CHEST Recent Advances in Chest Medicine

Diagnosis and Treatment of Connective Tissue Disease-Associated Interstitial Lung Disease

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Interstitial lung disease (ILD) is one of the most serious pulmonary complications associated with connective tissue diseases (CTDs), resulting in significant morbidity and mortality. Although the various CTDs associated with ILD often are considered together because of their shared autoimmune nature, there are substantial differences in the clinical presentations and management of ILD in each specific CTD. This heterogeneity and the cross-disciplinary nature of care have complicated the conduct of prospective multicenter treatment trials and hindered our understanding of the development of ILD in patients with CTD. In this update, we present new information regarding the diagnosis and treatment of patients with ILD secondary to systemic sclerosis, rheumatoid arthritis, dermatomyositis and polymyositis, and Sjögren syndrome. We review information on risk factors for the development of ILD in the setting of CTD. Diagnostic criteria for CTD are presented as well as elements of the clinical evaluation that increase suspicion for CTD-ILD. We review the use of medications in the treatment of CTD-ILD. Although a large, randomized study has examined the impact of immunosuppressive therapy for ILD secondary to systemic sclerosis, additional studies are needed to determine optimal treatment strategies for each distinct form of CTD-ILD. Finally, we review new information regarding the subgroup of patients with ILD who meet some, but not all, diagnostic criteria for a CTD. A careful and systematic approach to diagnosis in patients with ILD may reveal an unrecognized CTD or evidence of autoimmunity in those previously believed to have idiopathic ILD. ***CHEST 2013; 143(3):814–824***

Abbreviations: AIF-ILD = autoimmune-featured interstitial lung disease; ANA = antinuclear antibody; CTD = connective tissue disease; dc = diffuse cutaneous; HRCT = high-resolution CT; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; Jo-1 = histidyl transfer RNA synthetase; lc = limited cutaneous; LIP = lymphocytic interstitial pneumonia; NSIP = nonspecific interstitial pneumonia; OP = organizing pneumonia; RA = rheumatoid arthritis; SSc = systemic sclerosis; tRNA = transfer RNA; UIP = usual interstitial pneumonia

Connective tissue diseases (CTDs) cause a myriad of pulmonary complications, including bronchiolitis and bronchiectasis, pleuritis, and pulmonary hypertension. Interstitial lung disease (ILD) is a common and serious form of pulmonary involvement characterized by various patterns of inflammation and fibrosis on high-resolution CT (HRCT) scan and in lung biopsy specimen. Advances in the description of radiologic patterns and pathologic findings used in the idiopathic interstitial pneumonias are now being applied to patients with CTD, although some have argued for an alternate classification scheme based on the degree of cellularity and fibrosis.[1,2] The British Thoracic Society has published guidelines that address both idiopathic and secondary ILD, including CTD-ILD.[3] They suggest that a multidisciplinary approach is the "gold standard" for the diagnosis and management of patients with ILD, and in CTD-ILD, the approach should also include rheumatologists.

Although it is common for ILD to be diagnosed concurrent with or after CTD, some patients will present with ILD years prior to receiving a diagnosis of CTD.

Manuscript received March 20, 2012; revision accepted September 26, 2012.
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DOI: 10.1378/chest.12-0741

Additionally, some patients may have presentations dominated by or limited to pulmonary manifestations of autoimmune disease. Thus, it is crucial for pulmonologists to carefully evaluate for evidence of underlying CTD in all patients who present with ILD. Our clinical approach is shown in Table 1.

Little evidence guides which patients with CTD-ILD should receive immunosuppressive therapy targeting their underlying ILD. Some patients may not require therapy, and we do not routinely initiate therapy for patients with asymptomatic or mild ILD and may recommend serial monitoring of symptoms and pulmonary function. Although expert opinion and case series suggest a benefit to therapy in some patients, the level of evidence is not robust. When deciding whether a patient with CTD-ILD may benefit from immunosuppressive therapy, we evaluate the following factors: rate of disease progression, severity of lung disease, underlying CTD, likelihood of response based on radiographic and histopathologic patterns, patient age, and ability to comply with therapy and monitoring. Only with coordinated national registries and multicenter trials will a clear understanding of the pathophysiology and treatment of CTD-ILD be gained.

Here, we present recent advances in the diagnosis and treatment of ILD in the most common rheumatologic diseases complicated by ILD: systemic sclerosis (SSc), rheumatoid arthritis (RA), polymyositis and dermatomyositis, and Sjögren syndrome. We review data regarding the subgroup of patients with ILD who meet some, but not all, diagnostic criteria for a CTD.

Table 1—*Clinical Approach to Evaluating Patients With ILD for CTDs*

Clinical Evaluation	Approach
Key elements of history	Presence of: Rashes Raynaud phenomenon Constitutional symptoms Arthralgias Sicca symptoms Dysphagia Proximal muscle weakness
Physical examination	Evaluate for: Rashes Mechanic's hands Gottron papules Sclerodactyly Digital ulcers Synovitis Oral ulcers Proximal muscle weakness
Laboratory	Antinuclear antibody Anti-double-stranded DNA Anti-ribonucleoprotein antibody Anti-Smith antibody Anti-Scl-70 Anti-Ro (SSA) Anti-La (SSB) Rheumatoid factor Anticyclic citrullinated peptide Anti-Jo-1 antibody Creatine kinase Aldolase Erythrocyte sedimentation rate C-reactive protein
Pulmonary function testing, 6-min walk test	Perform at diagnosis and for serial monitoring: Total lung capacity FVC Dlco 6-min walk distance and oxygen saturation
Radiographic	All patients should undergo HRCT scan NSIP pattern seen most often in CTD-ILD
Pathologic	Utility of surgical lung biopsy specimen in established CTD-ILD unclear Biopsy samples from upper, middle, and lower lung fields OP and cellular NSIP more likely to respond to immunosuppressive treatment

Anti-Jo-1 = antihistidyl transfer RNA synthetase; anti-Scl-70 = autoantibodies targeted against type I topoisomerase; CTD = connective tissue disease; Dlco = diffusing capacity of lung for carbon monoxide; HRCT = high-resolution CT; ILD = interstitial lung disease, NSIP = nonspecific interstitial pneumonia; OP = organizing pneumonia; SSA = Sjögren syndrome antigen A; SSB = Sjögren syndrome antigen B.

Systemic Sclerosis

SSc is a heterogeneous systemic disorder characterized by excessive collagen deposition.[4] The diagnostic criteria for SSc[5] (Appendix 1) are currently being updated by professional rheumatology societies.[6]

Limited cutaneous (lc) SSc is skin thickening that is confined to distal extremities (below the elbows and knees) and above the clavicles. Diffuse cutaneous (dc) SSc is skin thickening that involves proximal extremities and the torso.[7] Traditionally, the development of pulmonary hypertension is considered more likely in patients with lcSSc, and the development of ILD is considered more likely in those with dcSSc.[8] In the Scleroderma Lung Study, there were no significant differences in the frequency of alveolitis on HRCT scan between lcSSc and dcSSc, suggesting that all patients with SSc are at risk for ILD.[7]

The majority of patients with SSc have esophageal involvement, with gastroesophageal reflux being a risk factor for the development and progression of ILD.[9] Esophageal dilation is a common radiographic abnormality found in 62% to 80% of patients with SSc, even in the absence of esophageal symptoms.[10] Savarino et al[11] compared 18 patients with SSc and ILD and 22 patients with SSc but without ILD. Patients with SSc-ILD had a higher frequency of both acidic and nonacidic

gastroesophageal reflux episodes and a higher number of reflux episodes that reached the proximal esophagus. Extent of pulmonary fibrosis on HRCT scan correlated with episodes of gastroesophageal reflux, supporting an association between reflux and fibrosis. Preliminary evidence has demonstrated that some patients with SSc-ILD may benefit from antireflux medications, including high-dose proton pump inhibitors and prokinetic medications[12]; however, validation studies are needed.

The median survival for patients with SSc-ILD is 5 to 8 years.[13] The most common radiographic findings for these patients are ground glass opacities and fibrosis.[14] The extent of disease on HRCT scan, combined with FVC, can be used to stage SSc-ILD and provide prognostic information.[15] Retrospective analyses suggest that patients with more severe reticular opacities on HRCT scan might be the most likely to benefit from cyclophosphamide therapy.[16]

The Scleroderma Lung Study was a randomized, double-blind, placebo-controlled trial of oral cyclophosphamide therapy ≤ 2 mg/kg/d for 12 months in 158 patients with SSc-ILD.[17] Treatment was associated with a slowing of the decline in pulmonary function (mean absolute difference in adjusted 12-month FVC, 2.53%; $P < .03$) and improvement in dyspnea, functional abilities, health-related quality of life, and skin thickening. Cyclophosphamide therapy was associated with a higher incidence of hematuria, leukopenia, and neutropenia. Comparing patients with lcSSc and dcSSc, there were no differences in baseline disease severity, severity-adjusted rate of progression, or response to cyclophosphamide. With the exception of improvement in dyspnea, the benefits of cyclophosphamide were no longer present at 24 months.[18]

Although trials have examined cyclophosphamide in patients with SSc-ILD, the benefit and utility of this therapy remain controversial. A Cochrane meta-analysis did not demonstrate clinically significant improvement in pulmonary function.[19] The European League Against Rheumatism recommends that cyclophosphamide be considered in SSc-ILD, with dose and duration of treatment adjusted according to the patient's course.[20]

Several case series have reported improvement or stabilization of lung disease in $>75\%$ of patients with SSc-ILD treated with mycophenolate mofetil.[21-23] These results led to an ongoing randomized, double-blind trial comparing mycophenolate to oral cyclophosphamide for patients with SSc-ILD.[24]

The role of hematopoietic stem cell transplantation has been studied in an open-label randomized trial of stem cell transplantation (n = 10) vs IV cyclophosphamide (n = 9) for patients with SSc and end-organ disease.[25] The majority of patients in both treatment groups had evidence of pulmonary involvement. Patients who received a stem cell transplantation had significant improvements in FVC within 12 months (rate of change, +15% vs −9% in control patients; $P = .006$), and 80% noted sustained improvement for at least 2 years. These results suggest that stem cell transplantation may be more beneficial than IV cyclophosphamide, but further studies in patients with SSc-ILD are needed.

Several case reports described the use of rituximab for patients with cyclophosphamide-refractory SSc-ILD.[26-28] Improvements in symptoms, in pulmonary function tests, and on HRCT scan were noted in all cases. In one patient, recurrent respiratory symptoms developed 1 year later, and rituximab therapy again produced a clinical response.[26]

Thus, a wide variety of immunosuppressive therapies have been used to treat SSc-ILD, with varying degrees of success. Medications used in patients with SSc-ILD and other CTDs are summarized in Table 2.

Pulmonary Hypertension in SSc-ILD

The development of pulmonary hypertension is a well-described complication of SSc. In SSc-ILD, pulmonary hypertension likely results from destruction of the pulmonary vasculature from progressive fibrosis and hypoxia-induced vascular remodeling. The 1-, 2-, and 3-year survival for these patients is 71%, 39%, and 21%, respectively.[4] Although therapeutic interventions for pulmonary hypertension in SSc have been tested, many trials excluded patients with ILD. Thus, until recently, little was known about the clinical characteristics and treatment options for patients with SSc-ILD and pulmonary hypertension.

Launay and colleagues[37] evaluated patients with SSc and pulmonary hypertension with (n=50) and without (n=47) ILD. Although baseline demographic differences existed, diffusing capacity of lung for carbon monoxide and mean pulmonary artery pressures were the same for both groups. The management of these patients was not standardized. Patients with SSc-ILD and mild pulmonary hypertension received bosentan (67%), sildenafil (7%), and no therapy (27%). Those with moderate to severe pulmonary hypertension received bosentan (69%), inhaled iloprost (9%), continuous IV epoprostenol (3%), and sildenafil (3%). The authors noted a trend toward worse survival for patients with SSc with ILD compared with those without ILD ($P = .08$).

Le Pavec et al[4] reported findings from a retrospective study of 70 well-characterized patients with SSc-ILD and pulmonary hypertension documented by right heart catheterization. All patients received oral anticoagulation, diuretics, and oxygen supplementation. Fifty-nine percent of the cohort had severe pulmonary hypertension, with mean pulmonary artery

Table 2—*Proposed Therapies for CTD-ILD*[a]

Medication	Dose[b]	Disease	Monitoring and Precautions	Refs
Prednisone	0.5-1 mg/kg/d up to 60 mg/d	SSc, RA, DM, PM, SS	Monitor blood glucose level, bone mineral density, weight, and mental status. Taper after 8-12 wk. Doses > 20 mg/d are not advised in SSc. If long-term use required, consider additional agents.	3, 29-32
Methylprednisolone	1 g/d IV for 3 d	Acute worsening CTD-ILD	Monitor blood glucose level, bone mineral density, weight, and mental status. Rule out infection before administration.	3
Azathioprine	1-2 mg/kg/d	SSc, RA, DM, PM, SS	Monitor CBC and hepatic function every 2 wk for first month, then monthly. Measure TPMT; if low, use smaller dose adjustments.	3, 29, 31-33
Cyclophosphamide	1-2 mg/kg/d po or 500-1,000 mg IV pulse every 4 wk	SSc, RA	Monitor CBC, renal function, and urinalysis at baseline, then twice monthly. Salvage therapy because of serious toxicities.	3, 17, 32
Mycophenolate mofetil	1.0-1.5 g bid	SSc, RA, DM, PM	Monitor CBC weekly for first month, twice monthly second and third month, then monthly	20, 32, 34, 35
Tacrolimus	1 mg bid	DM, PM	Monitor CBC, serum electrolytes/renal function, hepatic function, glucose level, and BP weekly for first month, twice weekly for second month, then monthly. Follow serum levels. Dose depends on trough level. Aim for trough level of 5-10 ng/mL. Renal toxicity occurs over time.	3, 36

DM = dermatomyositis; PM = polymyositis; RA = rheumatoid arthritis; refs = references SS = Sjögren syndrome; SSc = systemic sclerosis; TPMT = thiopurine methyltransferase. See Table 1 legend for expansion of other abbreviations.

[a]These therapies do not meet grade 1A evidence for use in CTD-ILD.

[b]All medications are given by mouth unless otherwise indicated.

pressures of ≥ 40 mm Hg. As first-line therapy, 46 subjects received an endothelin receptor antagonist and 20 a phosphodiesterase-5 inhibitor. Twenty-four percent improved by one or more World Health Organization functional classes, 64% were stable, and 12% deteriorated by one or more functional classes. The investigators were unable to identify variables predictive of response to therapeutic intervention. On multivariate analysis, worsening oxygenation ($P = .04$) and deteriorating renal function ($P = .03$) were risk factors for mortality.

These studies demonstrated that pulmonary hypertension develops in patients with SSc-ILD and that treatment results in clinical improvement or stabilization in some cases. Nonetheless, these results also highlight the need for therapeutic trials to determine which medications will be most beneficial for this unique subset of patients.

In summary, recent studies of SSc-ILD have demonstrated that (1) ILD develops in patients with both lcSSc and dcSSc, (2) esophageal dysfunction and gastroesophageal reflux may contribute to ILD in patients with SSc, and (3) pulmonary hypertension in SSc-ILD portends a poorer prognosis. Trials are needed to determine optimal treatment strategies.

Unlike other CTD-ILD, clinical trials have examined the impact of immunosuppressive treatment of SSc-ILD. In our opinion, the Scleroderma Lung Study should serve as a model for designing trials of therapy in other CTD-ILD. Although oral cyclophosphamide was associated with a slower decline in lung function, the magnitude of benefit was small and did not persist beyond the treatment period, leading to studies of other immunosuppressive agents in SSc-ILD.

Rheumatoid Arthritis

RA is a systemic, chronic inflammatory disease that commonly affects small joints. The diagnostic criteria for RA (Appendix 1) have been revised to enhance detection of earlier stages of disease.[38] The development of ILD is associated with shortened survival,[39] more severe underlying joint disease,[40] and tobacco use.[41] Current theories posit that tobacco use and RA act synergistically to cause inflammation and damage to epithelial and endothelial cells, which promotes the development of pulmonary fibrosis.[41] Although it is common for ILD to be diagnosed concurrent with or after RA, a population-based study suggests that

3.5% of patients with RA were given a diagnosis of ILD prior to the diagnosis of RA.[40]

Multiple radiographic and histopathologic patterns have been described for patients with RA-ILD, which have prognostic implications. Patients with RA with a usual interstitial pneumonia (UIP) pattern on HRCT scan have worsened survival compared with those with nonspecific interstitial pneumonia (NSIP) ($P = .02$).[42] Although patients with RA-ILD with an NSIP pattern may benefit from immunosuppressive therapy, there is insufficient evidence to determine the impact and utility of treating patients with a UIP pattern.[43] A study of patients with histopathologic UIP patterns demonstrated that patients with RA-ILD have improved survival compared with patients with idiopathic pulmonary fibrosis (IPF).[44]

For patients with newly diagnosed RA-ILD, first-line treatment is high-dose prednisone.[45] Evidence for the selection of additional immunosuppressive therapies is weak, consisting of case reports, case series, and registries. Older reports described the use of azathioprine or cyclosporine as treatment of RA-ILD.[45] Several newer agents have been cited in case reports and case series, including mycophenolate mofetil[46]; tumor necrosis factor-α inhibitors, specifically infliximab[29]; and the IL-6 receptor inhibitor tocilizumab.[34] Although these agents were reported to stabilize or improve respiratory status, recommendations for their routine use cannot be made without stronger evidence. The safety and efficacy of rituximab, a B-cell-depleting anti-CD20 antibody, is currently under investigation for patients with RA-ILD.[47]

Drug-induced pneumonitis is an important consideration in the differential diagnosis of patients with suspected RA-ILD. Clinicians should perform a thorough review of medication usage. The diagnosis of drug-induced pneumonitis requires exclusion of concurrent infection; radiographic evidence of interstitial or alveolar opacities; and, if available, histopathologic findings consistent with hypersensitivity pneumonitis or drug toxicity. The American College of Rheumatology recommends avoiding methotrexate in patients with RA and established ILD.[48] Some rheumatologists recommend that patients with RA starting methotrexate undergo a baseline chest radiograph and pulmonary function tests, which can be used for comparison if respiratory symptoms develop,[49] although this has not been incorporated into formal guidelines.

Although rare, leflunomide-induced pneumonitis has a significant impact on mortality. It is most common within the first 20 weeks of treatment and may be more common in patients with RA with previous exposure to methotrexate or with preexisting ILD, although these risk factors require further investigation.[50] Pulmonary toxicities from rituximab are well described.[51] Chronic rituximab-induced lung disease manifests as macronodular organizing pneumonia (OP), occurring weeks to months from the last drug infusion, and has been reported in patients with RA. The treatments for medication-induced pneumonitis include discontinuation of the offending medication and administration of high-dose corticosteroids.

In summary, a variety of radiographic and histopathologic patterns are seen in patients with RA-ILD. Given the therapies commonly used to treat RA, drug-induced pneumonitis is an important consideration in the differential diagnosis of RA-ILD. If the decision is made to treat RA-ILD, the first-line therapy is prednisone. There is little evidence to guide the use and selection of additional immunosuppressive therapies.

Dermatomyositis and Polymyositis

Dermatomyositis and polymyositis are characterized by skeletal muscle inflammation and often involve the skin and lungs (Appendix 1). Skin findings in dermatomyositis include a violaceous erythematous rash over the interphalangeal joints, knuckles, elbows or knees (Gottron sign), eyelids (heliotrope rash), or nape of the neck and upper chest or upper back and shoulders (V or shawl sign).[52] Some patients have amyopathic dermatomyositis characterized by minimal to no muscle involvement yet fulminant ILD, making awareness of these characteristic skin findings crucial for diagnosis.[53] An important variant is the antisynthetase antibody syndrome, which is defined by a positive serologic test for antiaminoacyl transfer RNA (tRNA) synthetase antibodies, such as the histidyl tRNA synthetase (Jo-1) antibody and one or more of the following: myositis; ILD; arthritis; fever; Raynaud phenomenon; or erythema, hyperkeratosis, and cracking of the lateral aspects of the fingers (mechanic's hands).[30,54]

Dermatomyositis and polymyositis are more common in women and black patients.[33,52] Environmental factors may trigger onset in individuals with a genetic predisposition to autoimmunity. Medications and malignancy may cause the initiation and maintenance of autoantibodies that also target muscle and lung.[55] It is estimated that up to 40 cases of statin-related ILD were reported to the US Food and Drug Administration for every 10,000 statin-associated adverse events.[56] A minority of these patients noted myalgias or myositis. A literature review identified malignancy in 1.3% to 7.5% of patients with a dermatomyositis- or polymyositis-related ILD, with a case report of resolution of the ILD and myositis after treatment of the underlying tumor.[57] These observations confirm that a careful medication review and age-appropriate cancer screening should be performed in all patients with dermatomyositis or polymyositis and ILD.

ILD is common (35%-45%) and presents prior to the onset of myositis in 18% to 20% of patients. Most patients with ILD have a chronic, slowly progressive course, but subacute worsening may occur.[33,54] A rapidly progressive form with acute hypoxemic respiratory failure from diffuse alveolar damage or fulminant OP is seen most often in patients with amyopathic dermatomyositis.[30,53] Pneumothorax and pneumomediastinum have been described in the setting of CTD-ILD, with the majority of patients noted to have dermatomyositis.[33] A summary of advances in ILD-associated dermatomyositis or polymyositis was published in *CHEST*.[30] This review highlights the variable and subtle presentations of these patients, requiring a high index of suspicion for the presence of ILD in the setting of myositis and for dermatomyositis or polymyositis in patients with seemingly idiopathic ILD or ARDS. In addition to electromyogram, MRI of proximal muscles may show skeletal muscle edema suggestive of inflammation, which may aid in diagnosis and guide muscle biopsy.[52]

Many patients with myositis-associated ILD will have minimally elevated creatine kinase or aldolase levels, with the diagnosis suggested by the presence of myositis-associated autoantibodies, such as an antinuclear antibody (ANA) titer or anti-Ro antibody (anti-SSA). Several myositis-specific autoantibodies, such as the tRNA synthetase antibodies, have now been described, can be detected at specialized laboratories, and are of sufficient specificity to confirm the diagnosis in the appropriate clinical setting.[55] Patients with negative ANA and anti-Jo-1 antibody findings may have tRNA synthetase antibodies such as anti-PL-12 (anti-alanyl-tRNA synthetase) autoantibodies, which in one series was associated with ILD in 90% of the patients.[58] In two small series, a positive anti-SSA in patients with Jo-1-positive antisynthetase syndrome was associated with increased fibrosis on HRCT scan.[59,60] A decreased response to therapy was also noted in one of these studies.[59]

Radiographic and pathologic findings in patients with ILD secondary to dermatomyositis or polymyositis are the most varied of all the CTD-ILD. NSIP is most commonly reported, but OP is frequently noted and may occur in combination with NSIP.[54] A study of patients with polymyositis and dermatomyositis showed that all patients with fatal ILD had ground glass opacities on HRCT scan, with consolidation being the principal finding in most nonfatal cases.[61] Poor outcome was associated with rapidly progressive respiratory failure and dermatomyositis.

$CD8^+$ T cells are believed to be the primary inflammatory mediators in polymyositis, with B cells and $CD4^+$ T cells noted in dermatomyositis and ILD.[30] These advances in understanding the inflammatory pathways have not led to breakthroughs in therapy partly because of the difficulty of performing trials in this small patient population. Corticosteroids have been the mainstay of therapy, but the response is variable, and some patients may require combination therapy.[33,60] Several case series attest to benefit from cyclophosphamide, but this is reserved for severe or refractory cases given its serious toxicities. There are case series of patients improving with treatment with tacrolimus and mycophenolate mofetil and case reports of improvement in refractory cases after rituximab and IV immunoglobulin.[33,35,36,62,63]

In summary, the following general principles of therapy have been suggested in reviews and guidelines: (1) Response of muscle and skin disease to therapy does not track with and cannot predict the response of ILD, (2) ILD associated with dermatomyositis, especially the amyopathic variant, may be more acute and severe and less responsive to therapy, and (3) early treatment with prednisone and additional immunosuppressive agents may result in improved outcomes for some patients.[33]

Sjögren Syndrome

Primary Sjögren syndrome is a chronic autoimmune disease in which lymphocytic infiltration destroys exocrine glands, causing mucosal dryness. Although lacrimal and salivary glands are most commonly affected, glandular dysfunction and impaired mucosal defense within the lung may increase susceptibility to pulmonary inflammation, predisposing to the development of parenchymal fibrosis.[64] Diagnostic criteria for Sjögren syndrome[65] are shown in Appendix 1.

Five-year survival for patients with Sjögren-ILD is 84%.[66] Common radiographic findings are ground glass opacities (45%-92%) and fibrotic honeycomb cysts (13%-43%).[66-68] Although parenchymal cysts are found less commonly than other radiographic patterns in patients with Sjögren-ILD (7%-17%),[64,67,68] multifocal cysts on HRCT scan raises clinical suspicion for Sjögren-ILD.

Several histopathologic patterns have been described, including NSIP, UIP, OP, and lymphocytic interstitial pneumonia (LIP).[69] LIP is a benign lymphoproliferative disease characterized by diffuse proliferation of polyclonal lymphocytes and plasma cells in the interstitium.[31] Its typical radiographic appearance is ground glass opacities with thin-walled cysts.[69] LIP was considered one of the most common pulmonary manifestations, but studies have demonstrated a much lower prevalence (0.9%-17%).[68,69] This may be secondary to revisions in histopathologic criteria for idiopathic interstitial pneumonias, particularly NSIP.[68] A case report noted clinical and radiographic improvement for a patient with Sjögren-ILD who had LIP

and was treated with corticosteroids, azathioprine, and hydroxychloroquine.[70] However, the authors noted other cases where fibrosis progressed despite immunosuppression. Another case series reported symptomatic improvement in one patient treated with rituximab.[71]

Additional case series have reported the effects of immunosuppressive therapy for Sjögren-ILD. In one series, patients were treated with prednisone and if needed, hydroxychloroquine, azathioprine, or cyclophosphamide.[68] One-half of the patients had a ≥ 10% increase in FVC or ≥ 15% increase in diffusing capacity of lung for carbon monoxide following therapy, whereas 28% experienced deterioration. The second series described 20 patients with Sjögren-ILD, 11 of whom were treated with azathioprine.[31] Six of these patients also received prednisone. FVC increased > 10% in seven patients who received treatment. Although these therapies demonstrated improvement in case series, clinical trials are needed before they can be recommended.

In summary, recent studies have demonstrated that (1) Sjögren-ILD is associated with various histopathologic patterns, including NSIP and LIP, and (2) the presence of multifocal cysts on HRCT scan should raise clinical suspicion for Sjögren-ILD. It is important for pulmonologists to recognize that Sjögren-ILD can result in severe disease. Evidence to guide treatment strategies remains limited.

Significance of Autoimmune Features

It is crucial to evaluate for underlying CTD in patients with ILD because CTD affects both prognosis and treatment. Performing this evaluation will yield a subset of patients with ILD who may have signs, symptoms, and serologic tests suggestive of an underlying autoimmune disease but who do not fulfill all diagnostic criteria for a specific CTD. Several studies suggested that these patients may have an undifferentiated CTD.[72,73] However, in the rheumatologic literature, undifferentiated CTD is a mild disease in which pulmonary fibrosis develops in < 1% of patients.[74,75] This has led to a lack of consensus between pulmonologists and rheumatologists about the terminology that should be used to describe these patients.[76]

We have proposed a new term, autoimmune-featured ILD (AIF-ILD), to describe this subset of patients with ILD who meet some, but not all, diagnostic criteria for a CTD (Appendix 1).[77] Of 200 patients with ILD who underwent a comprehensive, systematic evaluation for CTD, 32% met proposed criteria for AIF-ILD, suggesting that this may be a common entity. The majority of patients with AIF-ILD had multiple symptoms and multiple abnormal serologic tests. Clinical and demographic characteristics of patients with AIF-ILD differed from both IPF and CTD-ILD. The most common radiographic and histopathologic pattern for patients with AIF-ILD was UIP; NSIP was also noted. Although survival in patients with AIF-ILD was comparable to patients with IPF, those with AIF-ILD with an ANA titer ≥ 1:1,280 had improved survival.

Corte et al[73] evaluated 101 patients with idiopathic interstitial pneumonias who underwent surgical lung biopsy and found that 21% had symptoms and serologic tests suggestive of an underlying CTD. Two-thirds of the patients had an NSIP pattern on surgical lung biopsy, whereas one-third had a UIP pattern. There were no differences in survival between patients with and without autoimmune features. However, in the

Table 3—*Clinical Pearls for CTD-ILD*

CTD	Diagnosis	Management
Systemic sclerosis	Esophageal dilation on HRCT scan increases clinical suspicion.	Esophageal dysfunction and gastroesophageal reflux are common. Annual screening for pulmonary hypertension is recommended by the WHO.
Rheumatoid arthritis	Consider drug-induced pneumonitis for new or worsening ILD.	Radiographic and histopathologic findings of UIP portend a worse prognosis. Tobacco cessation is strongly recommended.
Dermatomyositis and polymyositis	Myositis may be subtle and present after ILD. Myositis-associated and -specific antibodies aid in diagnosis.	Early treatment with prednisone and additional immunosuppressive agents may improve outcomes.
Sjögren syndrome	Cysts on HRCT scan increase clinical suspicion.	Severe ILD, with UIP on HRCT scan and pathology, has been reported. LIP may be less common than other histopathologic patterns.
Autoimmune-featured ILD	Comprehensive and systematic evaluation will identify these patients. Seen in patients with UIP on HRCT scan and pathology.	Patients with ANA titer ≥ 1:1,280 may have improved survival.

ANA = antinuclear antibody; LIP = lymphocytic interstitial pneumonia; UIP = usual interstitial pneumonia; WHO = World Health Organization. See Table 1 and 2 legends for expansion of other abbreviations.

subset of patients with HRCT scan findings atypical for IPF and adjusted for disease severity, two characteristics were associated with improved survival: the presence of Raynaud phenomenon and women aged < 50 years.

In summary, these studies highlight the increasing recognition of patients with AIF-ILD. At present, their clinical, radiographic, and histopathologic characteristics remain heterogeneous. Although there are studies suggesting that an NSIP pattern is suggestive of an underlying autoimmune disease,[72] patients with a UIP pattern on HRCT scan or lung biopsy specimen can also have autoimmune features, which may portend a better prognosis.[77] It is likely that the diagnostic criteria that distinguish this group will be revised as larger patient populations are studied. Nonetheless, many important questions remain: Where in the spectrum of autoimmune lung diseases do these patients belong? Is the course of their disease different from that of patients with idiopathic interstitial pneumonias or CTD-ILD? Is there a benefit to treating these patients with immunosuppressive therapies, and if so, which ones? Additional studies are needed to address these issues.

Conclusion

Compared with idiopathic interstitial pneumonias, CTD-ILD is associated with a more favorable prognosis and, in some cases, may respond to immunosuppressive therapy. Thus, it is crucial to evaluate for underlying CTD in all patients presenting with ILD. Although CTD-ILD shares an underlying autoimmune dysfunction, differences in pathogenesis lead to varied clinical presentations. We have summarized new thinking in the diagnosis and management of CTD-ILD in Table 3.

Some patients with CTD-ILD will be treated with immunosuppressive therapy directed toward nonpulmonary systemic manifestations of their CTD. Specific monitoring of pulmonary disease is necessary because the course of ILD does not always follow systemic disease activity. Based on ILD disease severity and progression, some patients with CTD-ILD may benefit from immunosuppressive therapy directed toward ILD. Currently, there is little evidence to guide treatment strategies for patients with CTD in whom ILD develops. Well-designed, adequately powered clinical trials are urgently needed in CTD-ILD to guide the selection and optimal duration of immunosuppressive medications.

Acknowledgments

Financial/nonfinancial disclosures: The authors have reported to *CHEST* the following conflicts of interest: Dr Strek has received grants from the National Institutes of Health, ImmuneWorks, InterMune, and Gilead to conduct clinical trials in IPF. Dr Vij has reported that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

Appendix 1. Diagnostic Criteria for Connective Tissue Diseases

Systemic Sclerosis[5]

One major criterion or at least two minor criteria:

1. Major criterion; Proximal scleroderma
2. Minor criteria:
   a. Sclerodactyly
   b. Digital pitting scars of fingertips or loss of substance from distal finger pad
   c. Bibasilar pulmonary fibrosis

Rheumatoid Arthritis[38]

Score of ≥ 6 points:

1. Joint involvement
   a. One large joint (0 points)
   b. Two to 10 large joints (1 point)
   c. One to three small joints (2 points)
   d. Four to 10 small joints (3 points)
   e. More than 10 joints (at least one small) (5 points)
2. Serology
   a. Negative rheumatoid factor (RF) and negative anticyclic citrullinated peptide antibody (aCCP) (0 points)
   b. Low positive RF or aCCP (≤ 3 times the upper limit of normal (2 points)
   c. High positive RF or aCCP (> 3 times the upper limit of normal (3 points)
3. Acute phase reactants
   a. Normal C-reactive protein and normal erythrocyte sedimentation rate (0 points)
   b. Abnormal C-reactive protein or abnormal erythrocyte sedimentation rate (1 point)
4. Duration of symptoms
   a. < 6 weeks (0 points)
   b. ≥ 6 weeks (1 point)

Dermatomyositis and Polymyositis[54]

1. Symmetric weakness of proximal muscles with or without dysphagia or respiratory muscle involvement.
2. Characteristic histopathologic findings on skeletal muscle biopsy sample
3. Elevation of skeletal muscle enzymes: creatine kinase, aldolase, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase
4. Characteristic findings on electromyography
5. Dermatologic features, including
   a. Heliotrope discoloration of the eyelids with periorbital edema
   b. Scaly, erythematous dermatitis over the dorsa of hands, especially metacarpophalangeal and proximal interphalangeal joints
   c. Involvement of the knees, elbows, medial malleoli, face, neck, and upper torso

Primary Sjögren Syndrome[65]

- Any four of six criteria, provided that either histopathology (#4) or autoantibodies (#6) is positive
- Any three of the following four objective criteria: ocular signs (#3), histopathology (#4), salivary gland involvement (#5), autoantibodies (#6)

1. Ocular symptoms: at least one
   a. Daily persistent, dry eyes > 3 months
   b. Recurrent sensation of sand or gravel in the eyes
   c. Use of tear substitutes > tid
2. Oral symptoms: at least one
   a. Daily feeling of dry mouth > 3 months
   b. Recurrent or persistently swollen salivary glands
   c. Frequent consumption of liquid to swallow dry food
3. Ocular signs: at least one
   a. Positive Schirmer test
   b. Rose bengal score or other ocular dye score ≥ 4
4. Histopathology
   a. Salivary gland biopsy specimen demonstrating focal lymphocytic sialadenitis
5. Salivary gland involvement: at least one
   a. Decreased salivary flow
   b. Parotid sialography demonstrating diffuse sialectasias
   c. Abnormal salivary scintigraphy
6. Autoantibodies
   a. Antibodies to Ro (Sjögren syndrome antigen A), La (Sjögren syndrome antigen B), or both

Appendix Table 1—*Autoimmune-Featured Interstitial Lung Disease—At Least One Symptom/Sign and at Least One Abnormal Serologic Test*[77]

Symptom/Sign	Serologic Test
Weight loss	Antinuclear antibody titer ≥ 1:160
Dry eyes/dry mouth	Antidouble-stranded DNA
Oral ulcers	Anti-ribonucleoprotein antibody
Dysphagia	Anti-Smith antibody
Gastroesophageal reflux	Anti-Scl-70
Hand ulcers	Anti-Ro antibody (anti-SSA)
Raynaud phenomenon	Anti-La antibody (anti-SSB)
Leg/foot swelling	Rheumatoid factor
Joint pain/swelling	Anticyclic citrullinated peptide antibody (aCCP)
Morning stiffness	Anti-Jo-1 antibody
Rash	Antineutrophil cytoplasmic antibody
Proximal muscle weakness	CK
Photosensitivity	Aldolase

At least one symptom/sign and at least one abnormal serologic test. aCCP = anticyclic citrullinated peptide antibody; CK = creatine kinase anti-Jo-1 = antihistidyl transfer RNA synthetase; anti-Scl-70 = autoantibodies targeted against type I topoisomerase; SSA = Sjögren syndrome antigen A; SSB = Sjögren syndrome antigen B.

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