Connective Tissue Disease–Associated Interstitial Pneumonia and Idiopathic Interstitial Pneumonia: Similarity and Difference

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Interstitial lung diseases (ILDs) are increasingly recognized in patients with systemic diseases. Patients with early ILD changes may be asymptomatic. Features of ILD overlap among systemic diseases and with idiopathic variety. High-resolution computed tomography plays a central role in diagnosing ILDs. Imaging features are often nonspecific. Therapy- and complication-related lung changes would pose difficulty in diagnosing and classifying an ILD. Biology and prognosis of secondary ILDs may differ between different disease-related ILDs and idiopathic variety. Combination of clinical features, serological tests, pulmonary and extrapulmonary imaging findings, and pathology findings may help to diagnose ILDs.

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Connective tissue diseases (CTDs) represent a diverse group of immune-mediated systemic inflammatory diseases that frequently target the lungs, including the pulmonary interstitium, airway, pleura, and pulmonary vasculature. Interstitial lung disease (ILD) is common in many of these disorders, including systemic sclerosis (SSc) or scleroderma, rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and inflammatory myopathies such as polymyositis–dermatomyositis (PM-DM), mixed CTD (MCTD), and Sjogren syndrome (SS). ILD may present as a forme fruste of systemic disease, in some cases preceding extrapulmonary manifestations of CTD by years.1,2

ILD as the Initial Manifestation of CTD

Up to 15% of patients presenting with a diagnosis of ILD were diagnosed with CTD during their initial evaluation,3 and up to 25% of ILDs occur in patients with an undiagnosed CTD, sometimes making the distinction between idiopathic pulmonary fibrosis (IPF) and CTD-related ILD difficult.4 There are patients who present ILD and extrapulmonary features that do not meet the diagnostic criteria put forward for a systemic connective disease. It has been suggested that these patients may be categorized separately as having “lung-dominant CTD,” as their mode of presentation, disease progression, and prognosis may differ compared with patients with features of clear-cut diagnosis of a CTD.2 The frequency of ILD, thoracic manifestations, and typical interstitial imaging findings of systemic diseases are mentioned in Tables 1-3.

Systemic Sclerosis

SSc is a systemic autoimmune disease of uncertain etiology characterized by cellular and humoral autoimmunity, vascular injury, and tissue fibrosis. Its peak incidence is between 45 and 64 years, and it is more common in women (3:1 to 8:1 female predominance) and African Americans.5 It is subdivided into a limited cutaneous form, previously known as CREST
(Calcinosis, Raynaud’s syndrome, Esophageal dysmotility, Sclerodactyly, Telangiectasia) syndrome, and a diffuse cutaneous form, with varying degrees of skin, esophageal, lung, cardiac, and vascular involvement. Both forms can be progressive in nature. Pulmonary manifestations include both ILD and vascular pathology manifesting as pulmonary arterial hypertension (PAH). These pulmonary complications are now the leading cause of disease-related morbidity and mortality in patients with SSc. The African American population with SSc has greater disease severity, with 54% demonstrating ILD and 32% having severe ILD in a recent study. African American patients with SSc autoantibodies had ILD and PAH (antitopoisomerase I and anti-U3-RNP (ribonucleoprotein), respectively) more frequently than patients without autoantibodies. Changes of ILD on high-resolution computed tomography (HRCT) can be found in 55%-65% of unselected patients with SSc. The most common pulmonary finding is a pattern typical of nonspecific interstitial pneumonia (NSIP), with subpleural-predominant ground-glass opacities, reticulation, and traction bronchiectasis, without honeycombing. Other patterns, including usual interstitial pneumonia (UIP)-like fibrosis with peripheral honeycombing, are less common. The HRCT findings at initial presentation carry prognostic significance; patients with extensive ILD occupying 20% or more of lung volume experienced a rapid decline in pulmonary function in 1 study, whereas patients with less extensive lung abnormality occupying less than 20% of lung volume or no pulmonary involvement have relatively little progression of ILD at follow-up. Although some have suggested that ground-glass opacities on HRCT represent reversible inflammatory alveolitis, ground-glass opacity associated with bronchiectasis is recognized to represent irreversible fibrosis.

Several extrapulmonary thoracic findings on HRCT help suggest the diagnosis of SSc. Esophageal involvement appears as a dilated patulous esophagus often containing fluid or debris (Fig. 1) and has been described in up to 97% of patients with progressive SSc. These patients may also demonstrate stigmata of aspiration because of esophageal dysmotility, including bronchiectasis, mucus plugging, and tree in bud nodularity. Enlargement of central pulmonary arteries suggesting PAH may also be seen in SSc. This may be a result of restrictive lung disease or CTD-related vasculopathy in the absence of ILD. When lung disease is present, the severity of PAH may not directly correlate with severity of ILD. In a study by Condliffe et al, computed tomography (CT) pulmonary angiography findings of 89 patients with suspected SSc-related PAH were evaluated for diameters of pulmonary artery, qualitative grades of tricuspid regurgitation, and diameters of right and left ventricles. The investigators concluded that the cardiac chamber and great vessel measurements on CT correlate with invasive pulmonary hemodynamic measurements and have additive values obtained using echocardiography. The ratio between the diameters of cardiac ventricles may also have prognostic values in these patients. The severity and the extent of fibrosis as detected by HRCT may correlate with peak pulmonary artery pressures and may be the most reliable independent predictor of PAH.

HRCT also provides a sensitive method of detecting SSc-ILD. Analysis from the Scleroderma Lung Study–I, a large multicenter randomized clinical trial of oral cyclophosphamide vs placebo in 158 patients with symptomatic SSc-ILD, found that the most common HRCT findings at baseline were fibrosis (reticular opacity, traction bronchiectasis, and bronchiolectasis, 93%), ground-glass opacities (90%), and honeycombing (37%). A greater extent of pulmonary fibrosis on HRCT correlated well with lower forced vital capacity (FVC) and DLCO (Transfer factor) values on pulmonary function tests (PFTs). The extent of pulmonary fibrosis seen on HRCT scans was significantly negatively correlated with FVC ($r = -0.22$), diffusing capacity of the

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### Table 1 Frequency of Interstitial Lung Diseases in Various Systemic Diseases

<table>
<thead>
<tr>
<th>Diseases</th>
<th>Frequency of ILD (%)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid arthritis</td>
<td>20-30</td>
<td>Increased risk with cigarette smoking</td>
</tr>
<tr>
<td>Polymyositis-dermatomyositis</td>
<td>20-50</td>
<td>More common with antisythe antibodies</td>
</tr>
<tr>
<td>Systemic sclerosis</td>
<td>70</td>
<td>More common in diffuse disease; topoisomerase-1 antibodies</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>2-8</td>
<td>Usually in patients with multisystem disease</td>
</tr>
<tr>
<td>Mixed connective tissue disease</td>
<td>20-60</td>
<td></td>
</tr>
<tr>
<td>Sjögren syndrome</td>
<td>Up to 25</td>
<td></td>
</tr>
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</table>

### Table 2 Thoracic Manifestations of CTD

<table>
<thead>
<tr>
<th>SSc</th>
<th>RA</th>
<th>SLE</th>
<th>DM-PM</th>
<th>MCTD</th>
<th>SS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ILD overall</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>NSIP</td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>UIP</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>OP</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>LIP</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>DAD</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Airway</td>
<td>–</td>
<td>++</td>
<td>+</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Pleura</td>
<td>–</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Vascular</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>DAH</td>
<td>–</td>
<td>++</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Relative prevalence of thoracic findings in systemic sclerosis (SSc), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), dermatomyositis-polymyositis (DM/PM), mixed connective tissue disease (MCTD) and primary Sjögren syndrome (SS). Overall ILD prevalence is reported, along with individual ILD histologies, including nonspecific interstitial pneumonitis (NSIP), usual interstitial pneumonitis (UIP), organizing pneumonitis (OP), lymphocytic interstitial pneumonitis (LIP), and diffuse alveolar damage (DAD). Diffuse alveolar hemorrhage (DAH) is also considered.
lung for carbon monoxide \( r = -0.44 \), and total lung capacity \( r = -0.36 \). In the Scleroderma Lung Study–I, the extent of fibrosis seen on baseline HRCT scan was predictive of the progressive rate of decline in FVC in the placebo group. Conversely, patients with the most extensive fibrosis seen on baseline HRCT scans showed the greatest response to cyclophosphamide (CYC) treatment. In addition, the baseline degree of reticular disease on HRCT and extent of disease are independent predictors of mortality in SSc-ILD.

A baseline evaluation for ILD is critical in all patients with SSc and should be done with a combination of chest HRCTs and PFTs. In an analysis of 215 patients with SSc followed up in a clinical practice for 10 years, baseline PFTs and chest HRCTs were predictive of mortality risk. An increased extent of disease (as defined by the extent and coarseness of reticulation [fibrosis] and proportion of ground-glass opacity), >20% on HRCT, correlated with an increase in mortality (hazard ratio [HR] = 2.48, \( P < 0.0005 \)). Patients with a decreased baseline FVC <70% also had increased mortality risk (HR = 2.11, \( P = 0.001 \)). When the 2 modalities were combined in the risk assessment, patients with HRCT extent of ≥20% in addition to a FVC <70% had the highest mortality risk (HR = 3.46, \( P < 0.0005 \)).

### Rheumatoid Arthritis

RA is a relatively common collagen vascular disease, occurring in 1%-2% of the population, more frequently in women (3:1 female predominance), and typically between 25 and 50 years of age. Although RA is primarily characterized by synovial inflammation, extra-articular manifestations are seen in approximately half of patients with RA, and evidence of lung disease is seen in up to 80% of patients who are clinically suspected to have RA-associated ILD. A recent HRCT study demonstrated a 10%-12% incidence of ILD and 8% incidence of bronchiolitis in 1 RA cohort. Patients with RA-associated ILD have a higher mortality than those without RA-associated ILD, with approximately 80% dying of pulmonary complications. Risk factors for developing RA-associated ILD include advanced age, high titers of rheumatoid factor, carriage of the HLA-DRB1*1502 allele, and high tiers of anticyclic citrullinated peptide antibodies, which is associated with both airway disease and ILD.

Unlike most other CTDs, the predominant ILD histology in RA-associated ILD is UIP, found in up to 56% of patients. NSIP is also commonly seen, followed by organizing pneumonia (OP). The major patterns on HRCT in RA are subpleural reticulation with or without honeycombing (Fig. 2A),

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**Table 3 Typical HRCT Findings Suggestive of ILD Histology**

<table>
<thead>
<tr>
<th>HRCT Findings</th>
<th>NSIP</th>
<th>UIP</th>
<th>OP</th>
<th>LIP</th>
<th>DAD</th>
</tr>
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<tbody>
<tr>
<td>Bilateral symmetrical ground-glass opacities in a basal and peripheral distribution. Septal thickening and reticulation in 50% with associated traction bronchiectasis ± subpleural sparing. Honeycombing and consolidation are rare.</td>
<td>Basal and peripheral reticulation ± ground-glass opacities. Frequent traction bronchiectasis. Architectural distortion, reflecting lung fibrosis, with frequent honeycombing and lobar volume loss in advanced disease.</td>
<td>Areas of airspace consolidation with associated air bronchograms and mild cylindrical bronchiectasis. Adjacent ground-glass opacities are common. Basal distribution with peripheral or peribronchovascular predominance. Nodular foci of consolidation are common, including small bronchovascular nodules.</td>
<td>Ground-glass opacities with scattered thin-walled cysts, primarily in a perivascular distribution. Reticulation in 50%. Lung nodules and patchy consolidation may occur.</td>
<td>Ground-glass opacities with scattered thin-walled cysts, primarily in a perivascular distribution. Reticulation in 50%. Lung nodules and patchy consolidation may occur.</td>
<td>Bilateral patchy ground-glass opacities with geographic involvement and random distribution. Extent of involvement worsens with disease duration. Consolidations, typically basal within dependent portions of the lung. May organize with architectural distortion and traction bronchiectasis.</td>
</tr>
</tbody>
</table>

**Rheumatoid Arthritis**

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**Figure 1** Two axial HRCT sections from a patient with systemic sclerosis demonstrate lower lung–predominant peripheral reticulation, ground-glass opacity, and traction bronchiectasis typical of NSIP-like fibrosis (B). The upper lobes are relatively spared (A) but demonstrate a patulous, debris-filled esophagus typical of this disease (arrow).
ground-glass attenuation opacities (Fig. 2B), and areas of consolidation (Fig. 2C). There is also an airway-predominant pattern in RA, which manifests as bronchial wall thickening, bronchiectasis, and mosaic attenuation with air trapping (Fig. 2D). Several studies have demonstrated a good correlation between the imaging findings and lung biopsy results, particularly when the histology is UIP. The primary utility of HRCT in patients with RA is the reliable identification of patients with UIP-type ILD who carry a worse prognosis, similar to patients with IPF.

Patients with RA may also have pulmonary macronodules, which are typically asymptomatic. They are found more frequently in men, commonly in the upper and midperipheral lungs. The nodules may cavitate, enlarge, stay stable, spontaneously resolve, or newly appear on serial imaging. Unfortunately, the appearance of these nodules is nonspecific, usually necessitating follow-up imaging at a minimum, and bronchoscopy or even biopsy to exclude malignancy or infection (Fig. 3A and B). In essence, these nodules are a diagnosis of exclusion.

Extrapulmonary thoracic findings are common in RA, with pleural involvement more common than lung disease. Pleural thickening or effusion or both are seen in 38%-73% of patients on HRCT and in 40%-75% of patients with RA at autopsy. Large airway involvement is a less common finding in RA and includes cricoarytenoid arthritis, with abnormalities rarely identified on CT.

### Systemic Lupus Erythematosus

SLE is a complex rheumatologic condition with a broad spectrum of systemic involvement. It has an overall incidence of 2-11 persons per 100,000 a year; it is higher in women, who make up approximately 90% of patients with SLE, multiracial populations. In the African American population, the diagnosis is common among women of childbearing age; however, in other populations, it occurs more commonly in women older than 40 years. Respiratory symptoms and abnormal lung function are relatively common in patients with SLE, occurring in 63% and 66%, respectively, in a recent study. Thoracic manifestations are varied and include pleural disease, acute pneumonitis, alveolar hemorrhage, chronic ILD, and shrinking lung syndrome. Seropositivity for specific antinuclear antibodies including anti-RNP and anti-dsDNA has been linked with pulmonary and pleural involvement in SLE.

Patients with SLE may present emergently with sudden onset of fever, dyspnea, cough, pleuritic chest pain, and
hypoxia, resulting in a confusing clinical picture that mimics pulmonary infection, acute pulmonary embolus, acute lupus pneumonitis, or alveolar hemorrhage. Infections represent the second most frequent cause of death in patients with SLE and range from community-acquired pneumonia to those by atypical or opportunistic pathogens. The prevalence of acute lupus pneumonitis is difficult to estimate, and by best estimates ranges from 2%-10% in patients with SLE, with up to 50% of these patients developing acute lupus pneumonitis as their presenting manifestation of SLE. Chronic ILD is relatively rare, occurring in only 3% of patients with SLE. Some chronic ILD cases may develop after recovery from acute lupus pneumonitis or develop insidiously, with an increasing incidence of ILD with age and disease duration. Fewer than 1% of patients develop progressive loss of lung volume with associated dyspnea, a process known as shrinking lung syndrome. The pathogenesis of this condition is still unclear. The current thinking is that this condition is associated with diaphragmatic dysfunction related to diaphragmatic myopathy, phrenic neuropathy, or pleural adhesions. In the rare case of shrinking lung syndrome, there is frequently little radiographic abnormality other than reduced lung volumes with elevated diaphragms in patients with significant restrictive PFT abnormalities and with no significant pulmonary interstitial changes.

Imaging patterns in SLE are frequently nonspecific and may not correlate with patient symptoms. Several small studies have shown a relatively high rate of abnormal findings on HRCT, as found in 70% of a mixed population of asymptomatic and symptomatic patients with SLE and up to 93% of symptomatic patients with SLE. HRCT typically demonstrates lower lobe–predominant septal thickening, architectural distortion, and ground-glass opacities typical of NSIP with or without pleural effusions (Fig. 4A). In the acute setting, HRCT findings can range from minimal abnormality to diffuse ground-glass opacities or patchy consolidation or both, suggestive of diffuse alveolar damage. Patients with SLE may also present emergently with diffuse alveolar hemorrhage, which manifests as nonspecific diffuse alveolar opacities, often accompanied by hemoptysis.

Pleural disease is the most common extrapulmonary thoracic manifestation of SLE, with pleural effusions occurring in 30%-50% of patients. Lupus pleuritis frequently presents with the same confusing clinical symptoms as acute pulmonary...
manifestations described previously, particularly pleuritic chest pain. In patients with SLE and pleural effusions of uncertain etiology, thoracentesis with pleural fluid analysis, including the presence of antinuclear antibodies, may be helpful in differentiating lupus pleuritis from other disease processes.\(^{49,50}\) Other manifestations of lupus serositis include pericarditis, occasionally presenting with significant pericardial effusion (Fig. 4B). Patients with SLE may also demonstrate airway involvement such as bronchiectasis in up to 20% of patients or vascular involvement including stigmata of PAH in up to 11% of patients.\(^{14}\)

### Inflammatory Myopathies

Idiopathic inflammatory myopathies are a heterogeneous group of disorders characterized by subacute or chronic skeletal muscle inflammation and weakness. This group includes inclusion-body myositis, PM, and DM. PM and DM are frequently considered together as their signs and symptoms are similar, with the exception of cutaneous manifestations such as heliotrope rash on the upper eyelids and raised Gottron papules on the dorsal surface of the hands seen in DM. Pathologically, these are distinct entities. Because these diseases frequently coexist with other CTD and can be difficult to distinguish from each other, their exact prevalence is unknown, with estimates ranging from 6-10 per 1,000,000.\(^{51}\) PM-DM primarily affects women, with DM seen in both children and adults and PM seen after the second decade, and inclusion-body myositis primarily affects men older than 50 years.\(^{52}\) A subset of patients manifest a clinical syndrome known as antisynthetase syndrome, which is characterized by the presence of anti–aminocyl-tRNA synthetase antibodies (such as anti-PL-12, anti-PL-7, and anti-Jo-1), stigmata of PM-DM, ILD, arthritis, Raynaud phenomenon, and mechanic’s hands.\(^{53,54}\) Anti-Jo-1 is the best studied of the antisynthetase antibodies, with a prevalence of 1.2-2.5 per 1,000,000, at least 2:1 female predominance, and a strong correlation with ILD in patients with PM-DM.\(^{54,55}\)

In the general PM-DM population, the rate of ILD is variable, ranging from 5%-30%\(^{14}\) to as high as 65% or more in HRCT studies, with many asymptomatic patients having imaging findings of ILD.\(^{56}\)

HRCT most commonly demonstrates subpleural septal thickening, reticulation, and ground-glass opacities typical of an NSIP pattern. The presence of additional areas of consolidation suggesting OP is common and frequently coexists with the NSIP pattern on histopathology.\(^{57}\) Foci of OP on HRCT are typically seen as peripheral airspace opacities in the subpleural or peribronchovascular regions that vary in attenuation from ground glass to dense consolidation and may be bandlike, polygonal, or nodular in shape. Over time, these opacities may be migratory, clearing in one area and involving new areas. Crescentic opacities surrounding a focus of ground glass known as the atoll or reverse halo sign have been described as specific for OP.\(^{58}\) A UIP-type pattern is seen infrequently. Antisynthetase syndrome may have a distinct appearance, including basal-predominant septal thickening, ground glass, peribronchovascular consolidation, and associated loss of lung volume.\(^{54,59}\)

Additionally, the patients with PM-DM may develop respiratory complications such as hypoventilation from respiratory muscle weakness and aspiration from pharyngeal muscle weakness, potentially the most common respiratory complication in this population. Relatively few extrapulmonary thoracic manifestations of PM-DM are seen, with little associated airway or pleural involvement. Inflammatory myopathies can affect the heart in up to 75% of patients; however, much of this represents subclinical disease without obvious structural abnormality. Cardiovascular involvement is a relatively common cause of morbidity and mortality, with up to 45% of patients developing congestive heart failure. Therefore, imaging stigmata of heart failure or coronary artery disease may be related to the underlying CTD.\(^{60}\) These patients are also at an increased risk for malignancy, most commonly lung cancers.\(^{51}\)

### Mixed Connective Tissue Disease

MCTD is characterized by antiribonucleoprotein autoantibodies (specifically anti-U1-RNP) and a spectrum of clinical features such as Raynaud phenomenon, swollen hands, arthritis, serositis (with pleural and pericardial involvement), myositis, esophageal dysmotility, pulmonary hypertension, and ILD. It is debated whether this constellation of symptoms defines a unique CTD or represents an overlap between SLE, SSc, and PM-DM. In a recent study, the prevalence of MCTD was 3.8 per 100,000, with a strong female predominance of approximately 3:1 and age at onset in the third to fourth decade.\(^{62}\) This and other studies have demonstrated that pulmonary involvement is a common feature of MCTD, occurring in 52%-85% of patients on imaging. ILD is the most common pulmonary manifestation, with active ILD occurring in up to 66% of patients with MCTD.\(^{63}\) These patients form a spectrum of disease, from asymptomatic to advanced fibrosis, with significant mortality implications including a 20.8% mortality rate over 4.2 years for those with severe fibrosis.\(^{62}\) PAH occurs in 10%-45% of patients with MCTD and is also predictive of a poor prognosis, representing the most common cause of death in 1 study.\(^{64}\)

Much as the clinical signs or symptoms of MCTD represent an overlap of several other CTDs, the results of HRCT also reflect a combination of findings seen in other conditions. The most common findings follow the NSIP pattern, with lower lobe–predominant ground-glass opacities, nonseptal linear opacities, and peripheral reticulation (Fig. 5).\(^{63,65}\) Findings such as traction bronchiectasis, UIP-type honeycombing, and consolidation suggesting OP are less common. Other reports have suggested that ground-glass opacities are less common and that septal thickening or reticulation is the predominant finding; however, this may reflect differences in study population and possibly response to corticosteroid therapy as some studies have shown reversibility of abnormalities on HRCT finding following treatment.\(^{63,66}\) Other pulmonary findings may include low lung volumes related to respiratory muscle weakness, stigmata of aspiration or pneumonia or both, and rarely alveolar hemorrhage.\(^{14}\)
As seen in SLE, SSc, and PM-DM, patients with MCTD may also have extrapulmonary thoracic findings. Signs of PAH, including enlarged central pulmonary arteries and right heart enlargement, should be sought given the mortality implications. As with SSc, signs of esophageal dysmotility may be seen, including a patulous esophagus and retained debris. Pleural and pericardial effusions or thickening also occur, particularly in patients with SLE-dominant symptomatology, with pleural disease occurring in 12%-66% of patients with MCTD.

**Sjögren Syndrome**

SS is a relatively common autoimmune condition occurring in 0.1% of the general population and up to 3% of older adults, almost exclusively in women (up to 13:1 female: male ratio). It is characterized by lymphocytic infiltration of exocrine glands resulting in typical sicca symptoms such as dry eyes and mouth, with focal lymphocytic sialoadenitis on salivary gland pathology or positive results for the presence of antinuclear antibodies against ribonucleoproteins, Ro/SSA, or La/SSB. SS can occur either alone or in association with other CTDs, termed primary SS (pSS) and secondary SS, respectively. Thoracic involvement, including airway disease and ILD, is common in pSS; however, the prevalence depends on the patient population studied and method of diagnosis. Imaging evidence of thoracic involvement was found in 79% of patients on HRCT in one patient population, whereas only 11% of patients had clinically significant lung involvement in a separate study. SS can occur either alone or in association with other CTDs, termed primary SS (pSS) and secondary SS, respectively. Thoracic involvement, including airway disease and ILD, is common in pSS; however, the prevalence depends on the patient population studied and method of diagnosis. Imaging evidence of thoracic involvement was found in 79% of patients on HRCT in one patient population, whereas only 11% of patients had clinically significant lung involvement in a separate study. Patients with primary SS have an increased rate of respiratory infections owing to disease involvement of mucosal glands within the airways and resultant impaired microbial clearance. It can be difficult in some cases to differentiate scarring sequel to prior infection from parenchymal abnormalities related to ILD on imaging.

The most common histologic pattern observed in patients with pSS-related ILD is NSIP, with OP, lymphocytic interstitial pneumonia (LIP) and less frequently, UIP. The characteristic HRCT findings are ground-glass opacities, reticular opacities, and consolidation, generally in a lower lobe–predominant distribution. This constellation of findings suggests NSIP or OP if consolidations predominate. Thin-walled parenchymal cysts and small peripheral nodules may also be identified (Fig. 6) and can raise suspicion for LIP, particularly when seen in conjunction with ground-glass opacities. Unfortunately, although a CT diagnosis of NSIP positively correlates with histopathology in patients with pSS, other CT patterns show poor correlation with histology. Honeycombing is rare. Airway involvement is common in patients with pSS, with HRCT demonstrating bronchiectasis in up to 46% of patients and potentially resulting in an obstructive pattern at spirometry.

**Idiopathic ILD vs ILD in CTD**

Some clinical features can be used to discriminate between the ILD of CTD and idiopathic ILD. These generally include the demographics of the affected population, presence of serum antibodies, and to some degree, the findings on HRCT. IPF is defined as a chronic progressive fibrosing ILD of unknown origin characterized by UIP histology on surgical lung biopsy or findings typical of UIP on HRCT of the chest. The pattern of lower lung subpleural-predominant reticulation with honeycombing that may be accompanied by traction bronchiectasis is more than 95% specific for UIP. This UIP pattern typically has relatively little associated ground-glass opacity. IPF is
limited to the lung with serological evaluation unrevealing, including a nonspecific elevation of inflammatory markers.

The precise prevalence and incidence of IPF are unknown, but estimates range from 2-29 cases per 100,000 in the general population, with approximately 7-16 new cases per 100,000 a year. Patients with IPF are more frequently male and are typically in their sixth or seventh decade of life, with an increasing incidence with advancing age. Patients younger than 50 years are rarely diagnosed with IPF, and there is a strong association with cigarette smoking. Clinically, patients with IPF manifest with an insidious onset of dyspnea on exertion and bibasilar inspiratory crackles on auscultation. Importantly, other causes for these findings, including environmental exposure, drug toxicity, or systemic disease such as CTD must be excluded before a diagnosis of IPF can be made.4,76

In contrast to IPF, the demographics of CTDs are typically a younger and more frequently female patient population. Patients with CTD often present with multisystem disease, including a host of extrathoracic manifestations such as Raynaud phenomenon or articular involvement or both. Similarly, when patients with CTD develop pulmonary manifestations, they are typically multicompartmental, with varying degrees of lung, pleura, airway, and pulmonary vascular involvement (Table 1). Along with the variable clinical manifestations of CTD, the associated ILD may produce any of the established histologic patterns of ILD, including NSIP, UIP, LIP, cryptogenic OP, or diffuse alveolar damage.77 Although these patterns are seen with varying frequency in different disorders, the histologic calling card of CTD-related ILD is NSIP (Table 1).

Importantly, patients with CTD-related ILD have a better prognosis than IPF, with an approximately 70% 5-year survival compared with 20%-35% for IPF.78 Prognosis has a better prognosis than IPF, with an approximately 70% 5-year survival compared with 20%-35% for IPF.78 Prognosis has been best studied in SSc and RA, controlled for age, sex, smoking status, ILD histology, and pulmonary function testing results among other factors. Mortality is most closely associated with measures of disease severity at the time of diagnosis, including extent of fibrosis and pulmonary function abnormalities, with relatively less mortality difference observed based on ILD histology alone.10,12 RA is the one exception to this generalization, with several studies documenting mortality similar to IPF in patients with RA with UIP histology or typical imaging findings of UIP on HRCT. In 1 study, these patients had a median survival of 3.2 years.31,34,76 This has led some authors to suggest that treatment of RA-associated ILD should be determined by the underlying histopathology, with patients with NSIP receiving immunosuppressive therapy and patients with UIP referred for possible lung transplantation.34 The diagnosis and treatment of these patients are multidisciplinary in nature, with radiologists and HRCT playing a significant role in screening and monitoring patients with suspected or known CTD-related ILD. We have reviewed CTDs and their common thoracic manifestations, with an emphasis on HRCT findings that can help suggest the diagnosis of CTD-related ILD.

In patients with CTD with subacute or chronic thoracic symptoms, HRCT is an important diagnostic tool to perform a thorough evaluation of ILD. These patients may show a variety of findings, from stigmata of ILD to pleural disease, airway disease, or pulmonary hypertension. Although most patients with CTD-related ILD have NSIP pathology and associated nonspecific imaging findings, radiologists should seek out findings suggestive of a more specific histologic diagnosis whenever possible. Similarly, when faced with a new diagnosis of ILD, the radiologist should seek to differentiate between UIP and NSIP imaging patterns when possible and identify secondary imaging signs of undiagnosed CTD, such as a patulous esophagus, or pleural disease, as these findings would significantly alter the prognosis and clinical course compared with IPF. Acute symptoms frequently present a diagnostic challenge as the imaging findings associated with an acute exacerbation of ILD may overlap with those of pulmonary infections, aspiration, drug reactions, or other pathologies. Imaging is a key tool in the appropriate diagnosis and management of these patients and can provide referring clinicians with important information in the management of this difficult patient population.

Conclusions

CTDs represent a heterogeneous group of disorders that can produce a broad spectrum of thoracic pathologies on imaging.

References

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