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Thoracic Manifestations of Connective Tissue Diseases

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Connective tissue diseases (CTDs) are a common cause of chronic lung disease, and lung involvement, which can be the initial site of disease, is a major contributor to CTD-related morbidity and mortality. A variety of patterns of acute and chronic lung diseases are associated with CTD including diffuse alveolar damage, organizing pneumonia, diffuse alveolar hemorrhage, usual interstitial pneumonia, nonspecific interstitial pneumonia, and lymphoid interstitial pneumonia. Patients with CTD are also at increased risk for respiratory tract infection and treatment-related complications such as drug-induced lung injury. Radiologists should be familiar with the thoracic manifestation of CTDs so as to identify complications as well as suggest the possibility that CTD may be the underlying cause of lung disease. This article reviews the defined CTDs and describes and illustrates their associated radiographic and computed tomography findings.
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Introduction

The heterogeneous group of connective tissue diseases (CTDs), or collagen-vascular diseases, is a common cause of chronic lung disease. CTDs are systemic inflammatory conditions associated with circulating autoantibodies, which result in immune-mediated damage to tissues (Table 1). Rheumatoid arthritis (RA), systemic sclerosis (SSc), mixed CTD (MCTD), polymyositis (PM)/dermatomyositis (DM), and systemic lupus erythematosus (SLE) are the defined CTDs. Interstitial pneumonia with autoimmune features (IPAF) is now the preferred term to describe patients with diffuse lung disease and features of CTD who do not fulfill established criteria for the defined CTDs.[1]

Diffuse or interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH) are the most common manifestations of CTD in the lungs and account for substantial morbidity and mortality in patients with CTD.[2,3] Lung involvement may develop after a diagnosis of CTD is established or may be the presenting feature.[4,5] The lungs are commonly affected in all defined CTDs, and multicompartmental lung involvement is frequent. The extent and patterns of injury vary depending on the underlying CTD (Tables 2 and 3).[6,7]

Imaging

Chest radiography is often the initial imaging examination performed to evaluate patients with known or suspected lung involvement with CTD.[2] High-quality posteroanterior and lateral projections can show features of CTD including lung fibrosis, pulmonary hypertension, pleural effusion, and skeletal abnormalities.

High-resolution computed tomography (HRCT) is often performed to better evaluate lung findings detected on chest radiography or to assess for earlier manifestations of CTD not readily apparent on chest radiographs.[8] HRCT is ideally performed with a helical volumetric scan through the chest during end inspiration, extending from the thoracic through the diaphragm. Images should be reconstructed with both smooth (for soft tissue) and sharp (for lungs and bones) convolution kernels. Multiplanar reformations can aid in showing distribution of disease. Sequential expiratory images can help identify air trapping as a manifestation of small airways disease, and prone imaging can help distinguish dependent atelectasis from early lung involvement in suspected fibrosis.

Pulmonary magnetic resonance angiography and cardiac magnetic resonance imaging can be used to evaluate patients

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Table 1 Autoantibodies in CTDs

Autoantibody	CTD
ANA	Various CTDs (SLE, SSc, SS, PM/DM) Nucleolar staining suggests SSc
Anti-dsDNA	SLE
Anti-Ro	SLE, SS
Anti-La	SS, SLE
Anti-topoisomerase I (anti−Scl-70)	SSc
RF	RA, SS
Anti-CCP	RA
Anti-RNP	MCTD
Anti-tRNA synthetases (Jo-1, MDA-5)	PM/DM/ antisynthetase syndrome

Abbreviations: ANA, antinuclear antibody; CCP, cyclic citrullinated peptide; dsDNA, double-stranded DNA; MCTD, mixed connective tissue disease; PM/DM, polymyositis/ dermatomyositis; RA, rheumatoid arthritis; RF, rheumatoid factor; RNP, ribonucleoprotein; SLE, systemic lupus erythematosus; SS, Sjögren syndrome; SSc, systemic sclerosis.

with CTD and suspected pulmonary arterial and pericardial involvement.[9,10]

Patterns of Lung Injury

Organizing Pneumonia

Organizing pneumonia (OP) is a common response of the lung to a variety of injuries including infection, drug toxicity, and CTDs. OP is characterized histopathologically by plugs of granulation tissue including fibroblasts, myofibroblasts, and loose connective tissue. Inflammatory cells can be present, especially in the more acute phase of lung injury.[11,12]

The characteristic HRCT findings of OP include discrete areas of consolidation, ground-glass opacity, or both in a peripheral and peribronchial distribution (Table 4). Additionally, arcading foci of perilobular thickening can be present. Discrete foci of normal or ground-glass attenuation lung surrounded by a rim of consolidation are hallmarks of OP and are referred to as atoll or reversed halo signs. Air bronchograms are typically present in areas of consolidation, and the affected airways can be transiently dilated. Areas of OP can be transient or can wax and wane depending on underlying disease activity.[6,13]

OP can occur with any CTD but most commonly with PM and DM (Table 3).[14,15] It may be the presenting manifestation of myositis. Complicating matters is the fact that OP is also a common manifestation of drug reaction, and distinguishing drug-induced OP from CTD-associated OP can be challenging. Many patients will respond to therapy with corticosteroids, although ongoing lung injury can lead to pulmonary fibrosis.[16,17]

Nonspecific Interstitial Pneumonia

Nonspecific interstitial pneumonia (NSIP) is often associated with CTD and the most common pattern of lung injury in these patients. As with OP, NSIP may be the initial manifestation of CTD. NSIP occurs most often in SSc, MCTD, and PM/DM (Table 3).[14,15]

NSIP is a pattern of chronic lung injury characterized by spatially and temporally homogenous deposition of collagen into the alveolar walls with preservation of alveolar architecture. Associated mild-to-moderate interstitial inflammation can be present. Because OP may be the initial injury leading to NSIP in some patients, mixed patterns of NSIP and OP can be observed.[18]

HRCT findings of NSIP are variable and range from basal predominant ground-glass opacity to more extensive basal predominant fibrosis characterized by reticulation, traction bronchiectasis and bronchiolectasis, and lower lobe volume loss (Table 4). Relative subpleural sparing, present in up to 65% of patients, is highly suggestive of an NSIP pattern. Subpleural honeycombing is uncommon and is associated with more advanced lung injury.[19-21]

Usual Interstitial Pneumonia

Most patients with a usual interstitial pneumonia (UIP) pattern of lung injury have no known cause for their disease and are

Table 2 Most Common Patterns of Thoracic Involvement in Connective Tissue Diseases

Pattern	RA	SLE	SSc	MCTD	PM/DM	SS
ILD overall	++	+	+++	++	+++	++
PAH		+	+++	++	+	+++
Large airways	+++Cricoarytenoid arthritis	+	+	+	+	
Small airways	+++Both constrictive bronchiolitis and follicular bronchiolitis	+	+	+	+	+
Pleura	+++Most commonly affected, but often asymptomatic	+++	+	+	+	++
Other	+ Necrobiotic nodules	Rarely: DAH, Shrinking lung syndrome	+++Esophageal involvement	++Esophageal involvement	Aspiration Hypoventilation	Increased risk of lymphoma

Abbreviations: ILD, interstitial lung disease; PAH, pulmonary arterial hypertension; DAH, diffuse alveolar hemorrhage.

Table 3 Relative Prevalence of ILD in Connective Tissue Diseases

ILD Pattern	RA	SLE	SSc	MCTD	PM/DM	SS
ILD overall	++	+	+++	++	+++	++
NSIP	++	++	+++	++	+++	+++
UIP	+++	+	+	+	+	+
OP	++	+	+	+	+++	-
LIP	+	+	-	-	-	++
Common patterns	UIP > NSIP = OP > LIP	NSIP > UIP > LIP = OP	NSIP > UIP	NSIP > OP = UIP	NSIP = OP > UIP	NSIP > LIP > UIP

Abbreviations: LIP, lymphoid interstitial pneumonia; NSIP, nonspecific interstitial pneumonia; OP, organizing pneumonia; UIP, usual interstitial pneumonia.

diagnosed as having idiopathic pulmonary fibrosis (IPF). However, UIP can develop in patients with CTD, most commonly RA.[22] Cigarette smoking is major risk factor for UIP.[23]

UIP is well-defined histopathologic pattern of lung injury and is characterized by a pattern of spatial and temporarily heterogeneously abnormal lung with fibrosis intermixed with normal lung. Fibrosis is primarily located in the periphery of the secondary lobules. Fibroblastic foci are an important finding in UIP and consist of fibroblasts and myofibroblasts covered by type II pneumocytes or squamous metaplastic epithelium. Microscopic honeycomb changes can be present and consist of aggregates of cystic spaces surrounded fibrosis and often lined by columnar epithelium. Microscopic honeycombing is occult on HRCT, as the cysts are below the resolution of computed tomography (CT) and they are often filled with mucus or proteinaceous fluid.[24,25]

The characteristic findings of UIP on HRCT are subpleural and basal predominant reticulation with honeycombing. Traction bronchiectasis and architectural distortion are often present (Table 4). Findings of UIP on HRCT are irreversible and usually progress.[26] UIP carries a poor prognosis and differentiation from NSIP is important. Straight-edge sign describes fibrosis in the lung bases, sharply demarcated from the upper not involved lung (Fig. 1). Absence of this sign bilaterally is strongly associated with pathologic pattern of UIP.[27]

Desquamative Interstitial Pneumonia

Desquamative interstitial pneumonia (DIP) is rare pattern of chronic interstitial pneumonia characterized by the accumulation of pigmented macrophages throughout the lung. Alveolar architecture is preserved. Mild interstitial thickening and mild chronic inflammation may be present. DIP is considered by most authors to be part of the spectrum that includes respiratory bronchiolitis, where accumulation of pigmented macrophages occurs primarily in and around the respiratory bronchioles. Respiratory bronchiolitis and DIP comprise smoking-related diffuse lung disease, but DIP has been reported in patients with CTDs independent of smoking.[21,23]

HRCT features of DIP are variable but consistent primarily of ground-glass opacity and mild reticulation. The distribution is most commonly basal and peripheral predominant with only up to 20% of patients having a more diffuse distribution.[28] Overlap between HRCT findings of NSIP and DIP is considerable.[29,30]

Lymphoid Interstitial Pneumonia

Lymphoid interstitial pneumonia (LIP), although classified as a rare idiopathic interstitial pneumonia, is considered a lymphoproliferative disorder associated with CTD and immunodeficiency syndromes. It most commonly develops in patients with Sjögren syndrome (SS) but can occur in patients with RA and SLE (Table 3).[31-33]

Table 4 Typical HRCT Findings for Different Patterns

ILD Pattern	Typical
NSIP	Bilateral basal-predominant ground-glass opacities in peribronchovascular distribution with or without subpleural sparing. Reticulation and traction bronchiectasis can be seen with fibrotic NSIP. Honeycombing is rare.
UIP	Peripheral and basal-predominant reticulation with traction bronchiectasis/ bronchiolectasis. Architectural distortion, honeycombing, and volume loss in advanced disease.
OP	Areas of GGO or consolidation in basal distribution with peripheral or peribronchovascular predominance. Reverse halo sign (atoll sign) can be seen.
LIP	Ground-glass opacities with scattered thin-walled cysts, primarily in a perivascular distribution. Reticulation and nodules may occur.

Abbreviations: LIP, lymphoid interstitial pneumonia; NSIP, nonspecific interstitial pneumonia; OP, organizing pneumonia; UIP, usual interstitial pneumonia.

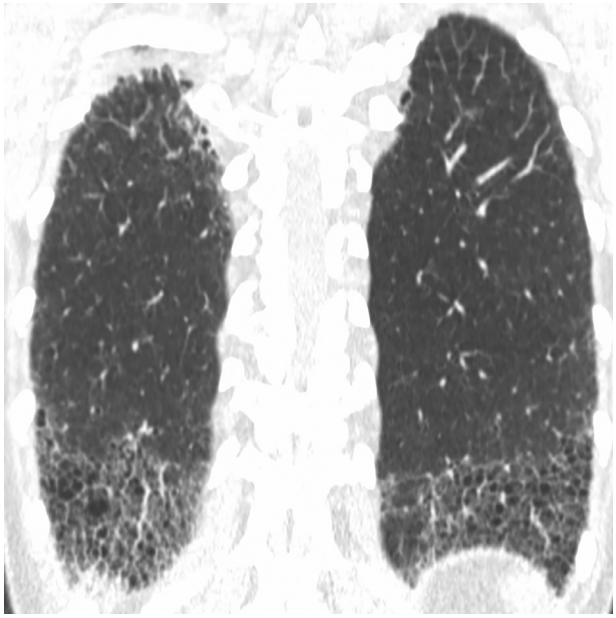

Figure 1 A 51-year-old male with RA and UIP. Coronal reformatted HRCT image shows basal predominant reticulation and honeycombing. The relatively horizontal interface between abnormal and normal lungs has been described as the "straight-edge sign." RA, rheumatoid arthritis; UIP, usual interstitial pneumonia.

LIP can have a similar histopathologic appearance to NSIP in some cases. However, with LIP, there is a distinct expansion and infiltration of the interstitium by lymphocytes and plasma cells.[18]

HRCT findings of LIP are quite variable and can overlap with those of NSIP and DIP. Common findings include basal predominant ground-glass opacity and thin-walled cysts (Table 4). The cysts associated with LIP are often associated with pulmonary blood vessels and are more variable in size compared to the diffuse cysts of lymphangioleiomyomatosis. Nodules reflecting nodular lymphoid hyperplasia or amyloid deposits can also be present.[34,35]

Defined Collagen Vascular Diseases

Rheumatoid Arthritis

RA is the most common CTD, affecting 1% of the population worldwide and approximately 1.5 million people in the U.S. RA predominantly affects patients between 30 and 60 years of age and is more common in females (female:male = 3:1); however, pulmonary involvement more commonly occurs in males.[36]

Lung abnormalities are present in 50%-70% CT in RA patients.[37] More recently, some authors proposed that the lung is an initial site of developing autoimmunity in RA.[38,39] Pulmonary complications are directly responsible for 10%-20% of all mortality.[40,41] RA can directly affect the lung parenchyma, airways, and the pleura.[42] Pulmonary infection and drug toxicity are frequent complications of RA.[43] Risk factors for developing lung disease include smoking, elevated rheumatoid factor titers, and seropositivity for anticyclic citrullinated peptide.[44]

The most common manifestation of RA is pleural disease. Pleural effusion develops in 5% of patients and is usually small and unilateral. Patients can be asymptomatic, and effusions can spontaneously resolve. However, on autopsy pleural effusion or thickening is found in 38%-73% of RA patients (Fig. 2).[45]

Airway involvement is very common in RA and includes constrictive bronchiolitis (also known as obliterative bronchiolitis), follicular bronchiolitis, and bronchiectasis. Symptoms or pulmonary function test abnormalities occur in 16%-68% of patients.[46] CT can show lung hyperinflation, mosaic attenuation on inspiratory images with air trapping on expiratory images, bronchial dilation, and bronchial wall thickening.[47] Prognosis for RA-associated constrictive bronchiolitis is variable, with some patients remaining stable while others have rapid decline with ensuing death.[48,49] The severity and progression of disease is not always concordant with articular involvement.[47] Follicular bronchiolitis is characterized by hyperplasia of bronchus-associated lymphoid tissue. On HRCT this manifests as centrilobular ground-glass attenuation nodules (Fig. 3).

Clinically significant RA-ILD occurs in approximately 10% of the RA population.[50] Mortality among RA patients with RA-ILD is increased by a factor of 3.[51] While, an NSIP pattern of lung disease is most common for other CTDs, a UIP pattern is the most common in patients with RA (Fig. 4), followed by NSIP and OP (Fig. 5; Table 3). Rarely LIP and DIP can occur (Fig. 6).[52-54] In general, CTD-associated ILD has better prognosis compared to idiopathic ILD: however, biopsy proven UIP in RA carries as poor prognosis as patients with IPF.[22] A study by Kim et al[53] showed that UIP pattern was present in 24% of RA patients (20/82) with median survival of 3.2 years, similar to patients with IPF. Female sex

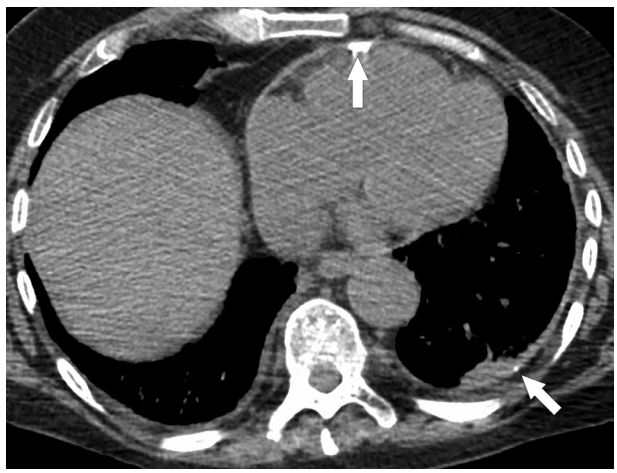

Figure 2 A 70-year-old male with longstanding serositis related to RA. Unenhanced CT image shows thickening and calcification (*arrows*) of the pericardium and left pleura. RA, rheumatoid arthritis.

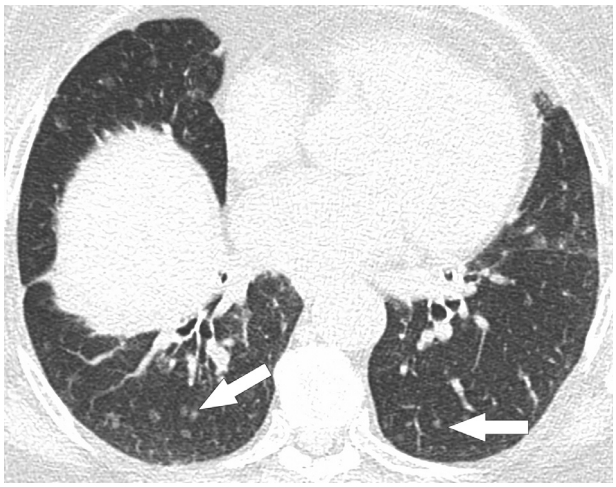

Figure 3 A 43-year-old female with RA and follicular bronchiolitis. HRCT images show poorly defined centrilobular ground-glass attenuation nodules (arrows). Courtesy of Arlene Sirajuddin, M.D. (Bethesda, MD). RA, rheumatoid arthritis.

and higher baseline diffusion capacity of carbon monoxide (DLCO) were associated with a better prognosis. Patients with a non-UIP pattern of lung disease had significantly better prognosis (median survival of 6.6 years). Of note, there is no definitive correlation between joint involvement and progression of lung disease.[55] Emphysema on CT has been reported in 27% of RA-ILD never-smokers and is independently associated with a definite UIP pattern on CT and a worsened outcome following adjustment for baseline disease severity.[56]

Another lung finding classically associated with RA is necrobiotic nodules (Fig. 7). These are typically asymptomatic and relatively uncommon on imaging (up to 5%), however, can be present in up to 32% of RA patients on biopsy.[57-59] The nodules vary in size from 5 to 50 mm, may be cavitary, and are typically located in the periphery of the mid and upper lungs. The nodules are typically asymptomatic, some of them may decrease in size spontaneously or with therapy (eg, rituximab).[60] Other nodules may grow, posing a diagnostic challenge, and biopsy may be necessary in some

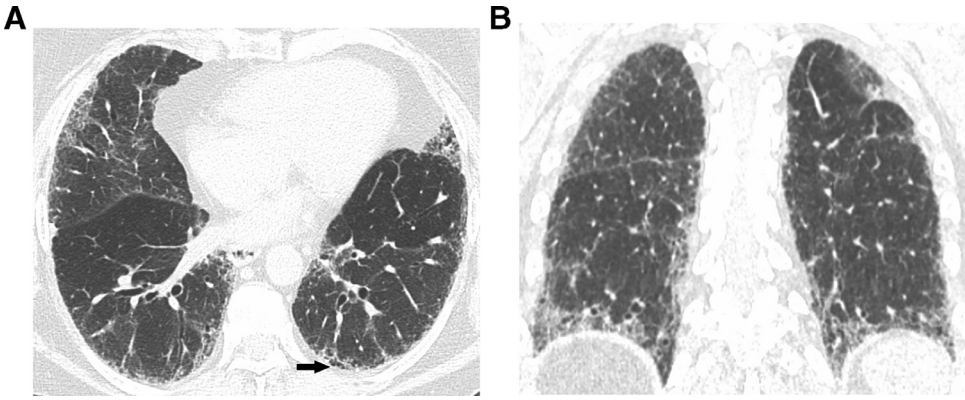

Figure 4 A 65-year-old female with rheumatoid arthritis and UIP. Axial (A) and coronal reformatted (B) HRCT images show subpleural and basal predominant reticulation with minimal honeycombing (*arrow*). UIP, usual interstitial pneumonia.

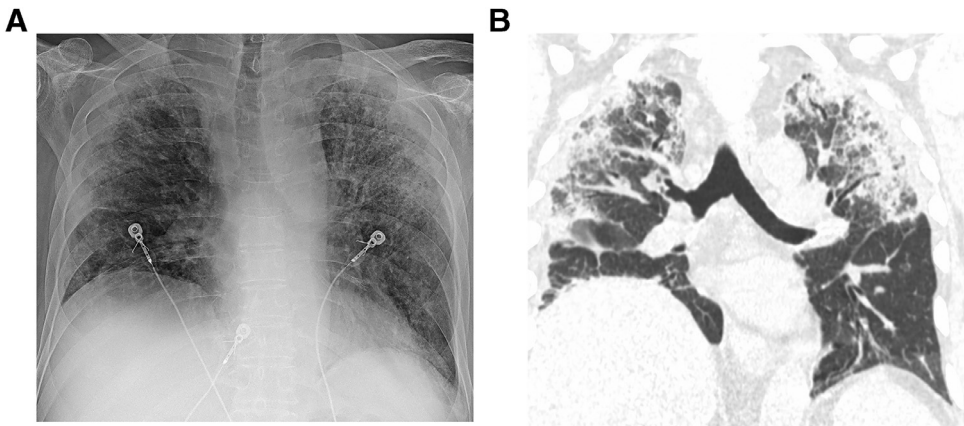

Figure 5 A 75-year-old male with rheumatoid arthritis and shortness of breath from organizing pneumonia. (A) Frontal radiograph shows upper lung predominant peripheral consolidation. (B) Coronal reformatted HRCT image shows identical findings. The differential diagnosis includes chronic eosinophilic pneumonia. Pleuropulmonary fibroelastosis could be considered if more upper lobe volume loss were present.

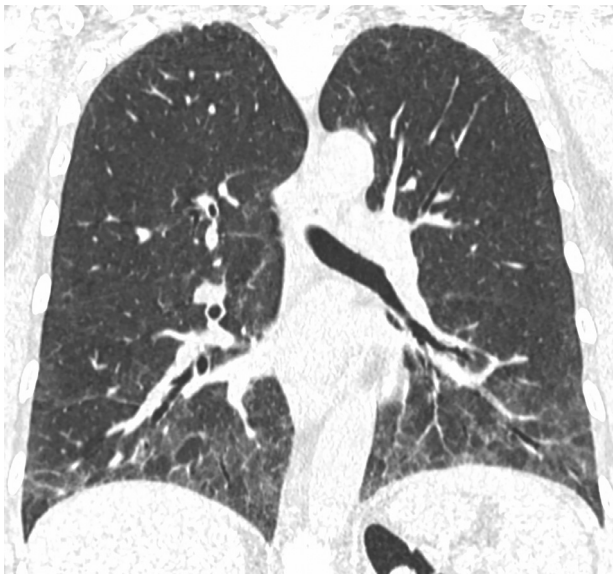

Figure 6 A 57-year-old female with RA and LIP. Coronal reformatted HRCT image shows basal predominant ground-glass opacity. The differential diagnosis would include NSIP and DIP. DIP, desquamative interstitial pneumonia; LIP, lymphoid interstitial pneumonia; RA, rheumatoid arthritis.

cases.[61] Rarely, rupture into the pleural space can lead to pneumothorax, pleural effusion, or empyema. Histopathologically, rheumatoid nodules have fibrinoid necrosis and granulomatous inflammation, similar to the subcutaneous nodules seen in RA.[59,62]

Vascular involvement by RA, including pulmonary RA-related vasculitis, is extremely rare.

Systemic Lupus Erythematosus

SLE affects mostly premenopausal females (female: male = 9:1) and is 6 times more common in African-Americans. The diagnosis of SLE can be difficult to establish because of the variety clinical manifestation, variable involvement of different organ systems, and an array of laboratory abnormalities.

The most common thoracic manifestation of SLE is pleural disease affecting up to 50% of patients.[63,64] Pleural effusion is typically small and can be unilateral or bilateral. Pericardial effusion and cardiomegaly occur in up to 35% of patients (Fig. 8). Pleuritic chest pain, pleural effusion, cough, shortness of breath, and fever are often presenting symptoms eventually leading to the diagnosis.

Similar symptoms, sometimes with associated hypoxia, can be seen in acute lupus pneumonitis, which occurs in 14% of patients with SLE and can also be a presenting manifestation.[65] The CT findings of acute lupus pneumonitis are identical to those of other acute lung injuries and include patchy consolidation or ground-glass opacity similar to OP or alveolar damage (Fig. 9). Pleural effusion is sometimes present. Mortality in acute lupus pneumonitis reaches 50%, and half of surviving patients develop chronic lung abnormalities.[65,66] The differential diagnosis primarily includes infection and drug toxicity.

In addition to infection and pneumonitis, acutely ill patients with SLE and respiratory symptoms should be evaluated for diffuse alveolar hemorrhage (DAH) keeping in mind that hemoptysis is not always present.[67] This is a rare (prevalence 2%-5%) but life-threatening complication of SLE with mortality of approximately 50%.[68] Radiographs show new bilateral lung opacities, corresponding to predominantly

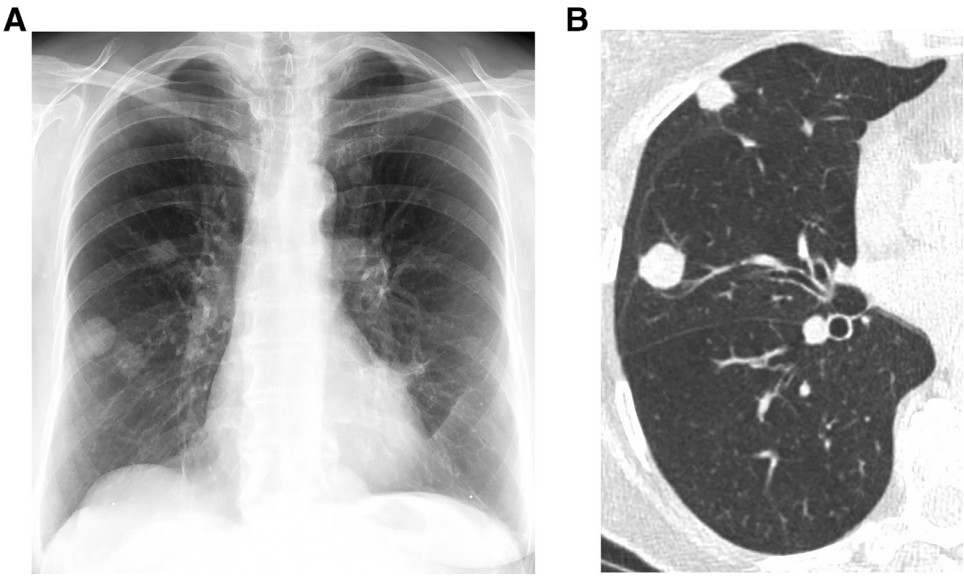

Figure 7 A 47-year-old female with slowly growing rheumatoid necrobiotic nodules. PA radiograph (A) and HRCT image (B) show multiple large well-defined nodules. PA, posteroanterior.

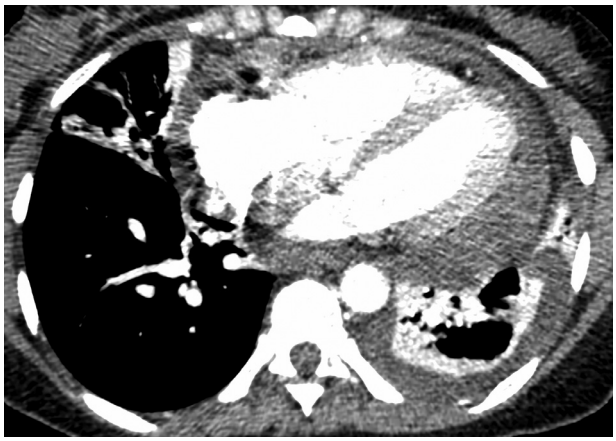

Figure 8 A 26-year-old female with SLE and chest pain. CT pulmonary angiogram shows pericardial and left pleural effusions. SLE, systemic lupus erythematosus.

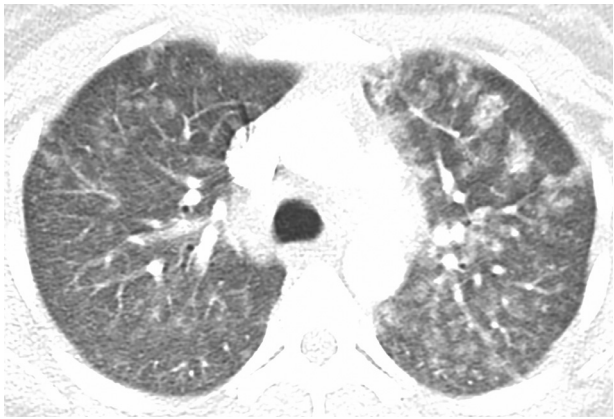

Figure 9 Female with SLE and acute lupus pneumonitis. CT image shows nodular foci of ground-glass opacity in both lungs. Courtesy of Howard Mann, M.D. (Salt Lake City, UT). SLE, systemic lupus erythematosus.

central consolidation and ground-glass opacities, with associated interlobular septal thickening on CT. Bronchoalveolar lavage can confirm the diagnosis and exclude infection.

Shrinking lung syndrome (SLS) occurs in about 1% of SLE patients and is characterized by progressive dyspnea, pleuritic chest pain, and progressive loss of lung volume without underlying lung fibrosis or pleural disease. The exact pathophysiology of SLS is unclear, but several mechanisms have been suggested including myopathy causing weakness of the diaphragm and respiratory muscles, diffuse diaphragm fibrosis, phrenic nerve palsy, and pleural inflammation. Imaging findings include small lung volumes with elevation of the diaphragm and basilar atelectasis in the absence of fibrosis or pleural disease. Helpful clues to the diagnosis include progressively smaller lung volumes and fluoroscopy of the diaphragm showing decreased diaphragmatic excursion. Pulmonary function tests also show diminished total lung capacity and restrictive physiology.[69] The diagnosis of SLS can be challenging, but it is important to consider this entity because high-dose corticosteroid treatment can reduce morbidity.[70,71]

ILD is uncommon in SLE, affecting about 3%-8% of patients, usually presenting as an NSIP pattern (Fig. 10).[72] Airway involvement is rare.

PAH affects 4%-5% of SLE patients[73] and is also associated with poor prognosis, especially during pregnancy. Risk factors for development of PAH includes positive anticardiolipin antibodies (or lupus anticoagulant) or anit-U1 ribonucleoprotein antibodies and Raynaud phenomenon.[74] Treatment includes vasodilators similar to idiopathic PAH and immunosuppressive agents.[75]

Additional vascular complications of SLE include recurrent venous or arterial thrombosis secondary to antiphospholipid antibodies. These patients are at increased risk for risk of pulmonary embolism, with potential for chronic pulmonary thromboembolic disease, stroke, and complications during pregnancy.

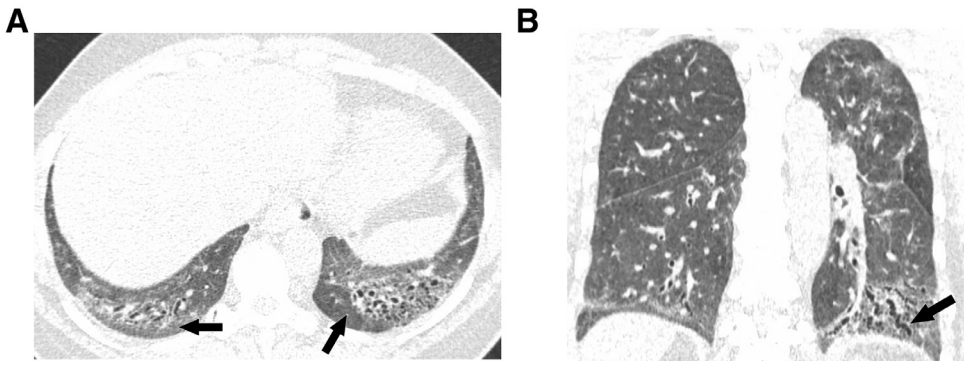

Figure 10 A 32-year-old female with SLE and NSIP. A. Axial HRCT image shows peribronchial ground-glass opacity and fine reticulation in the lung bases. Note the relative subpleural sparing (*arrows*). B. Coronal reformatted HRCT image shows the basal predominance and traction bronchiectasis (*arrow*). NSIP, nonspecific interstitial pneumonia; SLE, systemic lupus erythematosus.

Systemic Sclerosis/Scleroderma (SSc)

SSc is also more common in females (female:male = 6:1-8:1) but typically presents later in life than SLE, between 45 and 64 years of age.[76] In SSc, abnormal activation of the immune system leads to fibrosis and vasculopathy. This explains why ILD and PAH are the most common pulmonary manifestations of SSc. These are also the leading causes of morbidity and account for 33% and 28% of SSc associated mortality, respectively.[77] The disease is categorized as diffuse cutaneous (dcSSc) or limited (lcSSc), based on the extent of skin involvement. Calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia syndrome is a variant of limited scleroderma. ILD develops more frequently in dcSSc with antitopoisomerase I antibody (Scl70/ATA) and PAH is more common in the lcSSc with positive anticentromere antibody.[78,79]

Lung abnormalities are present on HRCT in 90% of patients with SSc,[80] most commonly an NSIP pattern (78%) with UIP occurring in 10%-15% of patients (Fig. 11).[81] Patients with SSc are at greatest risk of developing ILD within the first 4-5 years of disease onset. Most pulmonary functional decline usually occurs within the first 3-4 years with often relatively stable disease afterwards.[82] The clinical course is variable, from mild and stable disease to rapidly progressive fibrosis.[83] The 5- and 10-year survival from diagnosis was reported to be 74.9% and 62.5%, respectively. The mortality risk among SSc patients with ILD was 2.89 times compared to those without.[84] The major clinical risk factors for progression include decrease in DLCO, low of FVC in early stages of ILD, decrease in DLCO, gastroesophageal reflux, PAH, older age, and male sex.[85] The most important risk factor on CT is the extent of lung abnormalities with more than 20% of lung involvement at baseline associated with 3-fold increased risk of progression and mortality.[86] SSc-related ILD demonstrated often disproportionate involvement of the anterolateral upper lobes and posterosuperior lower lobes, referred to as the "4 corner sign." This is can be helpful distinguishing SSc-ILD from IPF.[87]

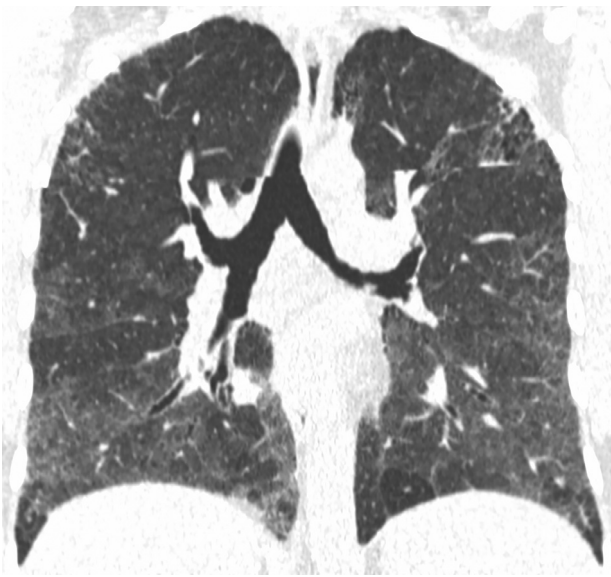

Figure 11 A 51-year-old female with SSc and NSIP. Coronal reformatted HRCT image shows basal predominant ground-glass opacity. SSc, systemic sclerosis.

Unlike ILD, PAH may be a late complication of the SSc and echocardiography is used as a screening tool. The reference standard for diagnosis of PAH is right heart catheterization. PAH is defined by a mean pulmonary arterial pressure $\geq$25 mm Hg with a pulmonary capillary wedge pressure $\leq$15 mm Hg. SSc and MCTD have the highest prevalence of PAH among CTD with PAH affecting 8%-35% of SSc patients.[88,89] PAH is more common in limited disease (lcSSc) and occurs in up to 50% of patients with calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia syndrome.[90] CT usually shows enlarged central pulmonary arteries, although normal-sized arteries do not exclude the diagnosis; mosaic attenuation can also be present.[91] The prognosis of SSc-PAH is worse compared to idiopathic or associated with other CTD. The survival in SSc-PAH has been reported 52% at 3 years, and 39% when associated with ILD (ILD-PAH).[92,93]

Esophageal involvement is seen in up to 97% of patients with SSc and can lead to recurrent aspiration, which contributes to fibrosis progression and more severe functional decline.[94] CT findings of aspiration include centrilobular nodules, peribronchial ground-glass opacity, endobronchial debris, or frank consolidation localized in the dependent lung. Bronchiectasis and scar result from recurrent aspiration and lung injury.

SSc often involves the heart, including the myocardium (patchy fibrosis), pericardium (pericarditis, pericardial effusion, and thickening), and rarely valvular disease.[95,96] Cardiac magnetic resonance imaging can assess cardiac involvement in SSc, delineating the extent of fibrosis and serving as a prognostic tool.[9,97] The incidence of pericardial involvement in SSc is about 50% on autopsy. Asymptomatic pericarditis is common, occurring in 16%-30% of patients.[98]

SSc increases the risk of cancer, including hematologic malignancies,[99] which can be related to disease itself or therapy. The increase risk of lung cancer can be attributed to ILD (Fig. 12).

Mediastinal lymphadenopathy can be seen in 30% of SSc patients,[98] usually reactive.

Sjögren Syndrome (SS)

SS is the second most common autoimmune disorder after RA affecting 0.1% of the population with prevalence of 3%-6% among older adults. It typically presents in the fourth and fifth decades of life with female predilection (female: male = 9:1-20:1 for primary SS).[100] It is characterized by lymphocytic infiltration of various organs, most commonly lacrimal and salivary glands and the respiratory tract. One-third of SS cases are secondary, associated with other CTDs most often RA, SLE, and SSc.

The most common pulmonary manifestation of SS is ILD, typically NSIP pattern, with a prevalence ranging between 28% and 61% and favorable prognosis.[101,102] Other ILD

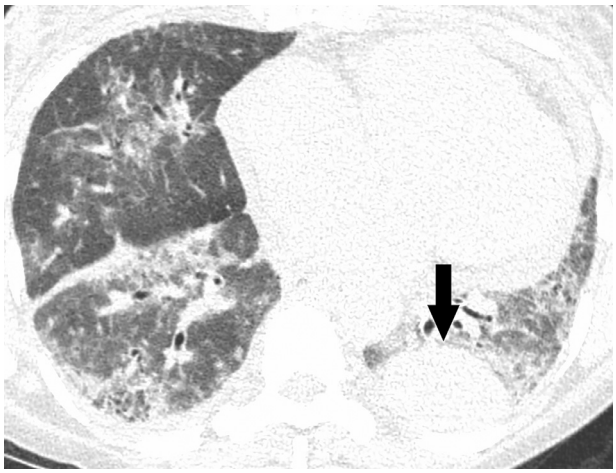

Figure 12 A 61-year-old female with SSc and squamous cell carcinoma on a background of NSIP. HRCT image shows basal peripheral and peribronchial ground-glass opacity and mild reticulation. The left lower lobe mass (*arrow*) was shown to be squamous cell carcinoma on ultrasound-guided core needle biopsy. NSIP, nonspecific interstitial pneumonia; SSc, systemic sclerosis.

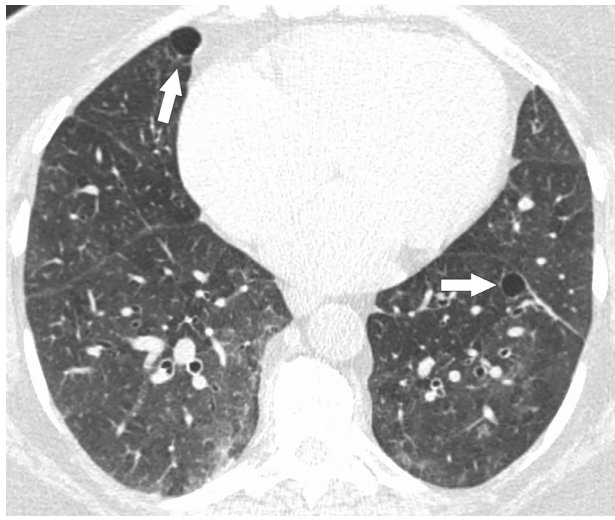

Figure 13 A 65-year-old female with SS and LIP. HRCT image shows patchy ground-glass opacity and two thin-walled perivascular cysts (arrows). The number of cysts in LIP is quite variable. LIP, lymphoid interstitial pneumonia.

patterns seen in SS include LIP, UIP, and OP.[101] LIP in seen in 10%-17% of SS (Fig. 13).[103]

LIP is characterized by polyclonal proliferation of lymphocytes and plasma cells with predominant interstitial involvement. LIP is categorized as both an interstitial pneumonia and a lymphoproliferative disorder.[33] On CT, the dominant features are ground-glass opacities, poorly defined centrilobular nodules, and thin-walled perivascular cysts,[31] typically smaller than 30 mm. There is random distribution of the cysts, although many cysts are associated with small vessels, with overall basal predominance of the findings.[6] Additional findings include reticular opacities, interlobular septal, bronchovascular thickening, and consolidation.

In SS, LIP can be seen in association with pulmonary amyloidosis.[104,105] The presence of calcified pulmonary nodules in conjunction with LIP should raise this suspicion.[31] However, distinguishing between LIP and cystic amyloidosis can be challenging and may require confirmation with biopsy.[106,107] Air cysts may also occur in patients with primary SS who do not have typical LIP, but other interstitial pneumonias, for example NSIP.[33]

In addition to ILD, SS can manifest with airways disease including follicular bronchiolitis and constrictive bronchiolitis.[108,109] Moreover, impaired ciliary clearance can lead to recurrent infection and bronchiectasis. Pleural involvement is uncommon and usually seen in secondary SS associated with RA or SLE.[103]

Patients with SS have a 9-35 times greater risk of developing lymphoma compared to general population,[110,111] occurring in about 5% of SS patients.[112] SS-associated lymphoma usually arises from the salivary glands or mucosa-associated lymphoid tissue of the stomach or lung; it usually has a good prognosis (Fig. 14). CT can help to distinguish LIP from pulmonary lymphoma[31]: cysts are characteristic of LIP, whereas larger nodules (>1 cm), consolidation, and effusions are suggestive of lymphoma.

Mixed Connective Tissue Disease (MCTD)

MCTD is a distinct clinical entity with clinical features of SLE, SSc, RA, or PM/DM in addition to high-titer antiribonucleoprotein (anti-U1ribonucleoprotein) antibodies. The disease affects predominantly young females (female: male = 9:1). Common clinical features include arthritis, Raynaud phenomenon, serositis (pleuritis and pericarditis), myositis, and esophageal dysfunction.[113]

Respiratory manifestations occur in up to 80% of patients[114] with ILD being the most common and affecting up to 66% of patients.[115] NSIP is the most common histopathologic pattern; rarely UIP and LIP occur. Esophageal dysmotility and gastroesophageal reflux are frequent, often associated with progression of ILD.[116]

PAH occurs in 10%-45% of patients[114] and is associated with a poor prognosis.[117,118]

Pleural thickening or effusion occurs in fewer than 10% of patients, typically in patients with SLE-like features.[8] Less common thoracic manifestations are alveolar hemorrhage, thromboembolism, mediastinal lymphadenopathy, and diaphragmatic and respiratory muscle dysfunction.[7]

Dermatomyositis/Polymyositis (DM/PM)

PM and DM are autoimmune myopathies characterized by inflammation in proximal skeletal muscles and occurs more common in females (female:male = 2:1). Patients with DM have also cutaneous manifestations (Fig. 15). DM has a bimodal age incidence: the juvenile form affects children around 10-15 years of age and the adult form typically starts

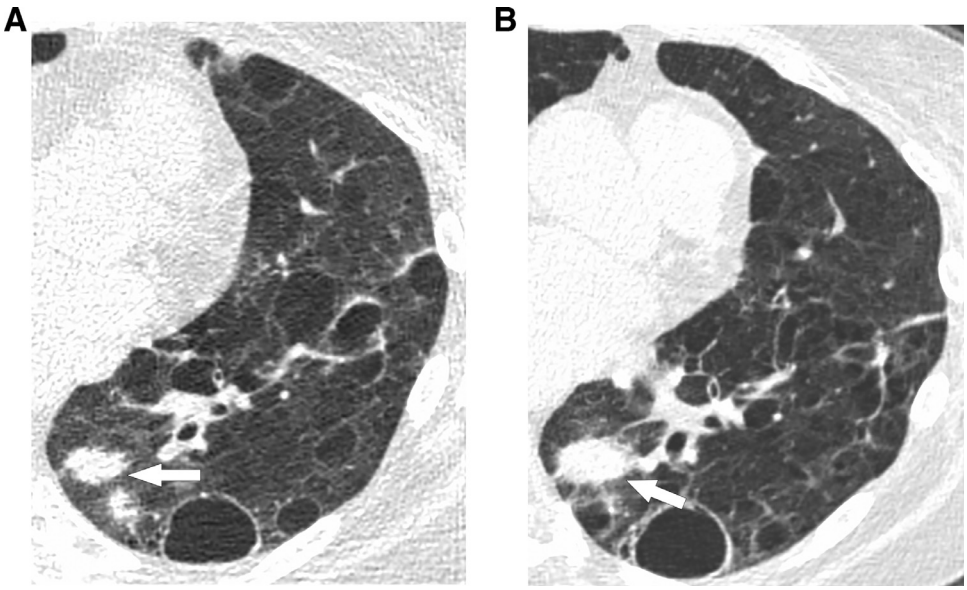

Figure 14 A 66-year-old female with SS and MALT lymphoma. (A) HRCT image shows multiple thin-walled perivascular cysts and two large left lower lobe nodules (*arrow*). HRCT image 3 months later shows growth of the dominant nodule (*arrow*), confirmed on needle biopsy to be lymphoma. MALT, mucosa-associated lymphoid tissue.

at 35-65 years of age. Late-onset (>50 years of age) is strongly associated with malignancy, more often seen with DM.[119,120] In a study by Hachulla, more than 50% of patients over 65 years old had an underlying malignancy.[121]

Thoracic manifestations occur in more than 50% of patients,[120] most commonly ILD, aspiration syndromes resulting from pharyngeal muscle weakness, and hypoventilation or respiratory failure caused by involvement of respiratory muscles.[122]

Antibodies seen in PM/DM tend to be mutually exclusive and are associated with distinctive clinical presentations.[123,124] Patients with antisynthetase antibodies may develop antisynthetase syndrome consisting of myositis and ILD. Sometimes fever, Raynaud phenomenon, skin thickening called "mechanic's hands," and esophageal dysmotility occur.[125] Anti−Jo-1 is the most common antisynthetase antibody (up to 30% of PM/DM patients) followed by anti−PL-7 and anti−PL-12. The presence of these antibodies indicates high risk of ILD, with up to 70% of patients with anti−Jo-1 positive developing ILD.[125-127] Anti-melanoma differentiation-associated gene 5 antibodies are associated with clinically amyopathic DM, rapidly progressive ILD (Fig. 16), severe skin manifestations, and poor prognosis.[128,129]

In PM/DM patients with ILD, NSIP is the most common pattern; however, OP is also relatively frequent, and different patterns may coexist (Fig. 17; Table 3). UIP and diffuse alveolar damage (DAD) are uncommon. The clinical course of PM/DM with ILD can be categorized in 3 groups: subclinical (up to 30%), slowly progressing, and rapidly progressive (up to 20%).[123,130] As with other CTDs, ILD may be present before clinically evident myositis and skin manifestations.[131] Pleural involvement and PAH are rare in PM/DM.

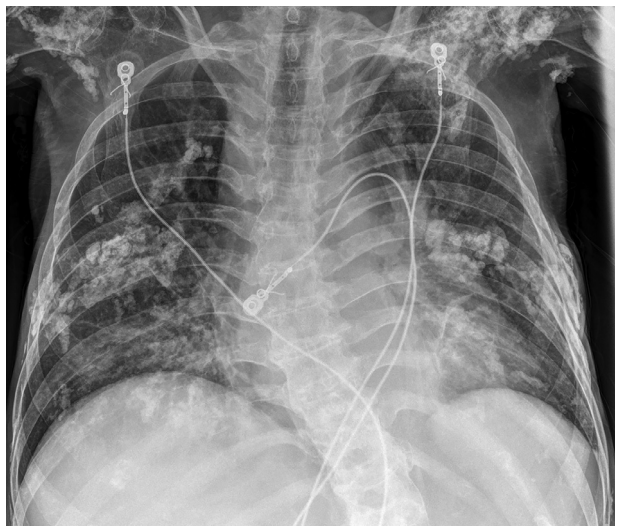

Figure 15 A 45-year-old female with longstanding dermatomyositis. Frontal chest radiograph shows extensive soft tissue calcinosis.

Interstitial Pneumonia With Autoimmune Features (IPAF)

In some patients with CTD, the presence of ILD may be the only imaging and clinically apparent abnormality. Therefore, patients presenting with ILD should undergo laboratory testing and thorough clinical evaluation before the diagnosis of IPF is made.[132] Furthermore, some patients with ILD have positive autoantibodies but do not meet criteria for diagnosis of a specific CTD. These patients have been classified as undifferentiated CTD-associated interstitial lung disease,

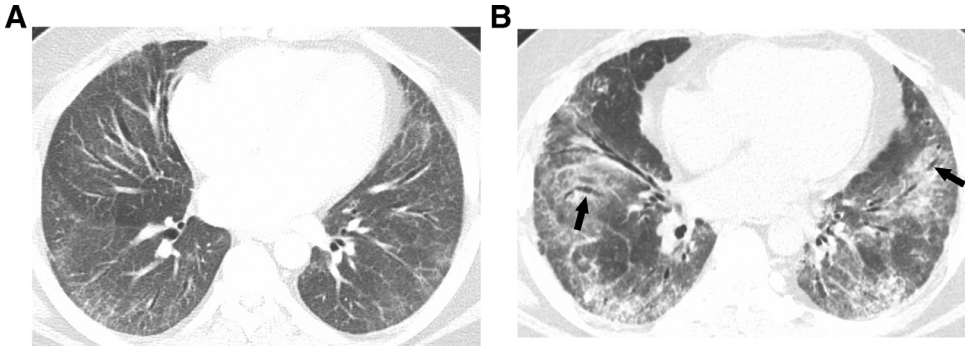

Figure 16 A 45-year-old male with amyopathic dermatomyositis and rapidly progressing lung disease. (A) HRCT image shows peripheral ground-glass opacity with relative subpleural sparing, suggesting an NSIP pattern. (B) HRCT image 3 months later shows worsening lung disease with volume loss, traction bronchiectasis (*arrows*). Courtesy of J. David Godwin, MD (Seattle, WA). NSIP, nonspecific interstitial pneumonia.

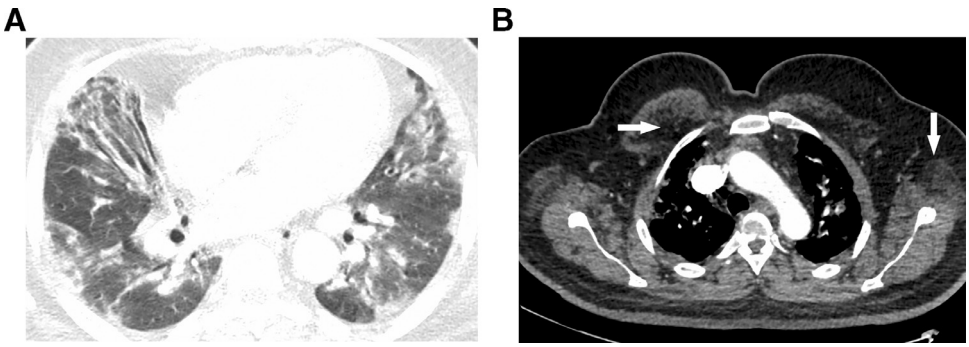

Figure 17 A 49-year-old female with polymyositis presenting with shortness of breath. (A) Contrast-enhanced chest CT (lung window settings) shows peripheral and peribronchial consolidation and ground-glass opacity consistent with organizing pneumonia. (B) Soft tissue windows settings shows striking atrophy of several chest wall muscles (*arrows*).

lung-dominant CTD, and IPAF. The latter term is preferred based on European Respiratory Society/American Thoracic Society consensus guidelines.[1] IPAF is defined based on clinical, serologic, and imaging criteria. Per definition, IPAF patients have imaging or pathologic findings of ILD, positive autoantibodies, and as signs and symptoms of CTD, yet without meeting criteria for a defined CTD. Regarding imaging findings, the European Respiratory Society/the American Thoracic Society consensus considered NSIP, OP, and LIP as patterns raising suspicion for IPAF, while UIP was considered nonspecific (Figs. 18 and 19). However, more recently it has been recognized that NSIP and UIP are the most common IPAF patterns.[133] Because involvement of several intrathoracic organs is common in patients with CTD, "multicompartmental involvement" is suggestive of IPAF. Examples include intrinsic airway disease (bronchiolitis or bronchiectasis), pulmonary vasculopathy (PAH), and pleural and pericardial effusion or thickening not explained by other pathologic process.

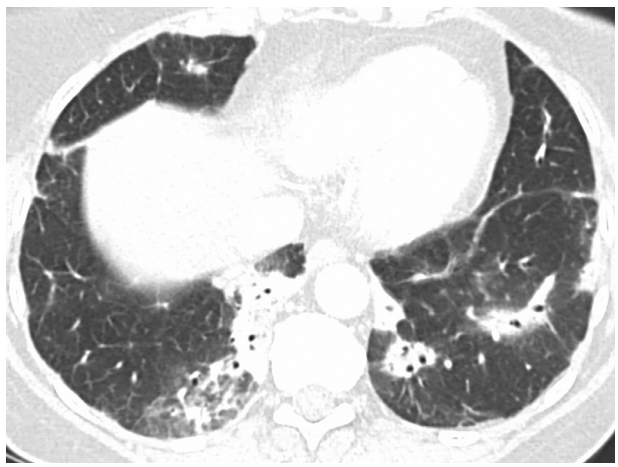

Figure 18 A 43-year-old female with IPAF. HRCT image shows bilateral peripheral and peribronchial foci of consolidation suggesting an organizing pneumonia pattern of lung injury. IPAF, interstitial pneumonia with autoimmune features.

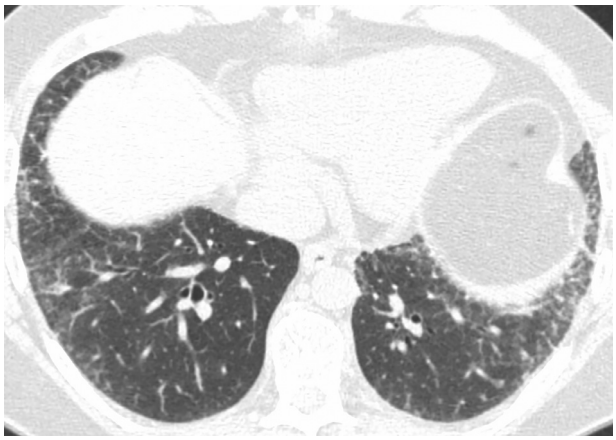

Figure 19 A 53-year-old male with IPAF. HRCT shows peripheral reticulation and ground-glass opacity in the lung bases. Surgical lung biopsy showed UIP pattern. IPAF, interstitial pneumonia with autoimmune features.

In the study by Ahmad et al, 7% of patients with ILD fulfilled criteria for IPAF.[134] The study included 57 patients and showed similar survival among IPAF and IPF patients. Oldham et al[135] showed patients with IPAF had overall worse survival than patients with CTD-ILD and marginally better than IPF patients. However, the subgroup of IPAF patients with pattern other than UIP had a prognosis similar to those with CTD-ILD. As expected, some IPAF patients eventually develop CTD, most of them within 5 years,[136] and need to be periodically re-evaluated.

Acute Lung Injury in CTD-ILD

Mortality is high in ILD-associated acute respiratory failure. The study by Gannon et al evaluated 126 consecutive adults with ILD admitted to an ICU for respiratory failure and demonstrated in-hospital mortality of 66%, and 1-year mortality of 80%.[137] Hospital and 1-year mortality rates were 41% and 54%, respectively, in a study by Zafrani et al.[138] In the latter study, factors independently associated with hospital mortality included PAH; traction bronchiectasis, honeycombing, or both on CT, and acute kidney injury. Additionally, fibrotic ILD with traction bronchiectasis and honeycombing was also associated with a worse outcome in a study by Gonçalves et al.[139]

Managing acute respiratory compromise in a CTD-ILD patient is challenging. The differential diagnosis is broad and includes acute exacerbation of fibrosis and infection, including opportunistic, since many of these patients are immunocompromised. While AE is typically treated with corticosteroids, infection requires antimicrobials and often reduction in immunosuppressive therapy. The distinction is difficult because of similar clinical presentations (eg, fever, cough, and dyspnea) and similar laboratory and imaging features.[140] Radiographs show new and worsening lung opacities correlating to new patchy ground-glass opacity and consolidation superimposed on the pre-existing ILD pattern.

Pulmonary edema is another cause for acute respiratory failure in CTD-ILD patients; however, this is relatively easier to exclude due to additional clinical signs and imaging features. In CTD patients, especially those treated with newer medications, drug-induced acute lung injury is another consideration. DAH can complicate CTD-ILD.[141] In a patient with SLE, acute lupus pneumonitis needs to be considered.

Acute exacerbation is a life-threatening complication in patients with CTD-ILD. Parambil et al reported 3 deaths from acute exacerbation of interstitial pneumonia among 18 patients during 13 years of observation.[101] A study by Tachikawa et al[142] reported 90-day mortality in acute exacerbation of 33% in CTD-ILD, which was significantly better than that of IPF (69%). The prognosis was similar to acute exacerbations of IPF in a study by Suda et al,[143] which included mainly patients with RA. Acute exacerbations associated with an NSIP pattern seem to be associated with better prognosis than acute exacerbations associated with a UIP pattern.[144]

Treatment-Related Findings

New biologic agents are very effective in treating autoimmune diseases, particularly RA. Examples include the tumor necrosis factor (TNF) inhibitors (etanercept) and anti-TNF-α antibodies (infliximab, adalimumab), interleukin-1 antagonists (anakinra), interleukin-6 receptor inhibitors (tocilizumab), anti-CD20 antibodies (rituximab), and T-lymphocyte inhibitors (abatacept). These medications can cause lung injury ranging from subclinical to life-threatening.[145-147] Drug-induced lung injury (DILI) can be acute, subacute, or chronic. There are several patterns of DILI, with OP being the most common. Other patterns include diffuse alveolar damage, DAH, eosinophilic pneumonia, noncardiogenic pulmonary edema, and constrictive bronchiolitis. These patterns overlap with injuries from CTD itself and may coexist making the diagnosis even more challenging. Additionally, a single agent can cause a variety of lung injury patterns. For example, methotrexate can cause OP, hypersensitivity reaction, DAD, and pulmonary fibrosis.[148-150] Patients with pre-existing lung disease are more susceptible to DILI. Therefore, patients with CTD-ILD may require pulmonary function tests and chest imaging before initiation of therapy. Disease-modifying antirheumatic drugs including leflunomide, rituximab, and TNF-α inhibitors, may cause pneumonitis or worsen pre-existing ILD in RA patients.[151] TNF-α antagonists can cause sarcoid-like reactions, which has to be distinguished from tuberculosis and may progress despite cessation of the therapy (Fig. 20).

The most frequent complication of treatment is infection[152] often secondary to immunosuppression and compounded by pre-existing impaired immunity secondary to underlying CTD. The most common infection in patients with CTD is community-acquired pneumonia but opportunistic organisms such as *Pneumocystis jirovecii,* cytomegalovirus, *Aspergillus, and Nocardia asteroides* complex should be considered.[153] Furthermore, newer medications combined with impaired cell-mediated

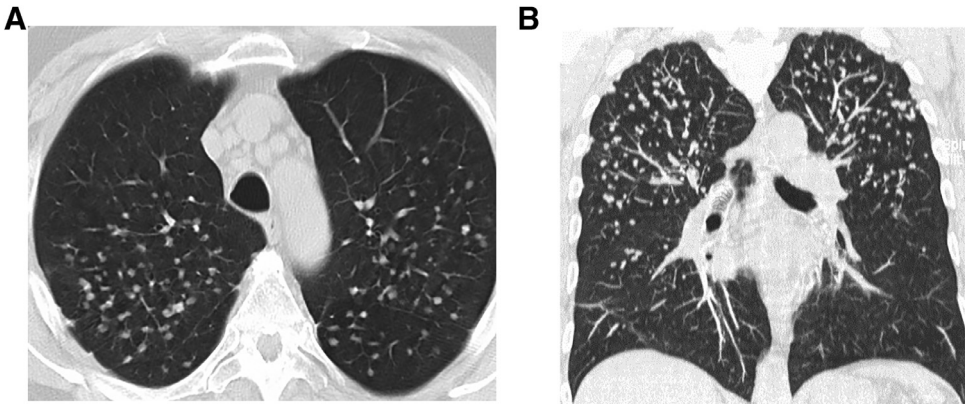

Figure 20 Sarcoid reaction in young male with RA treated with etanercept. Axial and coronal reformatted CT images show upper lobe predominate perilymphatic nodules. RA, rheumatoid arthritis.

immunity place patients at risk for primary tuberculosis or reactivation of latent infection. Additionally, long-term immunosuppressive therapy increases the risk of malignancy, especially lymphoma.[154]

Conclusion

The lungs are commonly affected in patients with CTDs, either as part of systemic involvement or the only organ system affected. Multicompartmental involvement is not uncommon with patients having airway, pleural, pericardial, pulmonary vascular, and cardiac involvement in addition to lung parenchymal involvement. CTD should always be a consideration in patients presenting with ILD, pulmonary hypertension or DAH, and unexplained serositis or airways disease. Treatment of CTD can limit progression of lung injury in some patients, helping to reduce morbidity and mortality. However, complications from treatment such as drug reaction and opportunistic infection can complicate matters. The radiologist plays a central role in diagnosis and surveillance of CTD-related complications and may be the first to suggest CTD as a possible diagnosis.

References

1. Fischer A, Antoniou KM, Brown KK, et al: An official European Respiratory Society/American Thoracic Society research statement: Interstitial pneumonia with autoimmune features. Eur Respir J 46:976-987, 2015
2. Capobianco J, Grimberg A, Thompson BM, et al: Thoracic manifestations of collagen vascular diseases. Radiographics 32:33-50, 2012
3. Woodhead F, Wells AU, Desai SR: Pulmonary complications of connective tissue diseases. Clin Chest Med 29:149-164, 2008.. vii
4. Vij R, Strek ME: Diagnosis and treatment of connective tissue disease-associated interstitial lung disease. Chest 143:814-824, 2013
5. Olson AL, Brown KK, Fischer A: Connective tissue disease-associated lung disease. Immunol Allergy Clin North Am 32:513-536, 2012
6. Lynch DA: Lung disease related to collagen vascular disease. J Thorac Imaging 24:299-309, 2009
7. Crestani B: The respiratory system in connective tissue disorders. Allergy 60:715-734, 2005
8. Franquet T: High-resolution CT of lung disease related to collagen vascular disease. Radiol Clin North Am 39:1171-1187, 2001
9. Lagan J, Schmitt M, Miller CA: Clinical applications of multiparametric CMR in myocarditis and systemic inflammatory diseases. Int J Cardiovasc Imaging 34:35-54, 2018
10. Mavrogeni S, Schwitter J, van Rossum A, et al: Cardiac magnetic resonance imaging in myocardial inflammation in autoimmune rheumatic diseases: An appraisal of the diagnostic strengths and limitations of the Lake Louise criteria. Int J Cardiol 252:216-219, 2018
11. Zare Mehrjardi M, Kahkouee S, Pourabdollah M: Radio-pathological correlation of organizing pneumonia (OP): A pictorial review. Br J Radiol 90:20160723, 2017
12. Torrealba JR, Fisher S, Kanne JP, et al: Pathology-radiology correlation of common and uncommon computed tomographic patterns of organizing pneumonia. Hum Pathol 71:30-40, 2018
13. Jokerst C, Purdy H, Bhalla S: An overview of collagen vascular disease-associated interstitial lung disease. Semin Roentgenol 50:31-39, 2015
14. Tansey D, Wells AU, Colby TV, et al: Variations in histological patterns of interstitial pneumonia between connective tissue disorders and their relationship to prognosis 44:585-596, 2004
15. Kim EA, Lee KS, Johkoh T, et al: Interstitial lung diseases associated with collagen vascular diseases: radiologic Radiologic and histopathologic findings 22(suppl_1): S151-S165, 2002
16. Dong X, Zheng Y, Wang L, et al: Clinical characteristics of autoimmune rheumatic disease-related organizing pneumonia. Clin Rheumatol 37:1027-1035, 2018
17. Yoo JW, Song JW, Jang SJ, et al: Comparison between cryptogenic organizing pneumonia and connective tissue disease-related organizing pneumonia. Rheumatology 50:932-938, 2011
18. Kligerman SJ, Groshong S, Brown KK, et al: Nonspecific interstitial pneumonia: radiologic, clinical, and pathologic considerations 29: 73-87, 2009
19. Silva CIS, Müller NL: Interstitial lung disease in the setting of collagen vascular disease. Semin Roentgenol 45:22-28, 2010
20. Lynch DA, Travis WD, Müller NL, et al: Idiopathic interstitial pneumonias: CT features 236: 10-21, 2005
21. Travis WD, Matsui K, Moss J, et al: Idiopathic nonspecific interstitial pneumonia: Prognostic significance of cellular and fibrosing patterns: Survival comparison with usual interstitial pneumonia and desquamative interstitial pneumonia. Am J Surg Pathol 24:19-33, 2000
22. Solomon JJ, Brown KK: Rheumatoid arthritis-associated interstitial lung disease. Open Access Rheumatol 4:21-31, 2012
23. Attili AK, Kazerooni EA, Gross BH, et al: Smoking-related interstitial lung disease: Radiologic-clinical-pathologic correlation 28:1383-1396, 2008
24. Society, A.J.A.J.R.C.C.M. In: American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001 and by the ERS Executive Committee, June 2001, 165:277-304, 2002

25. Vivero M, Padera RF: Histopathology of lung disease in the connective tissue diseases. Rheum Dis Clin North Am 41:197-211, 2015
26. Lynch DA, Huckleberry JM: Usual interstitial pneumonia: Typical and atypical high-resolution computed tomography features. Semin Ultrasound CT MRI 35:12-23, 2014
27. Zhan X, Koelsch T, Montner SM, et al: Differentiating usual interstitial pneumonia from nonspecific interstitial pneumonia using high-resolution computed tomography: The "straight-edge sign". J Thorac Imaging 33:266-270, 2018
28. Hartman TE, Primack SL, Swensen SJ, et al: Desquamative interstitial pneumonia: Thin-section CT findings in 22 patients. Radiology 187:787-790, 1993
29. Marten K, Milne D, Antoniou KM, et al: Non-specific interstitial pneumonia in cigarette smokers: A CT study. Eur Radiol 19:1679-1685, 2009
30. Craig PJ, Wells AU, Doffman S, et al: Desquamative interstitial pneumonia, respiratory bronchiolitis and their relationship to smoking. Histopathology 45:275-282, 2004
31. Hare SS, Souza CA, Bain G, et al: The radiological spectrum of pulmonary lymphoproliferative disease. Br J Radiol 85:848-864, 2012
32. Filipek MS, Thompson ME, Wang PL, et al: Lymphocytic interstitial pneumonitis in a patient with systemic lupus erythematosus: Radiographic and high-resolution CT findings. J Thorac Imaging 19:200-203, 2004
33. Egashira R, Kondo T, Hirai T, et al: CT findings of thoracic manifestations of primary Sjögren syndrome: Radiologic-pathologic correlation. Radiographics 33:1933-1949, 2013
34. Johkoh T, Müller NL, Pickford HA, et al: Lymphocytic interstitial pneumonia: Thin-section CT findings in 22 patients. Radiology 212:567-572, 1999
35. Silva CI, Flint JD, Levy RD, et al: Diffuse lung cysts in lymphoid interstitial pneumonia: High-resolution CT and pathologic findings. J Thorac Imaging 21:241-244, 2006
36. Massey H, Darby M, Edey A: Thoracic complications of rheumatoid disease. Clin Radiol 68:293-301, 2013
37. Bilgici A, Ulusoy H, Kuru O, et al: Pulmonary involvement in rheumatoid arthritis. Rheumatol Int 25:429-435, 2005
38. Demoruelle MK, Weisman MH, Simonian PL, et al: Brief Report: Airways abnormalities and rheumatoid arthritis–related autoantibodies in subjects without arthritis: Early injury or initiating site of autoimmunity? 64:1756-1761, 2012
39. Kelmenson LB, Kristen Demoruelle M, Deane KD: The Lungs as the Site of Initiation of RA, in Lung Disease in Rheumatoid Arthritis. In: Fischer A, Lee JS (eds): Springer International Publishing: Cham, 31-43, 2018
40. Minaur NJ, Jacoby RK, Cosh JA, et al: Outcome after 40 years with rheumatoid arthritis: A prospective study of function, disease activity, and mortality. J Rheumatol Suppl 69:3-8, 2004
41. Brown KK: Rheumatoid lung disease. Proc Am Thorac Soc 4:443-448, 2007
42. Baqir M, Ryu JH, The Non-ILD Pulmonary Manifestations of RA, in Lung Disease in Rheumatoid Arthritis. In: Fischer A, Lee JS, (eds): Springer International Publishing: Cham. 163−173, 2018
43. Amital A, Shitrit D, Adir Y: The lung in rheumatoid arthritis. Presse Med 40(1 Pt 2):e31-e48, 2011
44. Bryson T, Sundaram B, Khanna D, et al: Connective tissue disease-associated interstitial pneumonia and idiopathic interstitial pneumonia: Similarity and difference. Semin Ultrasound CT MR 35:29-38, 2014
45. Bouros D, Pneumatikos I, Tzouvelekis A: Pleural involvement in systemic autoimmune disorders. Respiration 75:361-371, 2008
46. Hayakawa H, Sato A, Imokawa S, et al: Bronchiolar disease in rheumatoid 154: 1531−1536, 1996
47. Perez T, Remy-Jardin M, Cortet B, Airways involvement in rheumatoid arthritis 157: 1658-1665, 1998
48. Lin E, Limper AH, Moua T: Obliterative bronchiolitis associated with rheumatoid arthritis: Analysis of a single-center case series. BMC Pulm Med 18:105, 2018
49. Lynch JP 3rd, Weigt SS, DerHovanessian A, et al: Obliterative (constrictive) bronchiolitis. Semin Respir Crit Care Med 33:509-532, 2012
50. Olson AL, Swigris JJ, Sprunger DB, et al: Rheumatoid arthritis−interstitial lung disease−associated mortality 183:372-378, 2011
51. Ahuja J, Arora D, Kanne JP, et al: Imaging of pulmonary manifestations of connective tissue diseases. Radiol Clin North Am 54:1015-1031, 2016
52. Kim DS: Interstitial lung disease in rheumatoid arthritis: Recent advances. Curr Opin Pulm Med 12:346-353, 2006
53. Kim EJ, Elicker BM, Maldonado F, et al: Usual interstitial pneumonia in rheumatoid arthritis-associated interstitial lung disease 35:1322-1328, 2010
54. Lee HK, Kim DS, Yoo B, et al: Histopathologic pattern and clinical features of rheumatoid arthritis-associated interstitial lung disease. Chest 127:2019-2027, 2005
55. Paulin F, Mercado JF, Fernández ME, et al: Correlation between lung and joint involvement in patients with rheumatoid arthritis and interstitial lung disease: A cross-sectional study. Rev Invest Clin 70: 76-81, 2018
56. Jacob J, Song JW, Yoon HY, et al: Prevalence and effects of emphysema in never-smokers with rheumatoid arthritis interstitial lung disease. EBioMedicine 28:303-310, 2018
57. Yousem SA, TV Colby, Carrington CB, Lung biopsy in rheumatoid arthritis 131:770-777, 1985
58. Cortet B, Flipo RM, Rémy-Jardin M, et al: Use of high resolution computed tomography of the lungs in patients with rheumatoid arthritis. Ann Rheum Dis 54:815, 1995
59. Alunno A, Gerli R, Giacomelli R, et al: Clinical, Epidemiological, and Histopathological Features of Respiratory Involvement in Rheumatoid Arthritis. BioMed research international 2017:7915340, 2017
60. Braun MG, Wagener P: [Regression of peripheral and pulmonary rheumatoid nodules under therapy with rituximab]. Z Rheumatol 72:166-171, 2013
61. Sargin G, Senturk T: Multiple pulmonary rheumatoid nodules. Reumatologia 53:276-278, 2015
62. Hakala M, Pääkkö P, Huhti E, et al: Open lung biopsy of patients with rheumatoid arthritis. Clin Rheumatol 9:452-460, 1990
63. Keane MP, Lynch JP 3rd: Pleuropulmonary manifestations of systemic lupus erythematosus. Thorax 55:159-166, 2000
64. Fenlon HM, Doran M, Sant SM, et al: High-resolution chest CT in systemic lupus erythematosus. Am J Roentgenol 166:301-307, 1996
65. Cheema GS, Quismorio FP Jr: Interstitial lung disease in systemic lupus erythematosus. Curr Opin Pulm Med 6:424-429, 2000
66. Matthay RA, Schwarz MI, Petty TL, et al: Pulmonary manifestations of systemic lupus erythematosus: Review of twelve cases of acute lupus pneumonitis. Medicine 54:397-409, 1975
67. Martinez-Martinez MU, Abud-Mendoza C: Predictors of mortality in diffuse alveolar haemorrhage associated with systemic lupus erythematosus. Lupus 20:568-574, 2011
68. Zamora MR, Warner ML, Tuder R, et al: Diffuse alveolar hemorrhage and systemic lupus erythematosus. Clinical presentation, histology, survival, and outcome. Medicine 76(3):192-202, 1997
69. Borrell H, Narváez J, Alegre JJ, et al: Shrinking lung syndrome in systemic lupus erythematosus: A case series and review of the literature. Medicine 95:e4626, 2016
70. Duron L, Cohen-Aubart F, Diot E, et al: Shrinking lung syndrome associated with systemic lupus erythematosus: A multicenter collaborative study of 15 new cases and a review of the 155 cases in the literature focusing on treatment response and long-term outcomes. Autoimmun Rev 15(10):994-1000, 2016
71. Deeb M, Tselios K, Gladman DD, et al: Shrinking lung syndrome in systemic lupus erythematosus: A single-centre experience. Lupus 27:365-371, 2018
72. Gutsche M, Rosen GD, Swigris JJ: Connective tissue disease-associated interstitial lung disease: A review. Curr Respir Care Rep 1:224-232, 2012
73. Prabu A, Patel K, Yee CS, et al: Prevalence and risk factors for pulmonary arterial hypertension in patients with lupus. Rheumatology 48:1506-1511, 2009
74. Cefle A, Inanc M, Sayarlioglu M, et al: Pulmonary hypertension in systemic lupus erythematosus: Relationship with antiphospholipid antibodies and severe disease outcome. Rheumatol Int 31:183-189, 2011

75. Kommireddy S, Bhyravavajhala S, Kurimeti K, et al: Pulmonary arterial hypertension in systemic lupus erythematosus may benefit by addition of immunosuppression to vasodilator therapy: An observational study. Rheumatology 54:1673-1679, 2015
76. Coral-Alvarado P, Pardo AL, Castaño-Rodriguez N, et al: Systemic sclerosis: A world wide global analysis. Clin Rheumatol 28:757-765, 2009
77. Steen VD, Medsger TA: Changes in causes of death in systemic sclerosis, 1972-2002. Ann Rheum Dis 66:940-944, 2007
78. Hamaguchi Y: Autoantibody profiles in systemic sclerosis: Predictive value for clinical evaluation and prognosis. J Dermatol 37:42-53, 2010
79. Walker UA, Tyndall A, Czirják L, et al: Clinical risk assessment of organ manifestations in systemic sclerosis: A report from the EULAR Scleroderma Trials And Research group database. Ann Rheum Dis 66:754-763, 2007
80. Schoenfeld SR, Castelino FV: Interstitial lung disease in scleroderma. Rheum Dis Clin North Am 41:237-248, 2015
81. Bouros D, Wells AU, Nicholson AG, et al: Histopathologic subsets of fibrosing alveolitis in patients with systemic sclerosis and their relationship to outcome 165:1581-1586, 2002
82. Chowaniec M, Skoczyńska M, Sokolik R, et al: Interstitial lung disease in systemic sclerosis: Challenges in early diagnosis and management. Reumatologia 56:249-254, 2018
83. Giacomelli R, Liakouli V, Berardicurti O, et al: Interstitial lung disease in systemic sclerosis: Current and future treatment. Rheumatol Int 37:853-863, 2017
84. Rubio-Rivas M, et al: Mortality and survival in systemic sclerosis: Systematic review and meta-analysis. Semin Arthritis Rheum 44:208-219, 2014
85. Steen V: Predictors of end stage lung disease in systemic sclerosis. Ann Rheum Dis 62:97-99, 2003
86. Moore OA, Goh N, Corte T, et al: Extent of disease on high-resolution computed tomography lung is a predictor of decline and mortality in systemic sclerosis-related interstitial lung disease. Rheumatology 52:155-160, 2013
87. Walkoff L, White DB, Chung JH, et al: The four corners sign: A specific imaging feature in differentiating systemic sclerosis-related interstitial lung disease from idiopathic pulmonary fibrosis. J Thorac Imaging 33:197-203, 2018
88. Mukerjee D, St George D, Coleiro B, et al: Prevalence and outcome in systemic sclerosis associated pulmonary arterial hypertension: Application of a registry approach. Ann Rheum Dis 62:1088-1093, 2003
89. Solomon JJ, Olson AL, Fischer A, et al: Scleroderma lung disease. Eur Respir Rev 22:6-19, 2013
90. Ungerer RG, Tashkin DP, Furst D, et al: Prevalence and clinical correlates of pulmonary arterial hypertension in progressive systemic sclerosis. Am J Med 75:65-74, 1983
91. Grosse C, Grosse A, CT Findings in diseases associated with pulmonary hypertension: A current review 30:1753-1777, 2010
92. Lefèvre G, Dauchet L, Hachulla E, et al: Survival and prognostic factors in systemic sclerosis-associated pulmonary hypertension: A systematic review and meta-analysis. Arthritis Rheum 65:2412-2423, 2013
93. Chung L, Liu J, Parsons L, et al: Characterization of connective tissue disease-associated pulmonary arterial hypertension from REVEAL: Identifying systemic sclerosis as a unique phenotype. Chest 138:1383-1394, 2010
94. Richardson C, et al: Esophageal dilatation and interstitial lung disease in systemic sclerosis: A cross-sectional study. Semin Arthritis Rheum 46:109-114, 2016
95. Lambova S: Cardiac manifestations in systemic sclerosis. World J Cardiol 6:993-1005, 2014
96. Ferri C, Giuggioli D, Sebastiani M, et al: Heart involvement and systemic sclerosis. Lupus 14:702-707, 2005
97. Chaosuwannakit N, Makarawate P: Value of cardiac magnetic resonance imaging in systemic sclerosis. Reumatologia 56:92-98, 2018
98. Farrokh D, Abbasi B, Fallah-Rastegar Y, et al: The extrapulmonary manifestations of systemic sclerosis on chest high resolution computed tomography. Tanaffos 14:193-200, 2015
99. Marasini B, Conciato L, Belloli L, et al: Systemic sclerosis and cancer. Int J Immunopathol Pharmacol 22:573-578, 2009
100. Patel R, Shahane A: The epidemiology of Sjögren's syndrome. Clin Epidemiol 6:247-255, 2014
101. Parambil JG, Myers JL, Lindell RM, et al: Interstitial lung disease in primary Sjogren syndrome. Chest 130:1489-1495, 2006
102. Ito I, Nagai S, Kitaichi M, et al: Pulmonary manifestations of primary Sjogren's syndrome: A clinical, radiologic, and pathologic study. Am J Respir Crit Care Med 171:632-638, 2005
103. Stojan G, Baer AN, Danoff SK: Pulmonary manifestations of Sjögren's syndrome. Curr Allergy Asthma Rep 13:354-360, 2013
104. Jeong YJ, Lee KS, Chung MP, et al: Amyloidosis and lymphoproliferative disease in Sjogren syndrome: Thin-section computed tomography findings and histopathologic comparisons. J Comput Assist Tomogr 28:776-781, 2004
105. Marchiori E, Zanetti G, Hocchegger B, et al: Cystic amyloidosis or lymphoid interstitial pneumonia associated with amyloidosis? A diagnostic challenge. Ann Thorac Surg 94:1041-1042, 2012. author reply 1042
106. Sakai M, Yamaoka M, Kawaguchi M, et al: Multiple cystic pulmonary amyloidosis. Ann Thorac Surg 92:e109, 2011
107. Chew KM, Clarke MJ, Dubey N, et al: Nodular pulmonary amyloidosis with unusual, widespread lung cysts. Singapore Med J 54:e97-e99, 2013
108. Shi JH, Liu HR, Xu WB, et al: Pulmonary manifestations of Sjogren's syndrome. Respiration 78:377-386, 2009
109. Flament T, Bigot A, Chaigne B, et al: Pulmonary manifestations of Sjogren's syndrome. Eur Respir Rev 25:110-123, 2016
110. Theander E, Henriksson G, Ljungberg O, et al: Lymphoma and other malignancies in primary Sjogren's syndrome: A cohort study on cancer incidence and lymphoma predictors. Ann Rheum Dis 65:796-803, 2006
111. Johnsen SJ, Brun JG, Gøransson LG, et al: Risk of non-Hodgkin's lymphoma in primary Sjogren's syndrome: A population-based study. Arthritis Care Res 65:816-821, 2013
112. Fragkioudaki S, Mavragani CP, Moutsopoulos HM: Predicting the risk for lymphoma development in Sjogren syndrome: An easy tool for clinical use. Medicine 95:e3766, 2016
113. Tani C, Carli L, Vagnani S, et al: The diagnosis and classification of mixed connective tissue disease. J Autoimmun 48-49:46-49, 2014
114. Prakash UB: Respiratory complications in mixed connective tissue disease. Clin Chest Med 19:733-746, 1998. ix
115. Bodolay E, Szekanecz Z, Dévényi K, et al: Evaluation of interstitial lung disease in mixed connective tissue disease (MCTD). Rheumatology 44:656-661, 2005
116. Fagundes MN, Caleiro MT, Navarro-Rodriguez T, et al: Esophageal involvement and interstitial lung disease in mixed connective tissue disease. Respir Med 103:854-860, 2009
117. Burdt MA, Hoffman RW, Deutscher SL, et al: Long-term outcome in mixed connective tissue disease: Longitudinal clinical and serologic findings 42:899-909, 1999
118. Vegh J, Szodoray P, Kappelmayer J, et al: Clinical and immunoserological characteristics of mixed connective tissue disease associated with pulmonary arterial hypertension. Scand J Immunol 64:69-76, 2006
119. Hill CL, Zhang Y, Sigurgeirsson B, et al: Frequency of specific cancer types in dermatomyositis and polymyositis: A population-based study. The Lancet 357:96-100, 2001
120. Schwarz MI: The lung in polymyositis. Clin Chest Med 19:701-712, 1998
121. Hachulla E: [Dermatomyositis and polymyositis: Clinical aspects and treatment]. Ann Med Interne (Paris) 152:455-464, 2001
122. Kalluri M, Oddis CV: Pulmonary manifestations of the idiopathic inflammatory myopathies. Clin Chest Med 31:501-512, 2010
123. Ha YJ, Lee YJ, Kang EH: Lung Involvements in Rheumatic Diseases: Update on the Epidemiology, Pathogenesis, Clinical Features, and Treatment. Biomed Res Int 2018:6930297, 2018
124. Jee AS, Adelstein S, Bleasel J, et al: Role of Autoantibodies in the diagnosis of connective-tissue disease ILD (CTD-ILD) and interstitial pneumonia with autoimmune features (IPAF). J Clin Med 6:51, 2017
125. Solomon J, Swigris JJ, Brown KK: Myositis-related interstitial lung disease and antisynthetase syndrome. J Bras Pneumol 37:100-109, 2011

126. Mimori T, Nakashima R, Hosono Y: Interstitial lung disease in myositis: Clinical subsets, biomarkers, and treatment. Curr Rheumatol Rep 14:264-274, 2012
127. Labirua A, Lundberg IE: Interstitial lung disease and idiopathic inflammatory myopathies: Progress and pitfalls. Curr Opin Rheumatol 22:633-638, 2010
128. Sato S, Hoshino K, Satoh T, et al: RNA helicase encoded by melanoma differentiation-associated gene 5 is a major autoantigen in patients with clinically amyopathic dermatomyositis: Association with rapidly progressive interstitial lung disease. Arthritis Rheum 60:2193-2200, 2009
129. Chen Z, Cao M, Plana MN, et al: Utility of anti-melanoma differentiation-associated gene 5 antibody measurement in identifying patients with dermatomyositis and a high risk for developing rapidly progressive interstitial lung disease: A review of the literature and a meta-analysis. Arthritis Care Res 65:1316-1324, 2013
130. Marie I, Hachulla E, Chérin P, et al: Interstitial lung disease in polymyositis and dermatomyositis. Arthritis Rheum 47:614-622, 2002
131. Yang Y, Fujita J, Tokuda M, et al: Chronological evaluation of the onset of histologically confirmed interstitial pneumonia associated with polymyositis/dermatomyositis. Intern Med 41:1135-1141, 2002
132. Tzelepis GE, Toya SP, Moutsopoulos HM: Occult connective tissue diseases mimicking idiopathic interstitial pneumonias. Eur Respir J 31:11-20, 2008
133. Nascimento ECTD, Baldi BG, Sawamura MVY, et al: Morphologic aspects of interstitial pneumonia with autoimmune features 142:1080-1089, 2018
134. Ahmad K, Barba T, Gamondes D, et al: Interstitial pneumonia with autoimmune features: Clinical, radiologic, and histological characteristics and outcome in a series of 57 patients. Respir Med 123:56-62, 2017
135. Oldham JM, Adegunsoye A, Valenzi E, et al: Characterisation of patients with interstitial pneumonia with autoimmune features 47:1767-1775, 2016
136. Cavagna L, Gonzalez Gay MA, Allanore Y, Matucci-Cerinic M. Interstitialpneumonia with autoimmune features: a new classification still on the move. Eur Respir Rev 2018 Jun 27;27(148). pii: 180047
137. Gannon WD, Lederer DJ, Biscotti M, et al: Outcomes and mortality prediction model of critically Ill adults with acute respiratory failure and interstitial lung disease. Chest 153:1387-1395, 2018
138. Zafrani L, Lemiale V, Lapidus N, et al: Acute respiratory failure in critically Ill patients with interstitial lung disease. PLoS One 9:e104897, 2014
139. Gonçalves AF, Campainha S, Nogueira C, et al: Interstitial lung disease in the intensive unit care setting. Revista Portuguesa de Pneumologia (English Edition) 22:179-180, 2016
140. Jones AT, du Bois RM, Wells AU: The pulmonary physician in critical care. Illustrative case 2: Interstitial lung disease. Thorax 58:361-364, 2003
141. Parambil JG, Myers JL, Ryu JH: Diffuse alveolar damage: Uncommon manifestation of pulmonary involvement in patients with connective tissue diseases. Chest 130:553-558, 2006
142. Tachikawa R, Tomii K, Ueda H, et al: Clinical features and outcome of acute exacerbation of interstitial pneumonia: Collagen vascular diseases-related versus idiopathic. Respiration 83:20-27, 2012
143. Suda T, Kaida Y, Nakamura Y, et al: Acute exacerbation of interstitial pneumonia associated with collagen vascular diseases. Respir Med 103:846-853, 2009
144. Park IN, Kim DS, Shim TS, et al: Acute exacerbation of interstitial pneumonia other than idiopathic pulmonary fibrosis. Chest 132:214-220, 2007
145. Hadjinicolaou AV, Nisar MK, Bhagat S, et al: Non-infectious pulmonary complications of newer biological agents for rheumatic diseases—A systematic literature review. Rheumatology 50:2297-2305, 2011
146. Roubille C, Haraoui B: Interstitial lung diseases induced or exacerbated by DMARDS and biologic agents in rheumatoid arthritis: A systematic literature review. Semin Arthritis Rheum 43:613-626, 2014
147. Bonniauda P, Beltramo G, Foignot C, et al: Pneumopathies non infectieuses induites par les biothérapies ciblées. Revue du Rhumatisme Monographies 85:184-190, 2018
148. Imokawa S, Colby TV, Leslie KO, et al: Methotrexate pneumonitis: review Review of the literature and histopathological findings in nine patients 15:373-381, 2000
149. Alarcón GS, Kremer JM, Macaluso M, et al: Risk factors for methotrexate-induced lung injury in patients with rheumatoid arthritis. A multicenter, case-control study. Methotrexate-lung study Group. Ann Intern Med 127:356-364, 1997
150. Kremer JM, Alarcón GS, Weinblatt ME, et al: Clinical, laboratory, radiographic, and histopathologic features of methotrexate-associated lung injury in patients with rheumatoid arthritis. A multicenter study with literature review. Arthritis Rheum 40:1829-1837, 1997
151. Roubille C, Haraoui B: Interstitial lung diseases induced or exacerbated by DMARDS and biologic agents in rheumatoid arthritis: A systematic literature review. Semin Arthritis Rheum 43:613-626, 2014
152. Araujo AGS, Borba HHL, Tonin FS, et al: A. Safety of Biologics Approved for the Treatment of Rheumatoid Arthritis and Other Autoimmune Diseases: A Disproportionality Analysis from the FDA Adverse Event Reporting System (FAERS). BioDrugs 2018 Jun 5
153. Di Franco M, Lucchino B, Spaziante M, et al: Lung Infections in Systemic Rheumatic Disease: Focus on Opportunistic Infections. Int J Mol Sci 18(2), 2017 Jan 29. pii: E293.
154. Menke DM, Griesser H, Moder KG, et al: Lymphomas in patients with connective tissue disease comparison of p53 protein expression and latent EBV infection in patients immunosuppressed and not immunosuppressed with methotrexate. Am J Clin Pathol 113:212-218, 2000