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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.

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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