Interstitial Lung Disease in the Connective Tissue Diseases

Danielle Antin-Ozerkis, MD[a,*], Ami Rubinowitz, MD[b], Janine Evans, MD[c], Robert J. Homer, MD, PhD[d], Richard A. Matthay, MD[e]

KEYWORDS

• Connective tissue • Interstitial lung disease • Inflammation • Immunity

The connective tissue diseases (CTDs) are a group of inflammatory, immune-mediated disorders in which a failure of self-tolerance leads to autoimmunity and subsequent tissue injury. Involvement of the respiratory system, particularly interstitial lung disease (ILD), is common and is an important contributor to morbidity and mortality. The CTDs in which ILD is most commonly observed include rheumatoid arthritis (RA), systemic sclerosis/scleroderma (SSc), polymyositis (PM)/dermatomyositis (DM), Sjögren syndrome, and systemic lupus erythematosus (SLE).

When clinically apparent, CTD-associated interstitial lung disease (CTD-ILD) most often presents with the gradual onset of cough and dyspnea, although rarely it may present with fulminant respiratory failure. ILD may be the first manifestation of systemic rheumatic disease in a previously healthy patient. Before making a diagnosis of ILD, other causes of parenchymal abnormalities, such as drug toxicity or opportunistic infection, must be ruled out. Among patients with known CTD, subclinical disease is common and raises difficult questions regarding screening, diagnosis, treatment, and the ability to tolerate planned therapies to address other systemic manifestations of disease.

The radiographic findings and histopathologic appearance of ILD among the CTDs closely resembles those of the idiopathic interstitial pneumonias. However, close examination of radiographs and pathologic tissue may offer clues to a diagnosis of underlying CTD. The diagnosis of idiopathic ILD should never be made without a careful clinical search for evidence of CTD, and long-term follow-up of patients with idiopathic disease should include repeated rheumatologic evaluation as new symptoms evolve.

Few controlled trials address primary therapy for the lung disease, although corticosteroids and immunosuppressive agents are often used. Response to therapy and prognosis varies with the underlying CTD as well as with the histopathologic pattern, although further study on these issues is needed because data are limited.

[a] Yale Interstitial Lung Disease Program, Pulmonary & Critical Care Medicine Section, Department of Internal Medicine, Yale University School of Medicine, 15 York Street, LLCI 101B, New Haven, CT 06510, USA
[b] Department of Diagnostic Radiology, Yale University School of Medicine, PO Box 208042, Tompkin's East 2, New Haven, CT 06520-8042, USA
[c] Rheumatology Section, Department of Internal Medicine, Yale University School of Medicine, PO Box 208031, 300 Cedar Street, TAC S-425D, New Haven, CT 06520-8031, USA
[d] Yale University School of Medicine, PO Box 208023, 310 Cedar Street, LH 108, New Haven, CT 06520-8023, USA
[e] Pulmonary & Critical Care Medicine Section, Department of Internal Medicine, Yale University School of Medicine, PO Box 208057, 300 Cedar Street, New Haven, CT 06520-8057, USA
* Corresponding author.
E-mail address: danielle.antin-ozerkis@yale.edu

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GENERAL APPROACH

Respiratory Symptoms

Patients with CTD-ILD are often asymptomatic early in the disease course and symptoms are usually nonspecific. Many patients present with dyspnea on exertion, fatigue, or cough. However, CTD-ILD in an asymptomatic patient may be discovered incidentally through radiographic abnormalities. Once lung function is significantly impaired, progressive dyspnea often develops. In time, diffusion defects lead to exertional hypoxemia. Increased dead space ventilation may also contribute to breathlessness. Ultimately, progressive fibrosis leads to increased work of breathing caused by high static recoil of the lung.[1]

The diagnosis of CTD-ILD may be delayed if patients attribute mild dyspnea to deconditioning and age. Limited functional status in patients with severe joint disease or significant muscle weakness may also contribute to delays in diagnosis. Conversely, the early onset of cough may lead to an earlier pulmonary evaluation. Other symptoms referable to the respiratory system include pleuritic chest pain secondary to serositis and other pleural involvement, or, rarely, the development of pneumothorax.[2,3] With advanced pulmonary fibrosis, pulmonary hypertension may develop, leading to symptoms of cor pulmonale, such as lower extremity edema and exertional chest discomfort or syncope.

Other Systems

In the patient with longstanding CTD, the underlying diagnosis is usually certain. However, in the patient with recent-onset ILD without a known CTD diagnosis, a detailed clinical history can uncover symptoms that suggest underlying CTD. For example, careful questioning regarding skin rashes may lead to the discovery of a heliotrope rash, Gottron papules, or so-called mechanic's hands in DM.[4] A history of skin thickening, telangiectasias, or digital nail pitting may suggest SSc.[5] Symptoms of acid reflux or regurgitation of food, or a history of dysphagia, may reflect underlying esophageal dysmotility and dysfunction, as seen in SSc and PM.[4,5] Musculoskeletal system complaints such as joint pain, swelling, and inflammation, as well as morning stiffness, may lead to a diagnosis of RA.[6] Swollen, tight skin on the fingers may be observed in SSc and PM, and a history of Raynaud phenomenon suggests underlying SSc, mixed CTD (MCTD), SLE, or PM.[5,7,8]

Physical Examination

Physical examination findings are often nonspecific but may include bibasilar fine, dry, velcro crackles in the patient with underlying lung fibrosis.[9] Late signs of CTD-ILD may include digital clubbing and evidence of right heart failure. Dermatologic and musculoskeletal signs of CTD, including skin rashes, sclerodactyly, skin thickening, mechanic's hands, synovitis, joint deformities, Raynaud phenomenon, and telangiectasias, may assist in uncovering primary or mixed diagnoses.

Serologic Testing

Serologic testing in patients with idiopathic ILD has historically been limited to antinuclear antibodies (ANA) and rheumatoid factor (RF). The most recent American Thoracic Society (ATS) guidelines on idiopathic pulmonary fibrosis cite only weak evidence in supporting recommendations to test ANA, RF, and anti–cyclic citrullinated peptide (anti-CCP) antibodies, but nonetheless recommend serologic testing in most patients.[10] This is recommended because it is clinically important to distinguish idiopathic from CTD-associated fibrotic lung disease. When careful evaluation for subtle historical and physical examination features is undertaken, it is estimated that at least 15% of patients have evidence of underlying CTD.[11] Nearly one-quarter of patients in one series who presented with presumed idiopathic interstitial pneumonia and negative ANA, but who had clinical findings of antisynthetase syndrome, were found to have antisynthetase antibodies.[12] Although not evidence based, some centers that specialize in the evaluation of patients with ILD routinely test for autoantibodies to Ro (anti-SSA) and La (anti-SSB), topoisomerase antibodies (anti–Scl-70), antisynthetase antibodies, antiribonucleoprotein (anti-RNP) antibodies, and anti-CCP antibodies, in addition to ANA and RF (**Table 1**).[13]

Pulmonary Function Tests

Typical pulmonary function test (PFT) abnormalities include restrictive physiology and diffusion impairment, the latter often predating other defects.[14,15] Exercise testing is an important, if underused, modality of testing patients with ILD, frequently unmasking exertional desaturation in the patient with a normal resting arterial saturation. Desaturation with exercise may be predicted by abnormalities in lung function,[16,17] and can be explained by a combination of inadequate pulmonary capillary recruitment with reduced time available for gas exchange, as well as reduced mixed venous oxygen content caused by areas of V/Q mismatch and intrapulmonary shunt.[18,19] In more advanced fibrosis, pulmonary vascular obliteration