprotein antibody may be an indicator of better outcome.[125] Conversely, patients with scleroderma-related PAH fare worse, particularly men older than 60 years with low systemic blood pressure (systolic <110 mm Hg) or 6-minute walk distance (<165 m) and severely abnormal hemodynamics (eg, right atrial pressure of 20 mm Hg).[126] Echocardiography may provide a simplified approach to prognostication.[127]

## CONCLUSION

The presenting features of CTD-ILD comprise a broad spectrum of clinical, imaging, and pathologic patterns. Diagnosis requires a comprehensive medical evaluation and multidisciplinary correlation of these features. In some patients, lung biopsy may be needed to clarify the nature of the lung disease. Distinguishing CTD-ILD from idiopathic forms of ILD, such as IPF, has treatment and prognostic implications but may be difficult in some patients as illustrated by the concept of IPAF. In general, immunosuppressive agents are used in the treatment of CTD-ILD, although the data supporting these treatment strategies are relatively sparse. The role of antifibrotic agents in CTD-ILDs remains to be defined. Complicating factors, such as gastroesophageal reflux disease and PH, need to be identified and managed accordingly.

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## REFERENCES

1. Fischer A, du Bois R. Interstitial lung disease in connective tissue disorders. *Lancet.* 2012;380(9842):689-698.
2. Fischer A, West SG, Swigris JJ, Brown KK, du Bois RM. Connective tissue disease-associated interstitial lung disease: a call for clarification. *Chest.* 2010;138(2):251-256.

3. Vij R, Strek ME. Diagnosis and treatment of connective tissue disease-associated interstitial lung disease. *Chest*. 2013;143(3): 814-824.

4. Fischer A, Antoniou KM, Brown KK, et al. An official European Respiratory Society/American Thoracic Society research statement: interstitial pneumonia with autoimmune features. *Eur Respir J*. 2015;46(4):976-987.

5. Fischer A, Swigris JJ, Groshong SD, et al. Clinically significant interstitial lung disease in limited scleroderma: histopathology, clinical features, and survival. *Chest*. 2008;134(3):601-605.

6. Flaherty KR, Colby TV, Travis WD, et al. Fibroblastic foci in usual interstitial pneumonia: idiopathic versus collagen vascular disease. *Am J Respir Crit Care Med*. 2003;167(10):1410-1415.

7. Marigliano B, Soriano A, Margiotta D, Vadacca M, Afeltra A. Lung involvement in connective tissue diseases: a comprehensive review and a focus on rheumatoid arthritis. *Autoimmun Rev*. 2013;12(11):1076-1084.

8. Zamora-Legoff JA, Krause ML, Crowson CS, Ryu JH, Matteson EL. Risk of serious infection in patients with rheumatoid arthritis-associated interstitial lung disease. *Clin Rheumatol*. 2016;35(10):2585-2589.

9. Park JH, Kim DS, Park IN, et al. Prognosis of fibrotic interstitial pneumonia: idiopathic versus collagen vascular disease-related subtypes. *Am J Respir Crit Care Med*. 2007;175(7):705-711.

10. Aparicio IJ, Lee JS. Connective tissue disease-associated interstitial lung diseases: unresolved issues. *Semin Respir Crit Care Med*. 2016;37(3):468-476.

11. Aduen JF, Zisman DA, Mobin SI, et al. Retrospective study of pulmonary function tests in patients presenting with isolated reduction in single-breath diffusion capacity: implications for the diagnosis of combined obstructive and restrictive lung disease. *Mayo Clin Proc*. 2007;82(1):48-54.

12. Marie I, Josse S, Decaux O, et al. Comparison of long-term outcome between anti-Jo1- and anti-PL7/PL12 positive patients with antisynthetase syndrome. *Autoimmun Rev*. 2012; 11(10):739-745.

13. Andersson H, Aalokken TM, Gunther A, et al. Pulmonary involvement in the antisynthetase syndrome: a comparative cross-sectional study. *J Rheumatol*. 2016;43(6):1107-1113.

14. Ohno Y, Koyama H, Yoshikawa T, Seki S. State-of-the-art imaging of the lung for connective tissue disease (CTD). *Curr Rheumatol Rep*. 2015;17(12):69.

15. Sverzellati N, Lynch DA, Hansell DM, Johkoh T, King TE Jr, Travis WD. American Thoracic Society-European Respiratory Society Classification of the Idiopathic Interstitial Pneumonias: advances in knowledge since 2002. *Radiographics*. 2015;35(7): 1849-1871.

16. Zamora-Legoff JA, Krause ML, Crowson CS, Ryu JH, Matteson EL. Progressive decline of lung function in rheumatoid arthritis-associated interstitial lung disease. *Arthritis Rheumatol*. 2017;69(3):542-549.

17. Moua T, Zamora Martinez AC, Baqir M, Vassallo R, Limper AH, Ryu JH. Predictors of diagnosis and survival in idiopathic pulmonary fibrosis and connective tissue disease-related usual interstitial pneumonia. *Respir Res*. 2014;15:154.

18. Lentz RJ, Taylor TM, Kropski JA, et al. Utility of flexible bronchoscopic cryobiopsy for diagnosis of diffuse parenchymal lung diseases. *J Bronchology Interv Pulmonol*. 2018;25(2): 88-96.

19. Raghu G, Anstrom KJ, King TE Jr, Lasky JA, Martinez FJ. Idiopathic Pulmonary Fibrosis Clinical Research Network. Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. *N Engl J Med*. 2012;366(21):1968-1977.

20. Doyle TJ, Dellaripa PF. Lung manifestations in the rheumatic diseases. *Chest*. 2017;152(6):1283-1295.

21. Travis WD, Costabel U, Hansell DM, et al. An official American Thoracic Society/European Respiratory Society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. *Am J Respir Crit Care Med*. 2013;188(6):733-748.

22. Nagai S, Handa T, Tabuena R, Kitaichi M, Izumi T. Nonspecific interstitial pneumonia: a real clinical entity? *Clin Chest Med*. 2004;25(4):705-715, vi.

23. Cipriani NA, Strek M, Noth I, et al. Pathologic quantification of connective tissue disease-associated versus idiopathic usual interstitial pneumonia. *Arch Pathol Lab Med*. 2012;136(10): 1253-1258.

24. Flaherty KR, Travis WD, Colby TV, et al. Histopathologic variability in usual and nonspecific interstitial pneumonias. *Am J Respir Crit Care Med*. 2001;164(9):1722-1727.

25. Henry TS, Little BP, Veeraraghavan S, Bhalla S, Elicker BM. The spectrum of interstitial lung disease in connective tissue disease. *J Thorac Imaging*. 2016;31(2):65-77.

26. Bryson T, Sundaram B, Khanna D, Kazerooni EA. Connective tissue disease-associated interstitial pneumonia and idiopathic interstitial pneumonia: similarity and difference. *Semin Ultrasound CT MR*. 2014;35(1):29-38.

27. Raghu G, Rochwerg B, Zhang Y, et al. An official ATS/ERS/JRS/ ALAT clinical practice guideline: treatment of idiopathic pulmonary fibrosis: an update of the 2011 clinical practice guideline. *Am J Respir Crit Care Med*. 2015;192(2):e3-e19.

28. Capobianco J, Grimberg A, Thompson BM, Antunes VB, Jasinowodolinski D, Meirelles GS. Thoracic manifestations of collagen vascular diseases. *Radiographics*. 2012;32(1):33-50.

29. Egashira R, Kondo T, Hirai T, et al. CT findings of thoracic manifestations of primary Sjogren syndrome: radiologic-pathologic correlation. *Radiographics*. 2013;33(7):1933-1949.

30. Debray MP, Borie R, Revel MP, et al. Interstitial lung disease in anti-synthetase syndrome: initial and follow-up CT findings. *Eur J Radiol*. 2015;84(3):516-523.

31. Tillie-Leblond I, Wislez M, Valeyre D, et al. Interstitial lung disease and anti-Jo-1 antibodies: difference between acute and gradual onset. *Thorax*. 2008;63(1):53-59.

32. Chung JH, Cox CW, Montner SM, et al. CT features of the usual interstitial pneumonia pattern: differentiating connective tissue disease-associated interstitial lung disease from idiopathic pulmonary fibrosis. *AJR Am J Roentgenol*. 2018;210(2): 307-313.

33. Wells AU, Margaritopoulos GA, Antoniou KM, Denton C. Interstitial lung disease in systemic sclerosis. *Semin Respir Crit Care Med*. 2014;35(2):213-221.

34. Goh NS, Desai SR, Veeraraghavan S, et al. Interstitial lung disease in systemic sclerosis: a simple staging system. *Am J Respir Crit Care Med*. 2008;177(11):1248-1254.

35. Gilbane AJ, Denton CP, Holmes AM. Scleroderma pathogenesis: a pivotal role for fibroblasts as effector cells. *Arthritis Res Ther*. 2013;15(3):215.

36. Mayes MD. Scleroderma epidemiology. *Rheum Dis Clin North Am*. 2003;29(2):239-254.

37. Steen VD, Medsger TA. Changes in causes of death in systemic sclerosis, 1972-2002. *Ann Rheum Dis*. 2007;66(7):940-944.

38. Tyndall AJ, Bannert B, Vonk M, et al. Causes and risk factors for death in systemic sclerosis: a study from the EULAR Scleroderma Trials and Research (EUSTAR) database. *Ann Rheum Dis*. 2010;69(10):1809-1815.

39. Morales-Cardenas A, Perez-Madrid C, Arias L, et al. Pulmonary involvement in systemic sclerosis. *Autoimmun Rev*. 2016;15(11):1094-1108.

40. Nikpour M, Baron M. Mortality in systemic sclerosis: lessons learned from population-based and observational cohort studies. *Curr Opin Rheumatol*. 2014;26(2):131-137.

41. Adler S, Huscher D, Siegert E, et al. Systemic sclerosis associated interstitial lung disease - individualized immunosuppressive therapy and course of lung function: results of the EUSTAR group. *Arthritis Res Ther*. 2018;20(1):17.

42. Steen VD, Conte C, Owens GR, Medsger TA Jr. Severe restrictive lung disease in systemic sclerosis. *Arthritis Rheum*. 1994;37(9):1283-1289.

43. Walker UA, Tyndall A, Czirjak L, et al. Clinical risk assessment of organ manifestations in systemic sclerosis: a report from the

EULAR Scleroderma Trials And Research group database. *Ann Rheum Dis.* 2007;66(6):754-763.

44. Steen VD, Lucas M, Fertig N, Medsger TA Jr. Pulmonary arterial hypertension and severe pulmonary fibrosis in systemic sclerosis patients with a nucleolar antibody. *J Rheumatol.* 2007;34(11):2230-2235.

45. Winstone TA, Assayag D, Wilcox PG, et al. Predictors of mortality and progression in scleroderma-associated interstitial lung disease: a systematic review. *Chest.* 2014;146(2): 422-436.

46. Morisset J, Vittinghoff E, Elicker BM, et al. Mortality risk prediction in scleroderma-related interstitial lung disease: the SADL model. *Chest.* 2017;152(5):999-1007.

47. Ryerson CJ, Vittinghoff E, Ley B, et al. Predicting survival across chronic interstitial lung disease: the ILD-GAP model. *Chest.* 2014;145(4):723-728.

48. Tashkin DP, Elashoff R, Clements PJ, et al. Cyclophosphamide versus placebo in scleroderma lung disease. *N Engl J Med.* 2006;354(25):2655-2666.

49. Tashkin DP, Roth MD, Clements PJ, et al. Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease (SLS II): a randomised controlled, double-blind, parallel group trial. *Lancet Respir Med.* 2016; 4(9):708-719.

50. Fischer A, Brown KK, Du Bois RM, et al. Mycophenolate mofetil improves lung function in connective tissue disease-associated interstitial lung disease. *J Rheumatol.* 2013;40(5): 640-646.

51. Steen VD, Medsger TA Jr. Case-control study of corticosteroids and other drugs that either precipitate or protect from the development of scleroderma renal crisis. *Arthritis Rheum.* 1998;41(9):1613-1619.

52. Bongartz T, Nannini C, Medina-Velasquez YF, et al. Incidence and mortality of interstitial lung disease in rheumatoid arthritis: a population-based study. *Arthritis Rheum.* 2010;62(6):1583-1591.

53. Olson AL, Swigris JJ, Sprunger DB, et al. Rheumatoid arthritis-interstitial lung disease-associated mortality. *Am J Respir Crit Care Med.* 2011;183(3):372-378.

54. Zhang Y, Li H, Wu N, Dong X, Zheng Y. Retrospective study of the clinical characteristics and risk factors of rheumatoid arthritis-associated interstitial lung disease. *Clin Rheumatol.* 2017;36(4):817-823.

55. Atkins SR, Turesson C, Myers JL, et al. Morphologic and quantitative assessment of CD20+ B cell infiltrates in rheumatoid arthritis-associated nonspecific interstitial pneumonia and usual interstitial pneumonia. *Arthritis Rheum.* 2006;54(2): 635-641.

56. Demoruelle MK, Deane KD, Holers VM. When and where does inflammation begin in rheumatoid arthritis? *Curr Opin Rheumatol.* 2014;26(1):64-71.

57. Hyldgaard C, Hilberg O, Pedersen AB, et al. A population-based cohort study of rheumatoid arthritis-associated interstitial lung disease: comorbidity and mortality. *Ann Rheum Dis.* 2017;76(10):1700-1706.

58. Kim D, Cho SK, Choi CB, et al. Impact of interstitial lung disease on mortality of patients with rheumatoid arthritis. *Rheumatol Int.* 2017;37(10):1735-1745.

59. Jani M, Hirani N, Matteson EL, Dixon WG. The safety of biologic therapies in RA-associated interstitial lung disease. *Nat Rev Rheumatol.* 2014;10(5):284-294.

60. ClinicalTrials.gov. Phase II study of pirfenidone in patients with RAILD (TRAIL1). https://clinicaltrials.gov/ct2/show/ NCT02808871. Accessed March 12, 2018.

61. Inoue T, Kanayama Y, Ohe A, et al. Immunopathologic studies of pneumonitis in systemic lupus erythematosus. *Ann Intern Med.* 1979;91(1):30-34.

62. Martinez-Martinez MU, Abud-Mendoza C. Predictors of mortality in diffuse alveolar haemorrhage associated with systemic lupus erythematosus. *Lupus.* 2011;20(6):568-574.

63. Flament T, Bigot A, Chaigne B, Henique H, Diot E, Marchand-Adam S. Pulmonary manifestations of Sjogren's syndrome. *Eur Respir Rev.* 2016;25(140):110-123.

64. Henderson LA, Loring SH, Gill RR, et al. Shrinking lung syndrome as a manifestation of pleuritis: a new model based on pulmonary physiological studies. *J Rheumatol.* 2013;40(3):273-281.

65. Kanakis MA, Kapsimali V, Vaiopoulos AG, Vaiopoulos GA, Samarkos M. The lung in the spectrum of antiphospholipid syndrome. *Clin Exp Rheumatol.* 2013;31(3):452-457.

66. Andrade C, Mendonca T, Farinha F, et al. Alveolar hemorrhage in systemic lupus erythematosus: a cohort review. *Lupus.* 2016;25(1):75-80.

67. Ryu JH, Myers JL, Swensen SJ. Bronchiolar disorders. *Am J Respir Crit Care Med.* 2003;168(11):1277-1292.

68. Yachoui R, Leon C, Sitwala K, Kreidy M. Pulmonary MALT lymphoma in patients with Sjogren's syndrome. *Clin Med Res.* 2017;15(1-2):6-12.

69. Baqir M, Kluka EM, Aubry MC, et al. Amyloid-associated cystic lung disease in primary Sjogren's syndrome. *Respir Med.* 2013; 107(4):616-621.

70. Nocturne G, Virone A, Ng WF, et al. Rheumatoid factor and disease activity are independent predictors of lymphoma in primary Sjogren's syndrome. *Arthritis Rheumatol.* 2016;68(4):977-985.

71. Connors GR, Christopher-Stine L, Oddis CV, Danoff SK. Interstitial lung disease associated with the idiopathic inflammatory myopathies: what progress has been made in the past 35 years? *Chest.* 2010;138(6):1464-1474.

72. Kang EH, Lee EB, Shin KC, et al. Interstitial lung disease in patients with polymyositis, dermatomyositis and amyopathic dermatomyositis. *Rheumatology (Oxford).* 2005;44(10):1282-1286.

73. Grau JM, Miro O, Pedrol E, et al. Interstitial lung disease related to dermatomyositis: comparative study with patients without lung involvement. *J Rheumatol.* 1996;23(11):1921-1926.

74. Stone KB, Oddis CV, Fertig N, et al. Anti-Jo-1 antibody levels correlate with disease activity in idiopathic inflammatory myopathy. *Arthritis Rheum.* 2007;56(9):3125-3131.

75. Satoh M, Tanaka S, Ceribelli A, Calise SJ, Chan EK. A comprehensive overview on myositis-specific antibodies: new and old biomarkers in idiopathic inflammatory myopathy. *Clin Rev Allergy Immunol.* 2017;52(1):1-19.

76. Solomon J, Swigris JJ, Brown KK. Myositis-related interstitial lung disease and antisynthetase syndrome. *J Bras Pneumol.* 2011;37(1):100-109.

77. Hallowell RW, Danoff SK. Interstitial lung disease associated with the idiopathic inflammatory myopathies and the antisynthetase syndrome: recent advances. *Curr Opin Rheumatol.* 2014;26(6):684-689.

78. Hervier B, Wallaert B, Hachulla E, et al. Clinical manifestations of anti-synthetase syndrome positive for anti-alanyl-tRNA synthetase (anti-PL12) antibodies: a retrospective study of 17 cases. *Rheumatology (Oxford).* 2010;49(5):972-976.

79. Hamaguchi Y, Fujimoto M, Matsushita T, et al. Common and distinct clinical features in adult patients with anti-aminoacyl-tRNA synthetase antibodies: heterogeneity within the syndrome. *PLoS One.* 2013;8(4):e60442.

80. Johnson C, Connors GR, Oaks J, et al. Clinical and pathologic differences in interstitial lung disease based on antisynthetase antibody type. *Respir Med.* 2014;108(10):1542-1548.

81. Kalluri M, Sahn SA, Oddis CV, et al. Clinical profile of anti-PL-12 autoantibody: cohort study and review of the literature. *Chest.* 2009;135(6):1550-1556.

82. Hervier B, Uzunhan Y, Hachulla E, et al. Antisynthetase syndrome positive for anti-threonyl-tRNA synthetase (anti-PL7) antibodies. *Eur Respir J.* 2011;37(3):714-717.

83. Schneider F, Yousem SA, Bi D, Gibson KF, Oddis CV, Aggarwal R. Pulmonary pathologic manifestations of anti-glycyl-tRNA synthetase (anti-EJ)-related inflammatory myopathy. *J Clin Pathol.* 2014;67(8):678-683.

84. Cavagna L, Caporali R, Abdi-Ali L, Dore R, Meloni F, Montecucco C. Cyclosporine in anti-Jo1-positive patients

with corticosteroid-refractory interstitial lung disease. *J Rheumatol*. 2013;40(4):484-492.

85. Labirua-Iturburu A, Selva-O'Callaghan A, Martinez-Gomez X, Trallero-Araguas E, Labrador-Horrillo M, Vilardell-Tarres M. Calcineurin inhibitors in a cohort of patients with antisynthetase-associated interstitial lung disease. *Clin Exp Rheumatol*. 2013;31(3):436-439.

86. Doyle TJ, Dhillon N, Madan R, et al. Rituximab in the treatment of interstitial lung disease associated with antisynthetase syndrome: a multicenter retrospective case review. *J Rheumatol*. 2018;45(6):841-850.

87. Lally L, Spiera RF. Pulmonary vasculitis. *Rheum Dis Clin North Am*. 2015;41(2):315-331.

88. Comarmond C, Crestani B, Tazi A, et al. Pulmonary fibrosis in antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis: a series of 49 patients and review of the literature. *Medicine (Baltimore)*. 2014;93(24):340-349.

89. Hervier B, Pagnoux C, Agard C, et al. Pulmonary fibrosis associated with ANCA-positive vasculitides: retrospective study of 12 cases and review of the literature. *Ann Rheum Dis*. 2009; 68(3):404-407.

90. Ando Y, Okada F, Matsumoto S, Mori H. Thoracic manifestation of myeloperoxidase-antineutrophil cytoplasmic antibody (MPO-ANCA)-related disease: CT findings in 51 patients. *J Comput Assist Tomogr*. 2004;28(5):710-716.

91. Homma S, Matsushita H, Nakata K. Pulmonary fibrosis in myeloperoxidase antineutrophil cytoplasmic antibody-associated vasculitides. *Respirology*. 2004;9(2):190-196.

92. Foulon G, Delaval P, Valeyre D, et al. ANCA-associated lung fibrosis: analysis of 17 patients. *Respir Med*. 2008;102(10): 1392-1398.

93. Hosoda C, Baba T, Hagiwara E, et al. Clinical features of usual interstitial pneumonia with anti-neutrophil cytoplasmic antibody in comparison with idiopathic pulmonary fibrosis. *Respirology*. 2016;21(5):920-926.

94. Abril A, Kwon M, Rojas C, Khoor A, Mira-Avendano I. SAT0519: interstitial lung disease in ANCA associated vasculitis patients: comparison with idiopathic fibrosis and interstitial pneumonia with autoimmune features. *Ann Rheum Dis*. 2018; 77(suppl 2):1115.

95. Tzelepis GE, Kokosi M, Tzioufas A, et al. Prevalence and outcome of pulmonary fibrosis in microscopic polyangiitis. *Eur Respir J*. 2010;36(1):116-121.

96. Fischer A, Lee JS, Cottin V. Interstitial lung disease evaluation: detecting connective tissue disease. *Respiration*. 2015;90(3): 177-184.

97. Fujita J, Ohtsuki Y, Yoshinouchi T, et al. Idiopathic non-specific interstitial pneumonia: as an ''autoimmune interstitial pneumonia''. *Respir Med*. 2005;99(2):234-240.

98. Kinder BW, Collard HR, Koth L, et al. Idiopathic nonspecific interstitial pneumonia: lung manifestation of undifferentiated connective tissue disease? *Am J Respir Crit Care Med*. 2007; 176(7):691-697.

99. Solomon JJ, Chartrand S, Fischer A. Current approach to connective tissue disease-associated interstitial lung disease. *Curr Opin Pulm Med*. 2014;20(5):449-456.

100. Corte TJ, Copley SJ, Desai SR, et al. Significance of connective tissue disease features in idiopathic interstitial pneumonia. *Eur Respir J*. 2012;39(3):661-668.

101. Vij R, Noth I, Strek ME. Autoimmune-featured interstitial lung disease: a distinct entity. *Chest*. 2011;140(5):1292-1299.

102. Assayag D, Kim EJ, Elicker BM, et al. Survival in interstitial pneumonia with features of autoimmune disease: a comparison of proposed criteria. *Respir Med*. 2015;109(10):1326-1331.

103. Dai J, Wang L, Yan X, et al. Clinical features, risk factors, and outcomes of patients with interstitial pneumonia with autoimmune features: a population-based study. *Clin Rheumatol*. 2018;37(8):2125-2132.

104. Yoshimura K, Kono M, Enomoto Y, et al. Distinctive characteristics and prognostic significance of interstitial pneumonia with

autoimmune features in patients with chronic fibrosing interstitial pneumonia. *Respir Med*. 2018;137:167-175.

105. Ahmad K, Barba T, Gamondes D, et al. Interstitial pneumonia with autoimmune features: clinical, radiologic, and histological characteristics and outcome in a series of 57 patients. *Respir Med*. 2017;123:56-62.

106. Chartrand S, Swigris JJ, Stanchev L, Lee JS, Brown KK, Fischer A. Clinical features and natural history of interstitial pneumonia with autoimmune features: a single center experience. *Respir Med*. 2016;119:150-154.

107. Oldham JM, Adegunsoye A, Valenzi E, et al. Characterisation of patients with interstitial pneumonia with autoimmune features. *Eur Respir J*. 2016;47(6):1767-1775.

108. Jee AS, Bleasel JF, Adelstein S, Keir GJ, Corte TJ. A call for uniformity in implementing the IPAF (interstitial pneumonia with autoimmune features) criteria. *Eur Respir J*. 2016;48(6):1811-1813.

109. Jee AS, Adelstein S, Bleasel J, et al. Role of autoantibodies in the diagnosis of connective-tissue disease ILD (CTD-ILD) and interstitial pneumonia with autoimmune features (IPAF). *J Clin Med*. 2017;6(5):E51.

110. Chartrand S, Lee JS, Fischer A. Longitudinal assessment of interstitial pneumonia with autoimmune features is encouraged. *Respir Med*. 2017;132:267.

111. Badesch DB, Raskob GE, Elliott CG, et al. Pulmonary arterial hypertension: baseline characteristics from the REVEAL Registry. *Chest*. 2010;137(2):376-387.

112. Condliffe R, Howard LS. Connective tissue disease-associated pulmonary arterial hypertension. *F1000Prime Rep*. 2015;7:06.

113. Hao Y, Thakkar V, Stevens W, et al. A comparison of the predictive accuracy of three screening models for pulmonary arterial hypertension in systemic sclerosis. *Arthritis Res Ther*. 2015;17:7.

114. Pagan RJ, Lee AS, Austin CO, Burger CD. Screening for connective tissue disease in pulmonary arterial hypertension. *South Med J*. 2014;107(10):666-669.

115. Pulmonary Hypertension Association. PH care centers: find a PH care center. https://phassociation.org/phcarecenters/accredited-centers. Accessed March 12, 2018.

116. Tselios K, Gladman DD, Urowitz MB. Systemic lupus erythematosus and pulmonary arterial hypertension: links, risks, and management strategies. *Open Access Rheumatol*. 2017;9:1-9.

117. Coghlan JG, Galie N, Barbera JA, et al. Initial combination therapy with ambrisentan and tadalafil in connective tissue disease-associated pulmonary arterial hypertension (CTD-PAH): subgroup analysis from the AMBITION trial. *Ann Rheum Dis*. 2017;76(7):1219-1227.

118. Burger CD, Long PK, Shah MR, et al. Characterization of first-time hospitalizations in patients with newly diagnosed pulmonary arterial hypertension in the REVEAL registry. *Chest*. 2014; 146(5):1263-1273.

119. Galie N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J*. 2016;37(1):67-119.

120. Rhee RL, Gabler NB, Sangani S, Praestgaard A, Merkel PA, Kawut SM. Comparison of treatment response in idiopathic and connective tissue disease-associated pulmonary arterial hypertension. *Am J Respir Crit Care Med*. 2015;192(9):1111-1117.

121. Zisman DA, Schwarz M, et al. Idiopathic Pulmonary Fibrosis Clinical Research Network. A controlled trial of sildenafil in advanced idiopathic pulmonary fibrosis. *N Engl J Med*. 2010; 363(7):620-628.

122. King TE Jr, Behr J, Brown KK, et al. BUILD-1: a randomized placebo-controlled trial of bosentan in idiopathic

pulmonary fibrosis. *Am J Respir Crit Care Med.* 2008; 177(1):75-81.

123. Raghu G, Million-Rousseau R, Morganti A, Perchenet L, Behr J; MUSIC Study Group. Macitentan for the treatment of idiopathic pulmonary fibrosis: the randomised controlled MUSIC trial. *Eur Respir J.* 2013;42(6):1622-1632.

124. Chung L, Liu J, Parsons L, et al. Characterization of connective tissue disease-associated pulmonary arterial hypertension from REVEAL: identifying systemic sclerosis as a unique phenotype. *Chest.* 2010;138(6):1383-1394.

125. Hachulla E, Jais X, Cinquetti G, et al. Pulmonary arterial hypertension associated with systemic lupus erythematosus: results from the French Pulmonary Hypertension Registry. *Chest.* 2018;153(1):143-151.

126. Chung L, Farber HW, Benza R, et al. Unique predictors of mortality in patients with pulmonary arterial hypertension associated with systemic sclerosis in the REVEAL registry. *Chest.* 2014;146(6):1494-1504.

127. Austin C, Burger C, Kane G, et al. High-risk echocardiographic features predict mortality in pulmonary arterial hypertension. *Am Heart J.* 2017;189:167-176.