Connective Tissue Disease–Associated Lung Disease

Amy L. Olson, MD[a], Kevin K. Brown, MD[a], Aryeh Fischer, MD[a,b,*]

KEYWORDS

• Connective tissue disease • Interstitial lung disease • Collagen vascular disease

KEY POINTS

- Patients with CTDs are at high risk for a number of pulmonary complications.
- A multidisciplinary, comprehensive evaluation is indicated for CTD patients with respiratory symptoms to explore a broad differential diagnosis that often includes respiratory infection, medication-associated lung toxicity, and autoimmune mediated lung injury.
- CTD-associated lung disease is often characterized by multi-compartment involvement: airways, lung parenchyma, pleura, and vascular.
- Lung disease may present at any time in the course of a CTD – and may even be the presenting manifestation of a CTD.
- Heightened surveillance for respiratory illness is indicated in the care of all patients with CTD.

INTRODUCTION

The designations of "connective tissue disease" (CTD) or "collagen vascular disease" are used interchangeably and refer to the spectrum of systemic autoimmune diseases characterized by autoimmune phenomena (eg, circulating autoantibodies) and autoimmune-mediated organ damage. Even though these disorders are grouped together, it is important to recognize that there is significant heterogeneity of clinical features associated with each specific CTD. The CTDs include rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis (SSc, scleroderma), poly-/dermatomyositis (PM/DM), primary Sjögren syndrome (SjS), mixed CTD (MCTD), and undifferentiated CTD (UCTD) (**Box 1**).

The lungs are a frequent target of autoimmune mediated injury in patients with CTD. There are multiple pulmonary manifestations; essentially every component of the respiratory tract is at risk and certain CTDs are associated with specific patterns of lung involvement (**Box 2** and **Table 1**).[1–4] As an example, some CTDs are more likely to be associated with airways disease or interstitial lung disease (ILD) than are others, but all patients with CTD are at risk for multicompartment lung involvement.

[a] Autoimmune and Interstitial Lung Disease Program, National Jewish Health, 1400 Jackson Street, Denver, CO 80206, USA; [b] Division of Rheumatology, National Jewish Health, 1400 Jackson Street, Denver, CO 80206, USA
* Corresponding author. Division of Rheumatology, 1400 Jackson Street, Denver, CO 80206.
E-mail address: fischera@njhealth.org

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Box 1
CTDs and other rheumatologic diseases associated with lung disease

Connective Tissue Diseases
Rheumatoid arthritis
Systemic lupus erythematosus
Systemic sclerosis (scleroderma)
Primary Sjogren's syndrome
Poly-/dermatomyositis (Anti-synthetase syndrome)
Mixed connective tissue disease
Undifferentiated connective tissue disease
Other "rheumatologic" disorders
Systemic vasculitis
  Polyangiitis with granulomatosis (Wegener's)
  Microscopic polyangiitis
  Churg-Strauss vasculitis
Spondyloarthropathy
Relapsing polychondritis
Behçet's disease
Antiphospholipid syndrome

Thus, the intersection of lung disease and CTD is complex because of the myriad pulmonary manifestations that can occur with any of these disorders. Furthermore, although many of the lung manifestations occur within the first few years of the CTD diagnosis, their development much later is not unusual, and they may even be the presenting feature of an underlying CTD.[5–11] In the following sections, we review the characteristics and impact of CTD-associated lung disease.

CATEGORIES OF LUNG INVOLVEMENT

It is important to consider several diagnostic possibilities when a patient with CTD presents with new respiratory symptoms (see **Box 2**). A wide range of differential diagnostic possibilities exist, and these may be grouped into the following categories: infection, drug-induced lung toxicity, direct pulmonary complications (eg, ILD); indirect complications (eg, hypoventilation secondary to myopathy); cardiovascular complications (eg, coronary artery disease or cardiomyopathy); and unrelated disease.[4] In particular, because cardiovascular complications are responsible for a significant proportion of the mortality seen in patients with CTD,[12] it is also important to consider ischemia and cardiomyopathy.

Respiratory Infection

Respiratory infections are common in CTD and account for significant morbidity and mortality. Predisposing risk factors for respiratory infection in patients with CTD include intrinsic abnormalities such as respiratory muscle weakness, airways disease, and underlying immune dysfunction. Furthermore, and perhaps most significant, many of these patients are on potent immunosuppressive medications.[13] Thus, patients with CTD are at increased risk for the development of infection, and when respiratory

Box 2
Primary and secondary pulmonary manifestations of CTDs

Primary manifestations

Pleural
- Pleurisy
- Effusion/thickening

Airways
- Upper
  - Cricoarytenoid disease
  - Tracheal disease
- Lower
  - Bronchiectasis
  - Bronchiolitis

Vascular
- Pulmonary arterial hypertension
- Vasculitis

Parenchymal
- ILD
- Diffuse alveolar hemorrhage
- Acute pneumonitis

Rheumatoid nodules

Secondary manifestations

Infections

Drug toxicity

Malignancy

Thromboembolism

Table 1
Most common CTD-associated pulmonary manifestations

	SSc	RA	Primary SjS	MCTD	PM/DM	SLE
Airways	–	++	++	+	–	+
ILD	+++	++	++	++	+++	+
Pleural	–	++	+	+	–	+++
Vascular	+++	–	+	++	+	+
DAH	–	–	–	–	–	++

The number of + signs indicates relative prevalence of each manifestation.

Data from Fischer A, du Bois R. Interstitial lung disease in connective tissue disorders. Lancet 2012;380(9842):689–98.

symptoms develop, thorough evaluation to exclude the presence of routine and opportunistic infections should be undertaken.[13–15]

Medication-Induced Lung Toxicity

Many of the anti-inflammatory and immunosuppressive medications used to treat CTD have been associated with the development of lung toxicity. These include aspirin, nonsteroidal anti-inflammatory drugs, sulfasalazine, methotrexate (MTX), cyclophosphamide, azathioprine, mycophenolate mofetil, D-penicillamine, leflunomide, and anti–tumor necrosis factor (TNF)α antagonists.[2,4,14–17] However, a diagnosis of drug-induced lung disease can be challenging – because the clinical presentation and radiographic and histologic patterns are nonspecific and frequently mimic either infection or primary CTD-associated pulmonary involvement. A comprehensive and updated list of medications with their reported pulmonary toxicities can be found online at www.pneumotox.com.

Of all the immunosuppressive medications used to treat patients with CTD, MTX is generally considered to have the most potential for pulmonary toxicity. Symptomatically, it is characterized by the subacute (during several weeks) onset of dyspnea, cough, and fever. However, acute (occurring over days), chronic (occurring over months), and a delayed reaction occurring after the discontinuation of MTX have all been described. Radiographically, a pattern of interstitial (with or without alveolar) infiltrates in the lower lung fields may be present, whereas the histopathologic patterns seen on surgical lung biopsy sample include a cellular (lymphoplasmacytic) interstitial infiltrate with or without granulomata and acute and organizing diffuse alveolar damage (DAD). Neither the duration nor the dose predicts MTX pulmonary toxicity, although underlying RA and male sex may be risk factors to its development.[4,16] Therapy includes the discontinuation of MTX and the initiation of steroids; mortality ranges from 13% to 22%.[16,18,19]

Cyclophosphamide, an alkylating agent often used in SSc-associated ILD, has rarely been associated with both early and delayed pulmonary toxicity.[20] Early toxicity typically occurs after 1 to 6 months of exposure, may result in nonspecific reticulonodular infiltrates on imaging, and is potentially reversible after withdrawal of the agent and initiation of glucocorticoid therapy. Delayed pulmonary toxicity occurs after months to years of therapy and is difficult to distinguish from ILD associated with the underlying CTD. Characteristic radiographic manifestations are reported to include lung fibrosis with bilateral pleural thickening. This form of toxicity is typically irreversible and may be progressive despite the cessation of drug.[4,20] Both azathioprine and mycophenolate mofetil are commonly used in the management of various forms of CTD – including CTD-associated ILD (CTD-ILD).[21] It is important that each has also been rarely associated with pulmonary toxicity ranging from DAD to lung fibrosis, and these effects have been reported to be dose related.[22–24]

During the past 15 years, the management of the rheumatic diseases has been revolutionized by the advent of targeted biologic therapy. In particular, the anti-TNFα antagonists have demonstrated a high degree of efficacy for RA, inflammatory bowel disease, psoriasis, ankylosing spondylitis, and miscellaneous other autoinflammatory diseases.[25] There have been numerous case reports describing the new development of diffuse parenchymal lung disease in patients being treated with each of these agents, suggesting a component of direct pulmonary toxicity associated with their use.[14,15,17,26–30] Even more significant than their potential for pulmonary toxicity, the class of anti-TNFα antagonists is highly immunosuppressive and patients treated with these agents are at high risk for typical and atypical respiratory infections.

Pulmonary Manifestations

The lung itself is a frequent target of autoimmune-mediated damage in patients with CTD, although the incidence of any particular complication varies by individual CTD (see **Box 2**). Within the lung, each of the unique anatomic compartments can be involved by 1 or more pathologic processes that adversely affects its ability to function normally, including cellular infiltration (inflammation), fibrosis, and architectural distortion. The airway, from the larynx to the bronchiole; the parenchyma; the vasculature; and the pleural can also be involved either individually or in some combination.[3,4] For example, in SSc, isolated pulmonary arterial hypertension, sole fibrosing ILD, or a combination of these processes is responsible for most associated deaths.[31]

ILD is a frequently identified entity in preexisting CTD; recent studies of CTD cohorts have shown radiographic prevalence rates of subclinical ILD ranging from 33% to 57%.[31–36] ILD is particularly common in patients who have SSc, PM/DM, RA, primary SjS, and MCTD. However, just because ILD is identified in a patient with CTD does not mean the 2 are necessarily related. For example, the presence of preexisting RA does not preclude, and may predispose toward, the development of lung injury as a result of other causes (eg, infection and drug-induced pneumonitis). In this regard, just as with any other patient who presents with diffuse parenchymal lung disease, a comprehensive evaluation is needed to explore all potential causes (eg, infection, drug-toxicity, environmental and occupational exposures, familial disease, smoking-related lung disease, and malignancy). Determining whether the ILD is associated with the preexisting CTD is decided through a process of elimination.[2]

Indirect Pulmonary Complications

Because of the systemic nature of CTD, virtually all organ systems are impacted. Indirect pulmonary complications are the result of abnormalities in extrathoracic aspects that have a direct bearing on lung function but not through a primary alteration of the underlying lung architecture per se. Such manifestations may include musculoskeletal abnormalities (eg, respiratory muscle weakness caused by myopathy in PM/DM), gastrointestinal diseases (eg, gastroesophageal reflux with aspiration in SSc), or immunologic (eg, immunodeficiency secondary to complement abnormalities in SLE), hematologic (eg, antiphospholipid antibody positivity), or cardiovascular dysfunction (eg, cardiomyopathy in PM/DM). Abnormalities in 1 or more of these systems often leads to clinically significant respiratory compromise even in the absence of underlying structural lung disease and further highlights the need for comprehensive assessments in the patient with CTD with respiratory symptoms.[2,4]

SPECIFIC CTDS

SSc (Scleroderma)

SSc is a systemic autoimmune disease characterized by autoimmunity, fibrosis, and widespread small-vessel vasculopathy. Lung disease is identified in most patients with SSc; indeed, ILD and pulmonary arterial hypertension (PAH) are the leading causes of mortality.[31,37] One of the cardinal features of SSc is thickening of the skin, and the extent of skin involvement defines its various subtypes. Limited cutaneous systemic sclerosis (LcSSc) is defined by skin thickening limited to body surface areas below the elbows and knees and not involving the trunk (chest or abdominal wall).[38] In contrast, diffuse cutaneous systemic sclerosis (DcSSc) is defined by more proximal and extensive skin thickening that includes sclerodermatous skin changes proximal to the elbows or knees or involving the trunk.[38] In addition, some patients have characteristic clinical features of SSc without overt evidence of skin thickening, and these

patients may be considered to represent a subset of LcSSc or are more accurately characterized as having SSc sine scleroderma (ssSSc).[39] Distinguishing these subtypes of SSc is important because they often have different clinical courses and have different patterns of lung involvement.[31,40]

LcSSc and ssSSc typically present insidiously and are characterized by minimal skin-associated symptoms. Raynaud phenomenon is seen in virtually all of these patients and may predate any subsequent manifestations by 10 to 15 years. Digital edema (puffy hands), palmar and facial telangiectasia, and gastroesophageal reflux disease are also identified in nearly all of these patients. SSc-specific autoantibodies provide particular insights into the type of lung disease that occur with LcSSc and ssSSc.[40] Those with anticentromere antibodies have the highest risk for PAH and are at much less risk for progressive ILD. In contrast, those with anti–Scl-70 antibodies are at highest risk for progressive ILD and a lower risk for PAH. An in-between category is composed of patients with SSc with positive nucleolar staining antinuclear antibodies (ANA) with a negative anti–Scl-70. These patients are considered to have an "isolated nucleolar" ANA and are at high risk for developing both progressive ILD and PAH.[31,40]

Patients with DcSSc present more acutely with a variety of symptoms. Active and diffuse skin thickening is often a prominent early feature. Digital edema, inflammatory arthritis, and symptoms of carpal tunnel syndrome also may be early findings. Constitutional symptoms of fatigue, malaise, weight loss, and low-grade fevers are common. Patients with DcSSc are at high risk for early progressive ILD and scleroderma renal crisis. As a group, DcSSc is associated with a worse prognosis than is LcSSc or ssSSc.

The 2 most common pulmonary manifestations of SSc are ILD and PAH – and these manifestations alone account for 60% of SSc-related deaths.[31,41] As a general rule, PAH tends to be a later manifestation in SSc and is most strongly associated with LcSSc, and either a positive anticentromere or isolated nucleolar ANA. Progressive ILD tends to be an earlier manifestation (within the first 5–7 years) and is most strongly associated with the presence of a positive anti–Scl-70 antibody or those with nucleolar-pattern ANA – in either LcSSc, DcSSc, or ssSSc subtype.[31,37] It is important to recognize that although these descriptions can be helpful to better understand and risk stratify patients based on precise clinical phenotype, both progressive ILD and PAH have been described in each of the subsets of disease and as early or late manifestations.

Airways Disease and Pleural Disease

Although evidence of airways disease on pulmonary function testing may be identified, clinically significant airways disease is rare.[42] These subtle abnormalities may be related to prior tobacco exposure or possible subclinical follicular bronchiolitis.[43,44]

Unlike other CTDs such as RA and SLE, symptomatic pleuritis and/or pleural effusions are uncommon in SSc.[4]

Vascular Disease

SSc-associated PAH may result from primary arteriopathy (histologically similar to idiopathic PAH with either plexiform lesions and/or concentric intimal obliteration of pulmonary vessels).[45] The true prevalence of PAH in SSc is unknown, but it is estimated that right-heart catheter-proved PAH has a prevalence of about 10%.[46] Risk factors for the development of SSc-PAH includes limited cutaneous disease, long-standing Raynaud phenomenon, extensive telangiectasia, positive anticentromere antibody or isolated nucleolar ANA, or isolated reduction in diffusing capacity for carbon monoxide (DL_{CO}).[46] The introduction of PAH-specific therapies has favorably impacted survival in SSc-PAH. Before the discovery and use of these agents in SSc- PAH, the 1-year survival

rate in SSc-PAH was 45%.[47] However, recent reported 1- and 3-year survival rates for patients with SSc-PAH are 78% and 47%, respectively.[48]

ILD

Proportionally, ILD is identified more often in SSc than in any other CTD; evidence of radiographic findings of ILD occurs in nearly all patients with SSc and clinically significant disease occurs in approximately 40% of patients (**Fig. 1**).[49] The most prevalent histologic pattern identified in SSc is fibrotic nonspecific interstitial pneumonia (NSIP) followed by the usual interstitial pneumonia (UIP) lung injury pattern.[50–53]

Aspiration/Gastroesophageal Reflux Disease

Esophageal dysmotility and gastroesophageal reflux disease are quite common in patients with SSc. Medication therapy with proton-pump inhibitors for gastroesophageal reflux disease and a proactive approach to prevent aspiration are usually advised.

Bronchogenic Carcinoma

The true risk of bronchogenic carcinoma in patients with SSc is unknown and the available data are conflicting.[54] Several large population-based epidemiologic studies have reported a significant increase in risk.[54] In a Swedish study from 1965 to 1983, the standardized incidence ratio for lung cancer in patients with DcSSc was 7.8 (95% confidence interval, 2.5–18.2).[55] Similar results were reported from an epidemiologic study in South Australia.[56] However, these results are tempered by 2 recent epidemiologic investigations conducted in the United States that did not show increases in the risk of lung cancer in patients with SSc.[57,58]

PM/DM

PM/DM are classified as idiopathic inflammatory myopathies. Both diseases are characterized by inflammatory muscle disease involving the proximal muscle groups, and DM is further defined by its characteristic cutaneous involvement.[59,60] Both are associated with underlying malignancy, with higher malignancy rates identified in DM.[61] Both are rare with an estimated annual incidence of less than 10 per 1 million population per year.[4,62] These diseases can affect any age group but have a bimodal incidence pattern with a peak in childhood (10–15 years of age) and a second peak

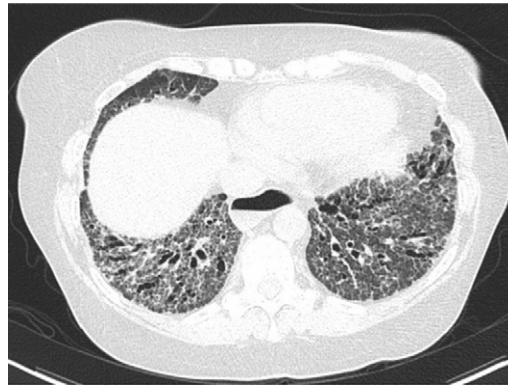

Fig. 1. HRCT of a patient with SSc demonstrating moderate bibasilar predominant ground-glass opacifications, reticulation, and traction bronchiectasis suggestive of fibrotic NSIP. Note the markedly dilated, fluid-filled esophagus characteristic of SSc.

between 35 and 65 years of age. Women are more commonly affected than men.[4,62] Some form of pulmonary involvement occurs in more than 50% of patients, and ILD is the most common and potentially most devastating pulmonary manifestation of PM/DM.[4,62] A subset of PM/DM is the antisynthetase syndrome, which is characterized by a combination of several clinical features that include inflammatory myopathy, ILD, fever, inflammatory arthritis, Raynaud phenomenon, "mechanic's hands," esophageal dysmotility, and the presence of an anti–transfer RNA–synthetase antibody (eg, anti–Jo-1, anti–PL-7, anti–PL-12).[9,63] Many patients with the antisynthetase syndrome may only with present partial features of the syndrome and inflammatory muscle disease may be absent or subclinical in nature.[9,63]

Airways Disease, Pleural Disease, and Vascular Disease

Both airway and pleural disease are rare.[62] Clinically evident pulmonary arterial hypertension is rare in PM/DM. If PAH is diagnosed, secondary causes should be thoroughly evaluated including respiratory muscle weakness resulting in hypoventilation, significant ILD, and underlying PM/DM-associated cardiomyopathy.[4]

ILD

ILD is the most common pulmonary manifestation of PM/DM, and its presence has been associated with increased morbidity and mortality (**Fig. 2**).[62,64,65] Clinically significant disease seems to occur in approximately 30%, whereas high-resolution computed tomography (HRCT) evidence of ILD may be present in more than 70% of patients with PM/DM.[62,64,65] Women with PM/DM are more likely to develop ILD, and the mean age at presentation is 50 years. ILD may be the presenting manifestation in many patients and is particularly common in those with the antisynthetase syndrome or in those who have a positive anti–transfer RNA–synthetase antibody.[63–65]

Based on the findings of histopathologic studies, NSIP is the most common pattern seen on surgical lung biopsy followed by UIP and organizing pneumonia.[66,67] An acute interstitial pneumonia-like disease occurs with an underlying histopathologic pattern of DAD. Similar to idiopathic acute interstitial pneumonia, the prognosis is poor.[68] The antisynthetase syndrome often has a characteristic HRCT pattern suggesting NSIP with overlapping organizing pneumonia with extreme bibasilar predominance

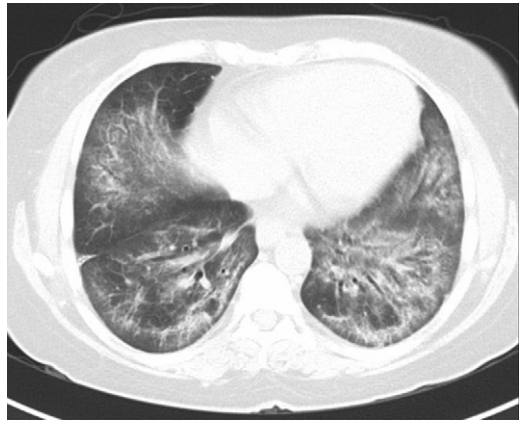

Fig. 2. HRCT image of a patient with the antisynthetase syndrome. Note the bibasilar distribution of ground-glass opacifications suggestive of nonspecific interstitial pneumonia and the consolidative features suggesting organizing pneumonia.

and reticular and ground-glass opacifications that to seem hug or "pancake" the diaphragm (see **Fig. 2**).[9]

Aspiration/Gastroesophageal Reflux Disease

Similar to SSc, esophageal dysmotility and gastroesophageal reflux disease are quite common in PM/DM. Medication therapy with proton-pump inhibitors for gastroesophageal reflux disease and a proactive approach to prevent aspiration are usually advised.

Complications of Muscle Weakness

Respiratory muscle weakness resulting in alveolar hypoventilation is a less common manifestation of PM/DM occurring in approximately 7% of patients.[4] Involvement of the hypopharyngeal and upper esophageal muscles results in dysphagia and aspiration. Aspiration pneumonia and repeated infections are frequent, occurring in as many as 20% of patients with PM/DM.[4]

RA

RA is a systemic autoimmune disease characterized by a symmetric, progressive, destructive, and chronic inflammatory polyarthritis.[69] It is the most common CTD and affects approximately 1% of the population worldwide. Women are twice as likely as men to be affected, and although it can occur at any age, the peak incidence is between the fourth and sixth decades.[4] Its extra-articular manifestations are frequent and may occur in virtually all organ systems. Pulmonary complications are common, may be the presenting manifestation of the disease, can impact every component of the respiratory tract, and account for 10% to 20% of deaths.[70–73]

Airways Disease

Upper airways

When assessed by direct laryngoscopy, the cricoarytenoid joint is affected in as many as 75% of patients with RA.[74] Symptoms of upper airways disease include hoarseness, sore throat, odynophagia, dysphagia, and globus.[4] Although the clinical importance of mild laryngoscopic changes are of uncertain significance, true cricoarytenoid arthritis can lead to life-threatening airway compromise – particularly in the setting of endotracheal intubation.[4] Less common upper airway complications include vocal cord paralysis (from involvement of the occipito-atlanto-axial joint with cervicomedullary compression), laryngeal rheumatoid nodules, secondary amyloidosis, and secondary SjS manifestations of xerostomia and xerotrachea.[4]

Lower airways

HRCT evidence of bronchiectasis is common; it has been noted in up to 58% of patients,[75] although the prevalence of clinically significant disease is considerably lower.[76] Symptoms (including dyspnea, cough, hemoptysis, and recurrent infections) and physiologic airway obstruction (including a reduced forced expiratory volume in 1 second [FEV_1], forced vital capacity [FVC], and forced expiratory flow 25%–75%) have been associated with its presence.[4] It is more common in long-standing RA, and fatalities from resultant recurrent infections and respiratory failure have been reported. Furthermore, the presence of bronchiectasis in a patient with RA being treated with anti-TNFα antagonist therapy may be an additional risk factor for the development of tuberculous and nontuberculous mycobacterial respiratory infection.

Similar to bronchiectasis, the prevalence of small airways inflammatory disease (bronchiolitis) in RA is unknown, but physiologic evidence of its presence occurs in 16% to 68% of patients.[77] HRCT seems to be more sensitive than pulmonary function

tests in its detection; in patients with RA with normal physiology, HRCT evidence of bronchiolitis (including air-trapping, heterogeneity in lung attenuation, and centrilobular nodules) has been reported in up to two-thirds of patients.[78] Symptomatic bronchiolitis classically presents with dyspnea and cough. Pulmonary physiology often reveals a reduced FEV_1, FEV_1/FVC ratio, and DL_{CO}; reduced airflow at low lung volumes; and an increased RV and RV/TLC ratio.[4] On surgical lung biopsy, either a cellular or fibrosing bronchiolar process is typically identified.[79] Cellular bronchiolar diseases include follicular bronchiolitis (more commonly) and, rarely, diffuse panbronchiolitis. Follicular bronchiolitis may be responsive to corticosteroids, whereas diffuse panbronchiolitis may respond to chronic macrolide therapy.[80] Fibrosing bronchiolar disease, termed obliterative bronchiolitis or constrictive bronchiolitis, is poorly responsive to immunomodulatory therapy and frequently leads to respiratory failure and death.[81]

Pleural Disease

Pleuritis and pleural effusions are common in men with established disease, high rheumatoid factor (RF) titers, and rheumatoid nodules.[4] Asymptomatic pleural effusion may be present in as many as 70% of patients, whereas symptomatic effusions occur in approximately 5%.[4] Because several other pleural diseases can occur in RA, including infection/empyema, sterile empyema, chylothorax, and malignancy, the cause of an unidentified effusion should be pursued. Biochemical characteristics of RA pleural effusions include (1) an exudative process; (2) a low pH (<7.3); (3) a decreased glucose level (<50% of the serum glucose level); (4) an elevated lactated dehydrogenase (>700 IU/L); and (5) an elevated RF titer.[4]

Parenchymal Disease

Rheumatoid nodules

Rheumatoid nodules are present in as many as 20% of patients with RA on HRCT and are the most common finding on surgical lung pathologic examination, occurring in as high as 33% of specimens.[82–84] Radiographically, they range in size from 1 millimeter to several centimeters. Multiple nodules may be present, and central cavitation occurs in approximately 50% of these lesions.[83,84] Histopathologically, these nodules comprise central fibrinoid necrosis with surrounding granulomatous inflammation. Although most often asymptomatic, they can result in symptoms secondary to complications (including pneumothorax, hydropneumothorax, and hemoptysis) and must be distinguished from infection and malignancy.[4,83,84]

Eosinophilic lung disease

Several case reports of eosinophilic pneumonia occurring in patients with RA have been published. Clinically, RA-associated eosinophilic pneumonia seems to be identical to idiopathic chronic eosinophilic pneumonia. The clinical features include fever, cough, dyspnea, weight loss, and a peripheral blood eosinophilia. Thoracic imaging demonstrates peripheral infiltrates, and bronchoalveolar lavage has an eosinophilic predominance.[4]

ILD

The reported prevalence of RA-associated fibrosing ILD (RA-ILD) varies significantly depending on the method of detection and the population examined. Using HRCT, ILD may be seen in more than 50% of all patients with RA.[4,32] However, clinically significant disease is less common and estimated to occur in approximately 10% of patients.[85] Unlike articular RA, which is more common in women, RA-ILD is more common in men.[4]

Although the nonspecific interstitial pneumonia NSIP pattern is the most common in the CTDs as a whole,[53] in RA, UIP seems to be the most common pattern.[53,86,87] Organizing pneumonia, DAD, lymphocytic interstitial pneumonia, and desquamative interstitial pneumonia histologic patterns have also been described. In patients with RA, DAD has been reported to occur both in those without preexisting ILD and in those with preexisting fibrotic ILD.[4] Recent studies have highlighted that ILD may be the first clinically apparent manifestation of RA and that patients without arthritis but with a positive anti-cyclic citrullinated peptide (anti-CCP) antibody and airways or parenchymal lung disease may represent a prearticular RA phenotype.[7,88]

SLE

SLE is the prototypic systemic autoimmune disorder, affects approximately 1 per 2000 persons, and occurs 6 times more often in women than in men.[4,89] It is characterized by autoantibody positivity and immune-mediated damage to virtually every organ system. Constitutional symptoms, serositis, mucocutaneous disease, musculoskeletal, renal, neurologic, and hematologic involvement are all common. Some form of pulmonary abnormality occurs in nearly all patients with SLE.[4,89]

Airways Disease

Laryngeal involvement in SLE is generally benign and includes laryngeal ulcerations, edema, and vocal cord paralysis, which is typically responsive to corticosteroid therapy. However, life-threatening airway complications including necrotizing vasculitis, subglottic stenosis, and epiglottis have been reported.[4,89] Although lower airways disease is identified on HRCT in approximately 20% of patients with SLE, clinically important airways disease is rare.[90,91] Bronchiolitis seems to occur more often in those with SLE along with secondary SjS.[72,89]

Pleural Disease

Pleuritis is the most common pulmonary manifestation of SLE. Pleuritic chest pain occurs in 35% to 60% of patients during the course of disease and may be the initial manifestation in 5% of patients.[72,89] Clinically evident pleural effusions are identified in nearly half of patients with pleurisy. Autopsy studies report pleural involvement in almost all and pleural effusions in approximately two-thirds of subjects. Pleural effusions are likely to be bilateral, small to moderate in size, and exudative. In comparison to RA, SLE effusions are more likely have a normal glucose and pH and lower lactated dehydrogenase levels. However, a diagnostic evaluation is indicated when a new effusion is seen because other causes must be excluded including infection (parapneumonic effusions/empyema), pulmonary embolism, and congestive heart failure. Symptomatic pleurisy typically responds to nonsteroid anti-inflammatory agents, and more severe disease may require immunosuppressive agents.[72,89]

Vascular Disease

Pulmonary hypertension may be the result of a primary vascular abnormality with histopathologic features similar to those in idiopathic PAH or SSc-PAH or as a result of a variety of cardiopulmonary disorders including ILD, thromboembolic disease, Libman-Sacks endocarditis, cardiomyopathy, diastolic dysfunction, or obstructive sleep apnea.[72]

Thromboembolic Disease

Antiphospholipid antibodies (aPL) are common in SLE, occurring in approximately one-third of patients. Their presence is associated with an increased risk of vascular thrombosis and fetal loss. In patients with SLE with aPL, the risk of thrombosis is approximately 6 times that of patients without aPL.[92] In addition to the thrombotic complications of disease including pulmonary emboli, aPL has been associated with PAH, diffuse alveolar hemorrhage (DAH), and DAD.[93]

Parenchymal Disease

Interstitial lung disease

Clinically significant ILD is less common in SLE than in the other CTDs. A longitudinal cohort study of 626 patients with SLE found that only 4% developed clinical or plain chest radiographic evidence of pulmonary fibrosis after a mean disease duration of 5.3 years. Like other CTDs-ILDs, the histologic patterns of SLE-associated ILDs mirror the patterns described for the idiopathic interstitial pneumonias, most commonly NSIP.[53,94]

DAH

DAH is one of the life-threatening pleuropulmonary manifestations of SLE. DAH is uncommon, occurring in less than 4% of tertiary hospital admissions for SLE, and is more likely to occur in patients with an established diagnosis of SLE.[95,96] At presentation, symptoms include the acute onset of dyspnea and cough, imaging studies may reveal new alveolar infiltrates, and laboratory data may confirm a declining hematocrit. The absence of hemoptysis should not exclude the diagnosis; approximately half of patients do not present with it, although it typically appears during the hospital course.[95,96] Further, the presence of hemoptysis in a patient with SLE does not always imply a diagnosis of DAH as it can occur in both pulmonary infections and acute lupus pneumonitis. Commonly patients with DAH will have evidence of active concurrent extrapulmonary disease with the most common being lupus nephritis.[95,96] The diagnosis can be confirmed with sequential bronchoalveolar lavage samples revealing an increasing red blood cell count.

The most common underlying histologic pattern on surgical lung biopsy is capillaritis, although patterns of both bland pulmonary hemorrhage and diffuse alveolar damage have been described.[95–97]

Acute lupus pneumonitis

The classically described clinical characteristics of acute lupus pneumonitis include the acute onset of fever, dyspnea/tachypnea, cough, and hypoxemia with radiographic evidence of bilateral patchy or diffuse infiltrates, typically with a basilar predominance and often resulting in acute respiratory failure.[4,89] The most frequent histologic pattern is DAD, although some have described a capillaritis. There has been debate about whether acute lupus pneumonitis is a distinct syndrome or whether it is actually representative of either diffuse alveolar hemorrhage (with or without capillaritis) or DAD/acute respiratory distress syndrome resulting from a specific cause (eg, infection).[4,89]

Shrinking lung syndrome

Shrinking lung syndrome (SLS) is a rare complication of SLE that results in unexplained dyspnea and restrictive physiology with low lung volumes in the absence of significant underlying pleuroparenchymal disease.[98] Although the cause of SLS is unknown, theories regarding its pathogenesis speculate about some degree of diaphragmatic dysfunction either caused by neuromuscular myopathy with respiratory muscle

weakness or limited diaphragmatic excursion caused by chronic pleural inflammation. The prognosis is favorable because most patients either improve or stabilize with therapy and death from SLS has rarely been reported.[98]

Syndrome of Acute Reversible Hypoxemia

The syndrome of acute reversible hypoxemia presents clinically with the acute onset of hypoxemia and a widened alveolar-arterial gradient with normal radiographic imaging studies. The pathophysiology of this syndrome is unknown, but one proposed mechanism is complement activation resulting in neutrophil aggregation within the pulmonary vasculature. A rapid and dramatic response to glucocorticoids is a characteristic finding in this syndrome[4,89]

PRIMARY SJÖGREN SYNDROME (SJS)

SjS is a systemic autoimmune disorder characterized by lymphocytic infiltration of the exocrine glands. The salivary and lacrimal glands are most often involved leading to the characteristic symptoms of disease including dry eyes (keratoconjuctivitis sicca) and dry mouth (xerostomia). The prevalence of primary SjS is estimated to be 0.5% to 1% in the population, whereas the prevalence of secondary SjS (ie, occurring in the setting of another CTD) is as high as 30%. Women are more commonly affected and most patients with SjS will have some form of pulmonary involvement.[4,99,100]

Airways Disease

Large airways

As many as 50% of patients with SjS develop a dry cough.[4] It is thought to result from xerotrachea – or desiccation of the tracheobronchial tree. Xerotrachea has been associated with reduced mucociliary clearance – which may result in obstructive physiology and predispose patients with SjS to recurrent infection and bronchiectasis.[4,100,101]

Small airways

Small airways disease, defined by the presence of reduced maximal expiratory flows at 25% and 50% of FVC, is the most common pulmonary abnormality, occurring in more than half of patients with SjS.[4] These physiologic abnormalities are typically mild and tend to remain stable. Histopathology studies of lung tissue from patients with SjS with more severe obstructive lung disease have revealed evidence of lymphocytic or follicular bronchiolitis.[102,103]

Pleural and pulmonary vascular disease complications are quite rare in patients with primary SjS and their presence should highlight the need for evaluation of alternative causes.

ILD

Clinically significant ILD is estimated to occur in 8% to 38% of patients with SjSs (**Fig. 3**).[4,104] A higher proportion of patients have subclinical ILD.[32] The most common histopathologic pattern identified in SjS is NSIP, but it is not uncommon to find the lung injury patterns of lymphocytic interstitial pneumonia, OP, or UIP in patients with SjS.[102,103,105]

Non-Hodgkin Lymphoma and Other Malignancies

The most serious complication of SjS is non-Hodgkin lymphoma (NHL): 1 in 5 SjS deaths are attributable to this malignancy.[4,106,107] The risk of NHL in SjS has been reported to be 16 to 44 times higher than matched control populations, with an estimated lifetime risk of 5% to 10%. Risk factors for the development of NHL include

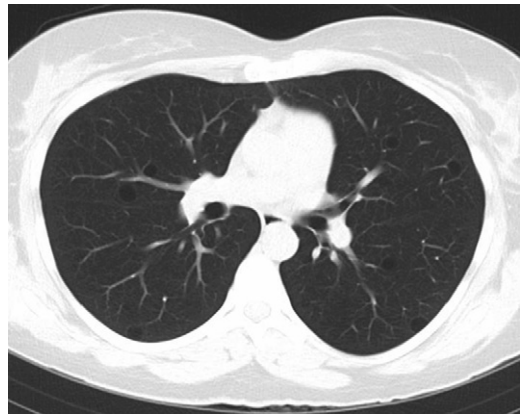

Fig. 3. HRCT image of a patient with primary SjS. This patient had the incidental finding of subclinical cystic lung disease most suggestive lymphocytic interstitial pneumonia.

a decreased CD4+/CD8$^+$ T-lymphocyte ratio, hypocomplementemia, and vasculitis of the skin. It arises most often in the salivary glands, but lymph nodes, bone marrow, solid organs (including the spleen, liver, and kidney), and mucosal sites including the stomach, skin, and lung are all at risk.[4,106,107] In patients with systemic NHL, lung involvement is estimated to occur in approximately 20%.[4,106,107]

MCTD

MCTD is a specific CTD that often resembles either SSc or SLE. It is characterized clinically by SLE or SSc-type symptoms but is distinguished from these and other CTDs by its serologic profile of a positive ANA along with an isolated positive anti-ribonucleoprotein antibody.[108,109] This means that patients are not classified as having MCTD if other autoantibodies are present along with the ribonucleoprotein antibody (eg, RF, anti-Smith, anti-dsDNA, anti-SSA, or anti-SSB). MCTD is often associated with similar pulmonary manifestations as SSc and these patients are thus incorporated into the concept of representing a "scleroderma spectrum" of disease. Practically speaking, patients with MCTD have similar pulmonary manifestations as SSc and as such require heightened surveillance for clinically significant ILD and recommended to undergo PAH screening similar to those with SSc.[46]

SUGGESTIVE FORMS OF CTD-ILD

Undifferentiated CTD

In addition to well-characterized forms of CTD, it is common to encounter patients who have partial or incomplete forms of CTD and these cases are often considered to have UCTD (**Table 2**).[110,111] UCTD has been generally defined as a condition manifesting with signs and symptoms suggestive of a CTD, along with ANA positivity, but not fulfilling existing rheumatologic classification criteria for any specific CTD.[110,111] Mosca and colleagues[110,111] have reported that about 60% of patients with UCTD will remain undifferentiated, and that when evolution to defined CTD occurs, it usually does so within the first 5 years of disease. UCTD may evolve into any of the CTDs but most often evolves into SLE. Patients with UCTD who do not develop a characterizable CTD are considered to have a mild clinical picture – or "stable" UCTD – characterized by the presence of arthralgias or arthritis, Raynaud phenomenon, leukopenia, anemia,

and dry eyes or dry mouth. An important distinguishing characteristic of UCTD is that *no major organ involvement* (eg, lung disease) has been described.[110–114]

A recent expert review on UCTD distinguishes "monosymptomatic UCTD" composed of single organ-dominant diseases (eg, ILD) that do not fulfill specific CTD criteria from that of stable, mild "oligosymptomatic UCTD."[111] The authors acknowledge that the concept of UCTD includes a wide spectrum of diseases ranging from "organ-dominant" conditions to "stable UCTD" to early CTDs or mild forms of CTDs.[111] They suggest that only persistently oligosymptomatic conditions–and not "organ dominant" disease–be classified as "UCTD." Mosca and colleagues[111] have proposed the following preliminary classification criteria for UCTD: (i) signs and symptoms suggestive of a CTD, but not fulfilling criteria for defined CTDs, (ii) positive ANAs, and (iii) a disease duration of at least 3 years.

The concept of UCTD has been of interest within the ILD community as well. In 2007, Kinder and colleagues[115] proposed a broader and less specific set of UCTD criteria and applied these criteria to a cohort of patients with idiopathic interstitial pneumonia (IIP). Retrospectively, they identified 28 subjects with an IIP who met their proposed criteria for UCTD and compared these subjects with a control group of 47 subjects with an IIP that did not meet their criteria. Interestingly, those whom they defined as having UCTD were more likely to be female, younger, and nonsmokers and were more likely to have ground-glass opacities on HRCT and NSIP on surgical lung biopsy. In all, 88% of those with idiopathic NSIP met their definition for UCTD and led the authors to conclude that most patients previously classified as having idiopathic NSIP have clinical, serologic, radiographic, and pathologic characteristics of autoimmune disease, and they proposed that idiopathic NSIP is the lung manifestation of UCTD.[115] The accompanying editorial pointed out several limitations of the Kinder study and argued against accepting the conclusion that idiopathic NSIP is UCTD.[116] Corte and colleagues[117] also recently called into question the clinical relevance of defining ILD patients as having UCTD and specifically called into question the application of the broader, less-specific UCTD criteria proposed by Kinder and colleagues. They retrospectively studied 45 patients with biopsy-proved NSIP and 56 patients with biopsy-proved UIP. They reported that CTD features are common in patients with IIP, with 31% of patients with NSIP and 13% of patients with IPF fulfilling the stricter, more traditional criteria for UCTD. However, when the broader, less specific, criteria of Kinder and colelagues for UCTD was applied, an astounding 71% of patients with NSIP and 36% of patients with IPF could be reclassified as having UCTD. Because of its lack of specificity, these and other authors have argued against further implementation of the Kinder set of criteria to define UCTD in patients with ILD.[1,10,117]

"Autoimmune-Featured ILD"

Vij and colleagues[118] have described a cohort of UIP-predominant ILD patients retrospectively identified as having a possible form of CTD-ILD (see **Table 2**). Among 200 patients who presented to an ILD referral center, 63 were considered to have "autoimmune- featured ILD" if they had a sign or symptom suggestive of a CTD, but with insufficient features to label as definite CTD, and a serologic test reflective of an autoimmune process. The cohort that met their case definition of autoimmune-featured ILD had a similar demographic profile as IPF: most were older (average age of 66 years) and male. The most common clinical symptoms in the autoimmune-featured ILD cohort were nonspecific symptoms of dry eyes or dry mouth (57%) and gastroesophageal reflux disease (44%). Seventy-five percent of those that met their case definition for autoimmune-featured ILD had a lung injury pattern of UIP. Finally, the survival of

Table 2
Proposed criteria for categories of suggestive forms of CTD-ILD

Proposed Category	Clinical Features	Laboratory or Histopathologic Findings
Undifferentiated CTD (stricter definition) (requires at least 1 clinical feature and 1 laboratory finding)	One or more of the following symptoms: Dry eyes or dry mouth, joint pain or swelling Raynaud phenomenon Proximal muscle weakness Morning stiffness	One or more of these autoantibodies: ANA (*high* titer) RF (high titer) Anti-Smith Anti-ribonucleoprotein Anti–double-strand DNA Anti-Ro Anti-La Anti–Jo-1 Anti-topoisomerase (Scl-70) Anti-centromere
Undifferentiated CTD (broader definition) (requires at least 1 clinical feature and 1 laboratory finding)	One or more of the following symptoms: Dry eyes or dry mouth Gastroesophageal reflux disease Weight loss Recurrent unexplained fever Joint pain or swelling Rash Photosensitivity Dysphagia Nonandrogenic alopecia Mouth ulcers Raynaud phenomenon Morning stiffness Proximal muscle weakness	One or more of these laboratory abnormalities: ANA (*any* titer) RF Anti-Ro Anti-La Anti–Jo-1 Anti-topoisomerase (Scl-70) Erythrocyte sedimentation rate (2× normal) C-reactive protein elevation
Lung-dominant CTD (requires all 3 listed clinical features and either 4a or 4b)	All of the following features: 1. NSIP, UIP, lymphocytic interstitial pneumonia, OP, DAD (or desquamative interstitial pneumonia if no smoking history), as determined by surgical lung biopsy or suggested by HRCT *and*	4a. Any *1* of these autoantibodies ANA >1:320 titer RF >60 IU/mL Anti–nucleolar ANA (any titer) Anti-centromere Anti-CCP

	2. Insufficient extrathoracic features of a definite CTD *and* 3. No identifiable alternative cause of IP *and*	Anti-Ro Anti-La Anti–double-strand DNA Anti-ribonucleoprotein Anti-Smith Anti-topoisomerase (Scl-70) Anti–transfer RNA synthetase Anti–PM-Scl 4b. *OR at least 2* of these histopathologic features: Lymphoid aggregates with germinal centers Extensive pleuritis Prominent plasmacytic infiltration Dense perivascular collagen
Autoimmune-featured ILD (requires at least 1 clinical feature and 1 laboratory finding)	One or more of the following symptoms: Dry eyes or dry mouth Gastroesophageal reflux disease Weight loss Foot or leg swelling Joint pain or swelling Rash Photosensitivity Dysphagia Hand ulcers Mouth ulcers Raynaud phenomenon Morning stiffness Proximal muscle weakness	One or more of these laboratory abnormalities: ANA $\geq$1:160 titer RF Anti-Ro Anti-La Anti-Smith Anti-ribonucleoprotein Anti-dsDNA Anti-topoisomerase (Scl-70) Anti-CCP Anti–Jo-1 Aldolase Creatine phosphokinase

Data from Fischer A, du Bois R. Interstitial lung disease in connective tissue disorders. Lancet 2012;380(9842):689–98.

those with autoimmune-featured ILD was similar to those with IPF and worse compared with CTD-ILD.[118] Arguing against the inclusion of nonspecific symptoms in the proposed criteria, only the presence of an ANA at greater than 1:1280 titer was associated with improved survival.

"Lung-Dominant CTD"

Fischer and colleagues[10] proposed a set of provisional classification criteria to define the cohort of individuals with suggestive forms of CTD-ILD as having "lung-dominant CTD" (LD-CTD) (see **Table 2**). A classification of LD-CTD would be reserved for those patients in whom the ILD has a "rheumatologic flavor" as supported by specific autoantibodies or histopathologic features and yet does not meet criteria for a defined CTD based on the lack of adequate extrapulmonary features to confer a diagnosis of definite CTD-ILD. The authors argued that implicit with the concept of LD-CTD is the recognition that specific autoantibodies and/or histopathologic features alone can be sufficient to classify a patient as having CTD-ILD.[10] The presence of objective extrapulmonary features highly suggestive of CTD (eg, Raynaud phenomenon, inflammatory arthritis) are important and will lend further support for an underlying CTD, but their absence should not preclude a classification of LD-CTD. The authors emphasized that their intent was that the concept of LD-CTD and the associated criteria should be viewed as provisional, and that they might serve as a platform for further multidisciplinary, multicenter investigations, including validation via prospective study.[10]

Several potential advantages to the introduction of this novel classification were suggested: (1) The criteria offered are objective and measurable. (2) Nonspecific symptoms (eg, dry eyes, myalgias, arthralgias, or gastroesophageal reflux disease), nonspecific inflammatory markers (eg, erythrocyte sedimentation rate or C-reactive protein), and low-titer ANA or RF are not included because of their high prevalence in patients without CTD. (3) Surveillance for evolution to characterizable forms of CTD is encouraged. (4) The diagnosis isolates them from the (default) category of IIP and provides a framework by which questions regarding this subset's natural history, pathobiology, treatment, and prognosis can be answered. (5) The classification allows their distinction from well-characterized forms of CTD, without attempting to redefine existing CTD categories (eg, UCTD).[10]

SUMMARY

The CTDs represent a heterogeneous spectrum of systemic autoimmune diseases and the lungs are a frequent target of autoimmune-mediated organ damage. Any of the lung compartments are at risk of injury, and multicompartment lung involvement is a frequent finding in the CTDs. The intersection of ILD and CTD is particularly complex: ILD may be present in subclinical forms, may be chronic and slowly progressive in nature, or may present as an acute, fulminant disorder. ILD is known to occur within a context of preexisting CTD, can be the presenting manifestation of a CTD, or can be identified in patients who have suggestive features of a CTD. The clinical care of patients with CTD is often enhanced by an understanding of these complex interactions and a multidisciplinary approach to evaluation and management.

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