Interstitial Lung Disease in the Connective Tissue Diseases

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KEYWORDS

• Connective tissue • Interstitial lung disease • Inflammation • Immunity

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

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

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

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

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Clin Chest Med 33 (2012) 123–149
doi:10.1016/j.ccm.2012.01.004

GENERAL APPROACH

Respiratory Symptoms

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

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

Other Systems

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

Physical Examination

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

Serologic Testing

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

Pulmonary Function Tests

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

Table 1
Autoantibody testing in the evaluation of ILD

Autoantibody	Type	Association with CTD
ANA	ANA	May be seen in various CTDs (SLE, SSc, SS, PM/DM) Nucleolar staining suggests SSc
dsDNA	Anti–dsDNA antibody	Highly specific for SLE
SSA	Anti-Ro antibody	SLE, SS, myositis associated
SSB	Anti-La antibody	Common in SS, 15% in SLE
Scl-70	Anti-DNA topoisomerase 1	Common in SSc (70% prevalence); high association with ILD
RF	RF	Sensitivity 60%–80% and specificity 60%–85% for RA
CCP	Anti-CCP antibody	Sensitivity 68% and specificity 96% for RA
RNP	Anti-U1 small nuclear RNP	High titers seen in MCTD
Jo-1, EJ, PL7, PL12, OJ	Anti-tRNA synthetases	Seen in DM/PM/antisynthetase syndrome

Abbreviations: ANA, antinuclear antibody; CCP, cyclic citrullinated peptide; dsDNA, double-stranded DNA; MCTD, mixed CTD; RF, rheumatoid factor; RNP, ribonucleoprotein; SSc, systemic sclerosis; SS, Sjögren syndrome.
Data from Refs.[13,283–285]

leads to resting arterial hypoxemia and profound exertional desaturation. It is crucial to identify exertional desaturation, because the use of supplemental oxygen and correction of exertional hypoxemia improves exercise endurance.[20]

Chest Imaging

The first suggestion of underlying ILD may arise from an abnormal chest radiograph, typically showing basilar, peripheral reticular, or reticulonodular opacities.[21] However, particularly in early disease, the chest radiograph may be normal.[22] High-resolution computed tomography (HRCT) of the chest is more sensitive than the chest radiograph, particularly in the evaluation of CTD-ILD. In some cases of CTD-ILD, the pattern and distribution of radiographic abnormalities observed on HRCT accurately predict the pathologic findings.[23]

Common features that may be present on HRCT include ground-glass opacities (hazy areas of increased parenchymal density that do not obscure the underlying lung markings), reticulation (a series of crisscrossing lines resulting in a weblike pattern), bronchiectasis, and micronodules.[21,24,25] The abnormalities in CTD-ILD occur predominantly at the periphery of the lung and are often associated with architectural distortion, traction bronchiectasis, and honeycombing. HRCT findings in CTD-ILD are indistinguishable from those of the idiopathic interstitial pneumonias.[26] The radiographic differential diagnosis most often includes usual interstitial pneumonia (UIP), nonspecific interstitial pneumonia (NSIP), desquamative interstitial pneumonia (DIP), and organizing pneumonia (OP) (**Table 2**). Mixed or unclassifiable patterns may also occur. Mosaic, heterogeneous lung attenuation caused by small airway obstruction with air trapping, as seen with bronchiolitis obliterans, can also be seen.

Among patients with idiopathic ILD, certain HRCT features predict the histopathologic findings of UIP, which is the pathologic equivalent of idiopathic pulmonary fibrosis (IPF).[24,27] In particular, the characteristic radiographic UIP pattern consists of peripheral, subpleural, basilar-predominant, reticular opacities in combination with basilar honeycombing, but without features, such as ground-glass opacities, that might suggest another form of ILD (**Fig. 1**). When present, these features have been shown to confidently predict the presence of pathologic UIP when surgical biopsy is obtained in idiopathic ILD.[28–30] The same correlation between radiographic and pathologic UIP likely occurs in patients with CTD-ILD.[31]

A radiographic NSIP pattern has also been described, in which the ILD is lower lobe predominant, often sparing the immediate subpleural area, and consisting of bilateral, patchy areas of ground-glass opacity with reticulation, architectural distortion, and traction bronchiectasis but without significant honeycombing (**Fig. 2**).[32–35] Correlation between this radiographic pattern and the histopathologic pattern of NSIP is not reliable.[33] Some characteristics in the inflammatory forms of CTD-ILD may suggest underlying abnormality, such as the peripheral, patchy alveolar opacities in OP, but the radiographic appearance in such cases is not specific and tissue may be required for diagnosis.[36] In CTD, it is common to see multiple

Table 2
Features of the common radiographic and pathologic patterns observed in CTD-ILD

	Distribution on HRCT	Typical Radiographic Features	Typical Pathologic Features
UIP	Peripheral, subpleural Basilar Bilateral	Reticular markings Traction bronchiectasis Honeycombing Minimal ground-glass opacities	Fibrosis with microscopic honeycombing Fibroblastic foci Heterogeneous lung involvement Subpleural distribution Absence of features suggesting alternative diagnosis
NSIP	Peripheral, subpleural Basilar Bilateral	Ground-glass opacities Reticular markings NSIP line Minimal or no honeycombing	Homogeneous interstitial fibrosis and/or inflammation Rare honeycombing
OP	Diffuse Often peripheral and patchy Occasionally peribronchovascular	Patchy ground-glass opacity and consolidation Sometimes nodular	Plugs of connective tissue in small airways Patchy distribution Little or no fibrosis Preservation of lung architecture Mild interstitial chronic inflammation
DAD	Diffuse	Ground-glass opacities Alveolar consolidation	Hyaline membranes Edema Diffuse distribution Uniform temporal appearance
LIP	Diffuse	Ground-glass opacities Centrilobular nodules Septal and bronchovascular thickening Thin-walled cysts	Diffuse interstitial infiltration by T lymphocytes, plasma cells, macrophages Alveolar septal distribution Lymphoid hyperplasia

Abbreviations: DAD, diffuse alveolar damage; LIP, lymphoid interstitial pneumonia.

Data from American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. Am J Respir Crit Care Med 2002;165(2):277–304.

radiographic patterns simultaneously. When observed over time, HRCT manifestations in CTD-ILD typically show progressive reticular and honeycomb change, with occasional acute exacerbations of disease, in which diffuse ground-glass opacities are superimposed on underlying fibrotic lung disease.[37] Progressive fibrosis on HRCT is associated with worse prognosis.[38] Despite the inability to clearly predict histology through the use of HRCT in all cases, many patients with CTD do not undergo surgical lung biopsy, because histopathologic diagnosis is thought unlikely to change management. It is only when clinical or radiographic features are atypical that biopsy is pursued.

Bronchoalveolar Lavage

Bronchoalveolar lavage (BAL) has long been advocated in the evaluation of CTD-ILD because it offers a noninvasive way to sample the cellular and protein composition of the lower respiratory tract in the absence of lung biopsy. Saline is instilled into the distal airways with the bronchoscope wedged in a subsegmental bronchus. Aliquots of fluid are then aspirated, forming the BAL fluid sample. The cellular differential in healthy adults consists predominantly of alveolar macrophages. Other leukocytes are present in smaller numbers, usually less than 15% lymphocytes, less than 3% neutrophils, and less than 2% eosinophils.[39] Research has focused on correlations between fluid characteristics and clinical features, including the presence or absence of ILD, the severity of ILD, progression of disease, and overall prognosis, as well as response to therapy.

Although BAL fluid analysis has been performed in all of the CTDs, it has received particular attention in SSc. In particular, the presence or absence of alveolitis has been described to reflect local

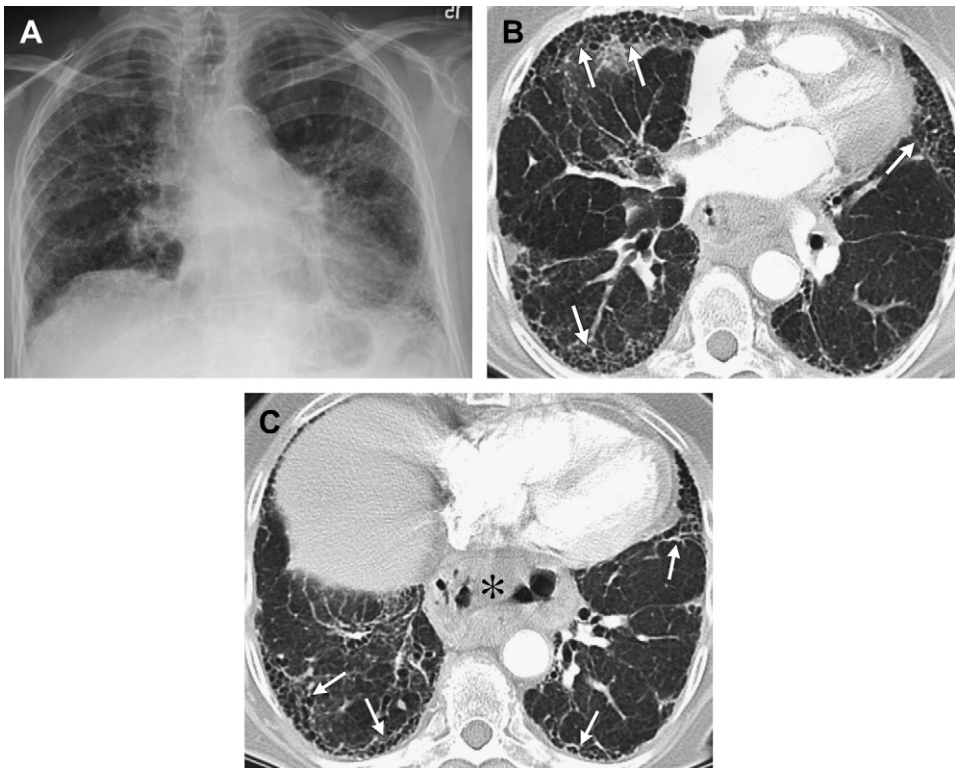

Fig. 1. A 73-year-old woman with a radiographic pattern of RA and UIP. Frontal chest radiograph (*A*) shows reduced lung volumes with lower lobe–predominant coarse interstitial markings compatible with pulmonary fibrosis. High-resolution (1.25-mm thick sections) computed tomography (CT) images at the level of the midthorax (*B*) and lower thorax (*C*) show peripheral reticular markings with architectural distortion and small subpleural cysts/honeycombing (*arrows*). The patient also has a large hiatal hernia (*asterisk*).

inflammation, in which neutrophils and eosinophils are predominant. Despite the correlation between BAL alveolitis and severity of lung disease in SSc, BAL cytology has not been consistently shown to correlate well with prognosis or response to therapy.[40] Similarly, in many of the other CTD-ILDs, BAL neutrophilia seems to correlate with poorer lung function but has not consistently proved useful for diagnosis or assessing prognosis and response to therapy.[41–44] Multiple biomarkers in BAL fluid have been proposed to give prognostic information, but no individual finding has been adequately replicated in larger studies.

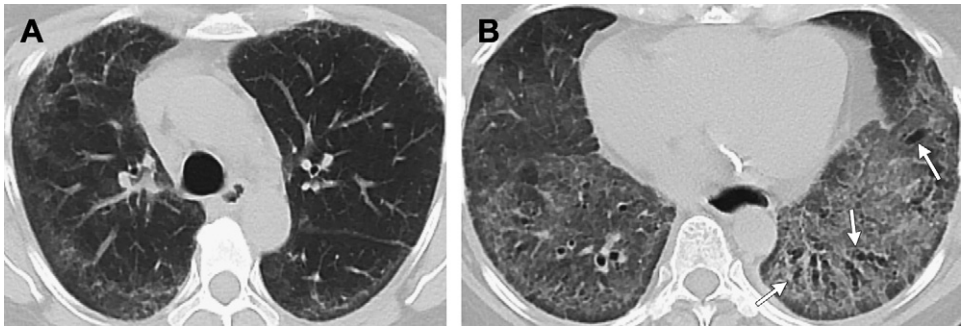

Fig. 2. High-resolution (1.25-mm thick sections) CT images obtained through the midthorax (*A*) and lower thorax (*B*) in a 57-year-old woman with scleroderma who presented with cough and shortness of breath. There are bilateral areas of ground-glass opacity with a peripheral distribution in (*A*) and lower lobe predominance (*B*), as well as reticular markings and traction bronchiectasis (*arrows*), all compatible with a nonspecific interstitial pneumonia (NSIP) pattern.

The promise of BAL sampling to give clinical information is likely limited by several issues. The largest constraint is a lack of standardization in the performance of the procedure. Some of the many variables between operators include the amount of fluid instilled, the pressure with which the fluid is aspirated, the location sampled and whether this is guided by HRCT abnormalities, which aliquots are examined and whether the first is discarded, and the skill of the technician examining the fluid.[45,46] Despite published guidelines, wide variability continues to exist and likely explains much of the inconsistent data that have resulted.[47,48] Another major factor in the inconsistent interpretation of BAL fluid results is that there are other explanations relevant to the CTD-ILD population for alterations in BAL cellularity, including infection, smoking, and recurrent aspiration.[46]

Despite these issues, BAL is an important adjunct in the evaluation of radiographic abnormalities, primarily in ruling out alternative diagnoses to CTD-ILD, including eosinophilia observed in some drug reactions, diffuse alveolar hemorrhage, and opportunistic infection.[49–51] Bronchoscopy with BAL should be considered in the evaluation of new air space opacities in any patient receiving immunosuppressive therapy.

Pathology

The major pathologic patterns recognized in CTD-ILD are the same as those recognized by the 2002 European Respiratory Society (ERS)/ATS reclassification of the idiopathic interstitial pneumonias (see **Table 2**).[52] UIP may be more common than NSIP in RA.[53] In other CTDs, particularly SSc and PM/DM, the NSIP pattern is the most common form (**Fig. 3**).[54,55] OP is more commonly observed in RA and PM/DM but may be present in SLE, Sjögren syndrome, and SSc (**Fig. 4**).[23] Diffuse alveolar damage (DAD), lymphoid interstitial pneumonia (LIP), and follicular bronchiolitis are less commonly observed patterns, but can complicate CTD.[2] Other findings, such as lymphoid hyperplasia and plasma cell infiltration, are more common in CTD-ILD and, when present pathologically, should suggest the diagnosis if CTD has not previously been suspected.[56] Another notable feature of CTD-ILD is that several pathologic patterns may be present in the same biopsy specimen.[2,57]

Prognosis in the idiopathic interstitial pneumonias is tightly linked with histopathologic pattern. UIP (IPF) carries a poor prognosis, whereas NSIP in general carries a significantly better prognosis.[16,30,58] Despite similar radiographic and pathologic characteristics to the idiopathic interstitial pneumonias, most forms of CTD-ILD have been shown to carry a better prognosis than idiopathic ILD.[26,59,60] Among the CTD-ILDs, however,

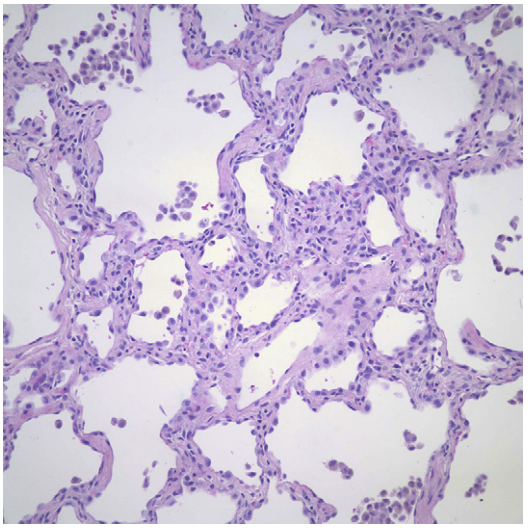

Fig. 3. NSIP. There is diffuse septal fibrosis with a mild mononuclear infiltrate, as well as mild diffuse type II cell hypertrophy. No organizing pneumonitis or fibroblast foci are seen. No granulomas or eosinophilic infiltrate are present. Honeycombing is absent. There is a mild accumulation of alveolar macrophages in the alveoli. 20× objective.

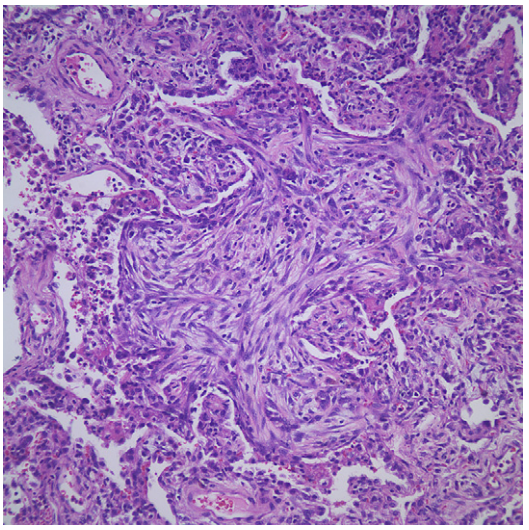

Fig. 4. OP. There is florid fibromyxoid granulation tissue within alveolar ducts and a moderate lymphoplasmacytic infiltrate. No hyaline membranes, necrosis, neutrophilic or eosinophilic infiltrate, or granulomas are seen. Established collagen fibrosis is not present, including lack of honeycombing. 10× objective.

RA may be the exception to this finding. Recent data suggest that the course of UIP in RA-ILD may be similar to that of IPF.[61]

Treatment of CTD-ILD

Immunosuppressive therapy

Many forms of CTD-ILD show responsiveness to immunosuppression. The decision to initiate immunosuppressive therapy should include an assessment of the likelihood of response as well as the risks and side effects of the medications. Corticosteroids have many potential toxicities, including glucose intolerance, bone loss, cataract development, delirium, and mood instability.[62] Underlying clinical characteristics, such as the patient's age and comorbidities (diabetes mellitus, osteoporosis, psychiatric disease) should be strongly considered. Frequently in CTD-ILD, a more prolonged course of therapy is warranted and the early addition of steroid-sparing medications can allow for lower doses of corticosteroids. Severity of disease, or particular CTD (such as SSc), may dictate the use of cytotoxic agents such as cyclophosphamide. These medications should only be prescribed by physicians familiar with their use and potential toxicities. Measures of objective improvement, including PFTs, exercise oximetry, and radiographic studies should be used; this is particularly true with the use of corticosteroids, which lead to an increase in energy level and mood, making subjective measures of patient assessment problematic. When patients either show progression despite ongoing therapy or show no improvement in the rate of decline in lung function after 6 months of therapy, discontinuation should be considered to avoid toxicity without the likelihood of benefit.

Supportive therapy

Measures intended to improve quality of life and decrease respiratory symptoms should be considered in all patients with CTD-ILD. Pulse oximetry testing can uncover resting and exertional hypoxemia. Even simple ambulation in the hallway can unmask exertional desaturation and the need for supplemental oxygen. The use of oxygen in the ILD population has not been studied in controlled trials in ILD, but is recommended to maintain saturations greater than 90% at rest or with exercise.[63] Similarly, nocturnal oxygen is used, based on data showing the negative impact nocturnal hypoxemia has on quality of life.[64] A wide variety of options are available to provide convenient, portable systems.

A large body of evidence shows that a structured form of exercise such as pulmonary rehabilitation improves muscle strength and endurance in chronic obstructive pulmonary disease (COPD).[65,66] Compelling data supporting the use of pulmonary rehabilitation in ILD are now increasing.[67–71] In addition to the benefits of improved exercise tolerance, patients with ILD may also benefit from education regarding oxygen use, breathing and pacing techniques, and social support.[65] Pulmonary rehabilitation can assist in the identification of anxiety and depression, a common problem for patients with chronic lung disease.[72]

Treatment of comorbidities

Patients with CTD-ILD frequently have comorbid conditions that need to be addressed concomitant with the ILD. Particularly in dyspneic patients, investigations for the presence of ischemic heart disease should be undertaken in patients with other cardiovascular risk factors. The risk for ischemic heart disease is increased among patients with ILD, and patients with SLE and RA are at risk for premature atherosclerosis.[73–75] Patients should also be counseled regarding smoking cessation. In particular, patients with some forms of pulmonary fibrosis have an increased risk of developing lung cancer, and CTD itself may carry some risk for malignancy.[63,76,77] The prevalence of obstructive sleep apnea may be high among patients with ILD, even in the absence of excessive sleepiness or obesity, and polysomnography should be considered.[78–80] Patients with ILD may be at increased risk for development of thromboembolic disease, and particularly patients with CTD such as SLE should have new complaints of leg swelling or shortness of breath evaluated with this in mind.[81,82]

There is a high prevalence of gastroesophageal reflux disease (GERD), often asymptomatic, among patients with IPF.[83,84] Some data suggest that GERD may be linked to the development of IPF and is correlated with worsening of disease.[85] Close ties between SSc lung disease and GERD are also suspected and many forms of CTD may be strongly associated with GERD.[86,87] The question of when to seek evidence of and to treat asymptomatic GERD is less clear.[63]

Pulmonary hypertension develops in a significant proportion of patients with ILD, often caused by the effects of chronic hypoxia and the destruction of capillaries by the fibrotic process.[88] In addition, pulmonary arterial hypertension (PAH) may complicate several of the CTDs, particularly scleroderma, MCTD, SLE, PM/DM, and more rarely RA.[89] Pulmonary hypertension contributes to diffusion impairment and symptoms. Right heart catheterization may be needed to further characterize the nature of the pulmonary hypertension, as well as to assess for any role of left heart dysfunction.[88,90] Therapy for the combination of

ILD and pulmonary hypertension is controversial but may be considered.[91,92]

Lung transplantation

Lung transplantation should be considered for patients with advanced, progressive CTD-ILD. Data suggest that carefully selected patients with CTD may have equivalent survival to other patients undergoing lung transplantation, particularly if esophageal dysfunction is addressed.[93–95] The Lung Allocation Score (LAS) tends to prioritize patients with advanced ILD.[96] Decisions regarding whether and when to list are difficult in CTD-ILD, because the rate of progression is difficult to predict, and a sudden, unanticipated exacerbation of disease may occur.[97] In the idiopathic interstitial lung diseases, fibrotic lung disease with a severely impaired diffusion capacity (DL_{CO}) (<39% predicted) predicts poor survival because of the underlying disease and this measure is often used to prompt evaluation for listing.[98] Lung transplantation requires the emotional and physical ability to tolerate a complex medical regimen of immunosuppressive therapy.[99]

RA

RA is a chronic inflammatory disease affecting the synovial lined joints and symmetrically involves the small joints of the hands and feet.[6] The diagnosis of RA has typically been made with the use of criteria proposed by the American Rheumatism Association in 1987.[6] However, the use of newer molecular markers such as anti-CCP antibodies has led to earlier diagnosis, reflected in the criteria proposed in 2010 by the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) (**Box 1**).[100,101] RA occurs most commonly in women between the ages of 35 and 50 years, although men are also affected.[102,103]

Pulmonary disease is a major source of morbidity and mortality in RA, manifesting most commonly as ILD, obstructive airways disease, rheumatoid nodules, and pleural involvement.[102] RA-associated ILD (RA-ILD) is often diagnosed in the setting of longstanding RA, but may present before or at the same time as arthritis and other rheumatologic complaints.[104] In general, RA-ILD tends to be slowly progressive; however, some patients may experience periods of sudden deterioration and approximately 10% of patients die of progressive respiratory failure.[37,105,106] Hospitalization for a respiratory cause predicts high mortality over the subsequent 5 years.[107] Risk factors for the development of RA-ILD include older age, male sex, and a history of cigarette smoking.[108]

Box 1
2010 ACR/EULAR criteria for the diagnosis of RA

1. Presence of synovitis in at least 1 joint
2. Absence of an alternative diagnosis to explain the synovitis
3. Score of at least 6 out of 10 from table given later
4. Evidence of longstanding or inactive disease with previous fulfillment of criteria

1. Joints	
2–10 large joints (shoulder, elbow, hip, knee, ankle)	1 point
1–3 small joints	2 points
4–10 small joints	3 points
More than 10 joints (at least 1 small joint)	5 points
2. Serology	
Low positive RF or anti-CCP	2 points
High positive RF or anti-CCP	3 points
3. Acute phase reactants	
Increased CRP or ESR	1 point
4. Duration of symptoms	
At least 6 weeks	1 point

Abbreviations: CRP, C-reactive protein; RF, rheumatoid factor.

Adapted from Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010;62(9):2574.

Early reports prompted increased awareness of ILD in RA.[109–112] Estimates of its prevalence vary, largely because of variations in the sensitivity of the modalities used. For example, ILD identified by chest radiograph alone in patients with RA was present in fewer than 5% of patients.[22] Studies using PFTs identified ILD in 33% to 41% of patients with RA and HRCT identified abnormalities in 20% to 63%, which has been confirmed by autopsy studies.[14,15,105,106,113–115] Retrospective population-based studies have estimated a lower rate of clinically significant ILD among patients with RA (6.3%–9.4%).[116,117] Although it is possible that HRCT and PFT identify abnormalities without clinical significance, it is also likely that significant ILD is underrecognized in this population.

Clinical Features

Generally, ILD occurs in patients with well-established RA.[118] However, up to 20% of patients have onset of ILD before the diagnosis of RA.[108] Patients with idiopathic ILD are often found to have RA-related autoantibodies such as RF and

anti-CCP but no articular findings of RA; some may eventually develop clinical RA.[119] The delay between presentation of lung disease and subsequent joint symptoms can be as long as 6 years.[108,120]

RA-ILD typically presents with progressive dyspnea, although cough and pleuritic chest pain may occur.[3] Physical examination findings are often nonspecific and may include bibasilar fine, dry, velcro crackles. Digital clubbing and evidence of right heart failure are late signs of RA-ILD.

Like other forms of CTD-ILD, PFTs in RA-ILD typically show restrictive physiology and diffusion impairment. A defect in DL_{CO} is often the earliest PFT finding in RA-ILD.[14,15] Exertional arterial oxygen desaturation may be present despite normal resting saturations and is predicted by abnormalities in lung function.[16,17]

Radiographic Features

The most common features on HRCT in RA-ILD are glass opacities, reticulation, bronchiectasis (**Fig. 5**), and micronodules.[21,24,25] In particular, the findings in RA-ILD have been grouped into 4 main patterns: a UIP pattern consisting of bibasilar subpleural reticulations and honeycombing; an NSIP pattern consisting of predominantly lower lobe reticulation and ground-glass opacities; a bronchiolitis pattern showing centrilobular micronodules and bronchiectasis or bronchiolectasis; and an OP pattern consisting of largely peripheral airspace consolidation and ground-glass opacities.[24] Based on several small studies, it is likely that the radiographic UIP pattern in RA-ILD predicts a pathologic finding of UIP.[31,53] It is not clear that the radiographic NSIP pattern similarly predicts its pathologic correlate.[33,121] Patients with a ground-glass–predominant pattern may have a better prognosis than those with well-established fibrosis.[37] On serial HRCT, RA-ILD may manifest radiographically with acute exacerbations of disease characterized by the onset of diffuse ground-glass opacities, or with progressive reticulation, traction bronchiectasis, and honeycombing.[37] Care should be taken with the interpretation of ground-glass opacities when present in a mosaic pattern. High-resolution inspiratory and expiratory images are needed to distinguish ground-glass opacities from small airways obstruction, in which the denser areas reflect normal lung adjacent to radiolucent areas of air trapping. This finding is observed in RA-associated bronchiolitis obliterans (**Fig. 6**).

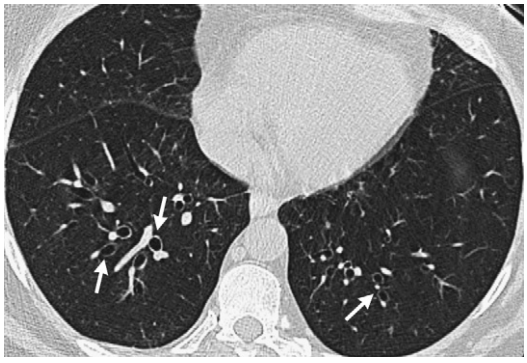

Fig. 5. A 56-year-old woman with RA and bronchiectasis. High-resolution (1.25-mm thick sections) CT image through the lower thorax shows mild, cylindrical bronchiectasis (*arrows*) in both lower lobes.

Pathologic Features

In contrast with the other CTD-ILDs, the pathology of RA-ILD shows a preponderance of UIP.[53] Certain features, such as lymphoid hyperplasia and plasma cell infiltration, as well as the presence of more than 1 pathologic process in the same biopsy specimen, are common in RA-ILD and should suggest the diagnosis (**Fig. 7**).[2,56,57] Some less common histopathologic patterns observed in RA include OP, follicular bronchiolitis, LIP, and DAD.[2] RA-ILD may not share the favorable prognosis that some other forms of CTD-ILD seem to carry.[122] Recent data suggest that the course of UIP in RA-ILD may be inexorable and fatal, as seen in IPF (idiopathic UIP).[61]

Diagnostically, the differentiation between infection, drug reaction, and underlying RA-ILD can be difficult, because many of the drugs used to treat RA can cause pulmonary toxicity

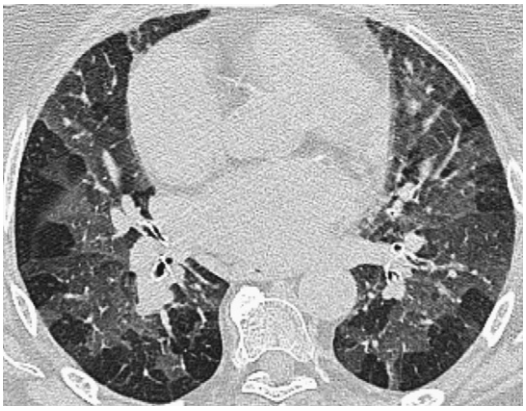

Fig. 6. A 65-year-old woman with RA and progressive shortness of breath secondary to bronchiolitis obliterans. High-resolution (1.25-mm sections) CT images performed during expiration at the level of the mid-thorax show multifocal lucent areas of moderate to severe air trapping. The greyer areas are normal lung at expiration.

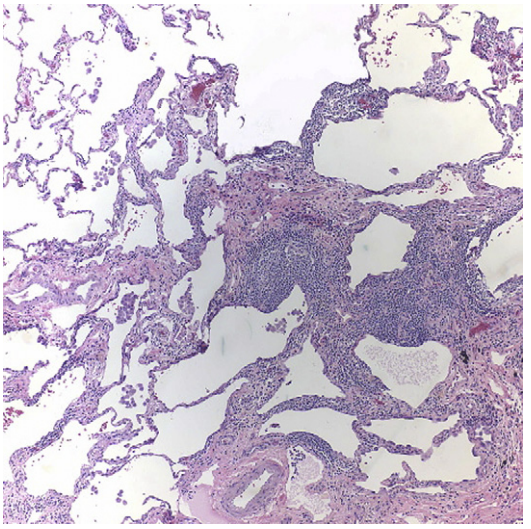

Fig. 7. Lymphoid hyperplasia. In the center of the image, there is a lymphoid follicle with a germinal center. Fibroblast foci and organizing pneumonitis are not present. There is established fibrosis. Although lymphoid hyperplasia in end-stage lung is nonspecific, in areas away from end-stage lung, this finding suggests collagen vascular disease. 4× objective.

(eg, methotrexate, leflunomide, and the TNF-α inhibitors etanercept, infliximab, and adalimumab) and can also predispose to opportunistic infection.[123–129] The diagnosis of RA-ILD should take into consideration the clinical features, the radiographic appearance, the pathology, and the temporal correlation with drug initiation.[130,131] Several different pathologic patterns may be consistent with drug toxicity, including cellular interstitial infiltrates, granulomas, tissue eosinophilia, and a DAD pattern with perivascular inflammation.[123,132]

Treatment

There are many unanswered questions pertaining to RA-ILD, in particular whether to treat subclinical disease and which therapies should be used. However, progressive lung disease is typically treated aggressively because response has been reported with corticosteroids, azathioprine, cyclosporine, and cyclophosphamide.[9,133,134] If there is no response, therapy can be discontinued to avoid toxicity without hope of benefit. Mycophenolate mofetil (MMF)has been reported to have a beneficial effect on CTD-ILD and may be considered in RA-ILD.[135,136] Data for the use of rituximab in RA-ILD are lacking. Some reports suggest that tumor necrosis factor α (TNF-α) inhibitors may be effective in RA-ILD, but others report cases of pulmonary toxicity in patients with underlying ILD.[127,128,137] Lung transplant referral should be considered in patients with severe fibrotic lung disease.

SYSTEMIC SCLEROSIS (SCLERODERMA)

SSc is a multisystem disorder characterized by endothelial and epithelial cell injury, fibroblast dysregulation, and immune system abnormalities that ultimately lead to systemic inflammation, fibrosis, and vascular injury.[138,139] Clinically, the disease is heterogeneous and may involve multiple organ systems, most commonly the respiratory system, the skin, and the digestive system. Pulmonary involvement is the leading cause of morbidity and mortality among patients with SSc.[140] ILD is exceptionally common among patients with SSc, historically found in 28% of patients, and with the use of HRCT in more than 65% of all patients with SSc and up to 93% of patients with abnormal PFT results.[141,142] Clinically significant ILD is found in at least 40% of patients, and is a major contributor to morbidity and mortality.[143] At autopsy, most patients have microscopic evidence of lung fibrosis.[144] Clinically significant ILD is more commonly observed in diffuse SSc than in the limited form, but all types of SSc, including SSc sine scleroderma (SSc without skin involvement) may be complicated by ILD.[145,146]

PFTs

Early ILD in SSc is often asymptomatic and is detected only by PFT and HRCT abnormalities. In particular, the earliest sign of SSc-associated ILD (SSc-ILD) on PFT is a decrement in DL_{CO}, which correlates better than other lung function parameters with extent of radiographically evident ILD by HRCT.[147] In particular with SSc, decrements in DL_{CO} can reflect concomitant pulmonary vascular disease and evaluation should be undertaken to distinguish between ILD and pulmonary arterial hypertension.[148] Declines in both forced vital capacity (FVC) and DL_{CO} at diagnosis correlate well with severity of disease and with overall prognosis.[149] In particular, an FVC less than 80% predicted at diagnosis strongly predicts both the severity of decline in FVC percent predicted over the subsequent 5 years, as well as time to decline in DL_{CO} less than 70% predicted.[150] In addition, among patients with early SSc, FVC less than 50% strongly predicts mortality.[151] Most of the deterioration in FVC seems to occur in the first 2 years after diagnosis, making initial screening and follow-up PFTs particularly important during that period.[152] Patients with antitopoisomerase antibodies (anti–Scl-70) may be at higher risk for

this more rapid decline.[153] Low 6-minute walk distance correlates with functional impairment in SSc-ILD, but may not be a reliable outcome measure for use in clinical trials, because it can be affected by musculoskeletal issues, including pain, weakness, and vascular insufficiency, as well as by concomitant PAH.[154]

Radiographic Features

As with all CTD-ILD, HRCT is more sensitive than the chest radiograph at identifying ILD in SSc as well as in characterizing the extent of fibrosis.[155] Radiographic features in SSc-ILD typically resemble those described in NSIP, characterized by subpleural ground-glass opacities and fine reticular markings with traction bronchiectasis, but little or no honeycombing (**Fig. 8**).[156] The presence of ground-glass opacities on initial computed tomography (CT) is a predictor for progression to more advanced fibrosis, whereas an initial CT without ground-glass opacities predicts a lack of progression for most patients.[157] Despite long-held presumptions that ground-glass opacities represent active alveolitis and inflammation, their presence may often reflect fine fibrosis and be irreversible despite therapy in SSc-ILD.[158] Intraobserver and interobserver variability has hampered the use of HRCT data for research and clinical assessment; however, computer-aided models may offer some improvement in reliability.[159,160] Combined staging systems, incorporating simple measurements of radiographic lung involvement with PFT data, may improve predictions of disease progression and mortality but also require further study.[161]

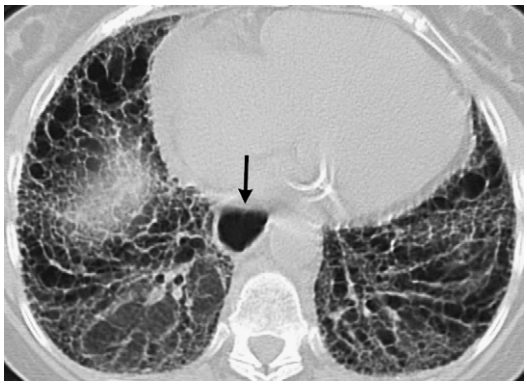

Fig. 8. A 58-year-old woman with scleroderma and fibrotic NSIP. Axial CT image through the lower thorax shows reticular markings, architectural distortion, and extensive traction bronchiectasis compatible with pulmonary fibrosis. A dilated distal esophagus (*arrow*) is also present.

Other clues to the presence of scleroderma that can be detected on chest CT include a dilated esophagus and the presence of soft tissue calcification.[162] Because esophageal dysmotility is common in these patients, they are also at increased risk of aspiration pneumonia, which can be seen at imaging as dependent areas of consolidation and ground-glass opacity, as well as small, clustered centrilobular nodules.[86]

Pathologic Features

The most common histopathologic pattern in SSc-ILD is NSIP, with a minority of biopsies showing UIP or end-stage fibrosis.[149] Unlike the marked contrast in survival seen between idiopathic UIP (IPF) and idiopathic NSIP, there seems to be little difference in mortality based on histopathologic subsets in SSc.[54,149] For this reason, surgical biopsy is generally not obtained in SSc-ILD unless atypical features are present. More recently, a central distribution of radiographic abnormalities on CT has been associated with the pathologic finding of centrilobular fibrosis and clinical evidence of esophageal reflux in SSc.[87] This finding suggests that there may be a causal link between subclinical aspiration and some forms of SSc-ILD. Abnormal esophageal motility, decreased lower esophageal sphincter pressure, and gastroparesis can all contribute to reflux in SSc and chronic aspiration may occur.[163] Among patients with more severe esophageal dysfunction, PFT parameters are more severely impaired, and there is an increased frequency of radiographically apparent ILD.[164–167] Over time, these patients seem to have more rapid progression of lung impairment.[167] It is not clear whether this association is causal for most patients or whether simultaneous worsening of lung and gastrointestinal (GI) disease reflects progression of fibrosis in multiple organ systems.

Treatment

Treatment in SSc-ILD has typically been targeted at the inflammatory component of the disease, although with only modest improvement in outcomes. Prednisone and other corticosteroids were used in the past but, with the discovery of a link between high-dose steroid use and scleroderma renal crisis, this has fallen out of favor.[168] Most studies of other immunosuppressive agents have included low dose of prednisone and, for this reason, it is often included in treatment regimens.

Multiple small, uncontrolled trials have suggested a beneficial effect of cyclophosphamide on symptoms, lung function, radiographic

abnormalities, and survival.[169–171] The Scleroderma Lung Study I was the first randomized, placebo-controlled trial to evaluate the effect of oral cyclophosphamide on lung function in SSc-ILD.[172] Cyclophosphamide had a statistically significant, although modest (2.53%), positive effect on the primary outcome of difference in FVC percent predicted at 1 year.[172] Some important secondary outcomes such as dyspnea, skin thickening, and health-related quality of life were also improved. Cyclophosphamide was associated with increased short-term toxicity in the study, and is known to have long-term risks including increased risk for bladder cancer and other malignancies.[173] Subset analysis has suggested that the group most likely to benefit from treatment includes those patients with more severe restriction and fibrosis at baseline, although this remains unproven.[172,174] Long-term follow-up showed that the beneficial effects of cyclophosphamide on lung function were lost by 24 months.[174] Despite the small absolute change in FVC percent predicted, it has been suggested that the stability of lung function attained in treated patients may represent the true success in SSc-ILD and that immunosuppressive therapy to prevent progression of disease may be required long-term.[175]

Methods to diminish the toxicity of treatment include alteration in the administration of cyclophosphamide from daily oral administration to monthly infusions, which minimize the cumulative dose; switching from cyclophosphamide after 6 to 12 months to another, less toxic agent such as azathioprine or MMF; or replacing cyclophosphamide by initiating therapy with such agents.[175–177] MMF has shown some early promising results in small studies and further data are awaited.[178,179] The Scleroderma Lung Study II, which is ongoing, is examining the role of MMF as primary therapy for SSc-ILD compared with cyclophosphamide. Azathioprine has similarly been used when less severe disease is present, or when the side effects of cyclophosphamide are prohibitive. This agent may offer some efficacy but is not well studied and is limited by side effects in a substantial minority of patients.[180] It is more frequently used for maintenance after cyclophosphamide and seems to offer some usefulness in this regard.[181]

Other agents have been evaluated as potential alternatives to cyclophosphamide; however, none has fulfilled its promise. The endothelin-1 inhibitor bosentan was proposed for its antifibrotic effects in SSc skin and lungs, but failed to show treatment efficacy in SSc-ILD.[182] Imatinib mesylate, a tyrosine kinase inhibitor, interferes in several profibrotic pathways and has been proposed for use in SSc. Uncontrolled trials suggest improvement in skin scores with modest improvement in FVC as well.[183] Further study is needed to assess the role of imatinib in SSc-ILD; however, no effect was seen in a recent study in IPF.[184] Rituximab, an inhibitor of B-cell proliferation, has been shown in a small study of patients with SSc-ILD to improve FVC and DL_{CO}.[185] Other biologic agents and newer therapies require further study, including pirfenidone and anti–connective tissue growth factor antibodies. Early data have supported the role of stem cell transplantation in SSc, with improvement in ground-glass opacities on HRCT as well as FVC.[186] Trials in the United States and Europe are enrolling patients to examine this high-risk strategy more fully.[187]

Lung transplantation may be considered for advanced fibrotic lung disease but has been controversial. SSc is considered a systemic disease that may increase overall morbidity and mortality after transplantation. In particular, concern has been raised about the role of gastroesophageal reflux caused by motility issues in SSc that may predispose to chronic graft dysfunction. However, among carefully selected patients, early (1-year) and late (4-year) mortality seems to be similar to that of other groups, and patients with severe fibrotic lung disease without concomitant advanced GI or renal disease should be referred for evaluation.[93,95,188]

IDIOPATHIC INFLAMMATORY MYOPATHIES

The idiopathic inflammatory myopathies (IIMs) are autoimmune disorders typically affecting the skeletal muscle, leading to inflammation and proximal muscle weakness.[189,190] Systemic involvement, including inflammation of the skin, lung, joints, and GI tract may be present.[191] In particular, the presence of ILD has long been recognized and contributes significantly to morbidity and mortality.[192–194] There are several subtypes of the IIMs, all of which may be complicated by ILD, including PM, DM, amyopathic DM (ADM), and the antisynthetase syndrome.

Criteria for classification of the IIMs are still in evolution. Initial diagnostic criteria proposed by Bohan and Peter[189,190] included the presence of symmetric proximal muscle weakness in combination with increased serum muscle enzymes, typical electromyography and muscle biopsy findings, and typical rash; these criteria continue to be clinically useful. However, evolving immunohistochemical and pathologic features, as well as the discovery of myositis-related autoantibodies such as the anti-tRNA synthetase Jo-1, have led

to the proposal of other classification schemes, although none is universally accepted.[195,196]

Clinical Features

The clinical presentation of PM/DM typically involves the subacute onset of proximal muscle symptoms, which may include myalgias, muscle fatigue, or frank weakness, in which patients complain of difficulty rising from a chair or lifting objects. In cases of DM, skin manifestations are present and may include the heliotrope rash, a violaceous discoloration of the eyelids; periorbital edema; Gottron papules, maculopapular erythematous lesions present on the extensor surface of the metacarpophalangeal and proximal interphalangeal joints of the hands; the shawl sign, poikilodermatous macules on the shoulders, arms, or upper back; and mechanic's hands, a scaly, cracked, hyperkeratotic erythema found on the lateral and palmar surfaces of hands and fingers, which has specific histopathologic features.[197,198]

Several pulmonary manifestations may be seen in the IIMs and are a major contributor to morbidity and mortality.[199,200] Primary muscle weakness may lead to hypoventilation and respiratory failure, and may be complicated by pneumonia caused by weak cough and poor airway clearance.[201–203] Aspiration pneumonia may occur because of respiratory muscle weakness but most commonly reflects the presence of skeletal muscle dysfunction in the pharynx and upper esophagus.[202]

Interstitial lung disease is the most common pulmonary complication of the IIMs, although, like other CTD-ILDs, the incidence of myositis-associated ILD (MA-ILD) is greatly affected by the mode of ascertainment, with high rates observed with the combined use of PFTs and HRCT. In a recent prospective study of patients with a new diagnosis of PM or DM, many of whom had no respiratory symptoms, 78% of patients were shown to have some lung involvement as defined by radiographic evidence (chest radiograph or HRCT abnormalities) or restrictive physiology and diffusion impairment on PFTs (total lung capacity and DL_{CO} <80% predicted).[204] Among a population of patients with anti–Jo-1 antibodies, 86% were shown to have ILD.[205] These numbers may be overestimates based on the lack of HRCT evidence of ILD for all patients, but they do suggest that parenchymal involvement is common and should be aggressively sought.

MA-ILD may occur concomitantly with the onset of myositis or skin rash but may precede the diagnosis of IIM.[194,206] Cases of DM with typical skin rash in association with ILD may occur without biochemical evidence for muscle involvement, and is known as ADM.[207] The clinical course of MA-ILD is variable, ranging from a total lack of symptoms to fulminant hypoxemic respiratory failure, although many patients present subacutely and experience chronic, progressive disease.[199] Dyspnea and cough are the most common symptoms reported in MA-ILD. Almost one-third of patients with MA-ILD are asymptomatic, showing the need for evaluation of these patients with PFTs and chest imaging.[208] DM, and particularly ADM, may be more associated with an acute and fatal presentation, which is characterized by histopathologic findings of DAD, and resistance to treatment.[207,209,210] The strongest predictor for the onset of ILD in IIM is the presence of antisynthetase antibodies, particularly anti–Jo-1.[208,211]

The antisynthetase syndrome has been described to include ILD, myositis, arthritis, fever, Raynaud phenomenon, and mechanic's hands.[212] In many cases, only a few features are present, and, in many, the lung manifestations may predominate. In addition to anti–Jo-1, other antisynthetase antibodies (such as anti-PL7, anti-PL12, anti-EJ) have been associated with the development of ILD with IIM.[213] Particular antibodies may be more or less strongly associated with the development of ILD or myositis and subtypes based on antibody specificity may predict clinical course.[214,215] Among the myositis-associated antibodies, the presence of anti-SSA in conjunction with anti–Jo-1 has been associated with more severe and progressive ILD.[216,217]

Pulmonary Function Testing

PFTs are important in the assessment of MA-ILD and help assess disease severity and response to therapy. They also help to distinguish between the role of MA-ILD and diaphragmatic weakness, although this may not be straightforward.[218] Like other forms of ILD, PFTs in MA-ILD show restrictive physiology and reduced DL_{CO}. However, respiratory muscle insufficiency is also characterized by reductions in FVC and total lung capacity as well as reduction in other tests such as the maximum voluntary ventilation (MVV) and maximal inspiratory pressure (MIP) and expiratory pressure (MEP).[203] Reductions in the DL_{CO} may also be the result of pulmonary hypertension, which can coexist with ILD, or be caused by atelectasis from diaphragmatic weakness.[218]

Radiographic Features

HRCT findings are similar to those in other forms of CTD-ILD. In MA-ILD, the most common abnormalities are ground-glass opacities, reticular markings, and alveolar airspace opacities

(Fig. 9).[219] Honeycombing is less common. The radiographic findings suggest the underlying disorder (ie, dense consolidation reflecting DAD and OP; honeycombing reflecting UIP); however, these findings are not specific.[219] Micronodules, linear opacities, and traction bronchiectasis may also be observed.[219] Some studies have suggested that dense, peripheral consolidation in a pattern consistent with OP is associated with a better prognosis, whereas ground-glass opacities predict a worse outcome.[220,221]

Pathologic Features

Surgical lung biopsy is not typically obtained in the diagnosis of MA-ILD, and the role of pathologic diagnosis remains controversial. In studies reporting pathologic findings in MA-ILD, most patients have NSIP, with UIP and OP as the next most frequent possibilities, and DAD in a minority of patients.[218] Although some studies have suggested that DAD carries a poorer prognosis than either OP or cellular NSIP, it is not clear that pathologic pattern alters treatment choice, and other studies have not confirmed an impact of histopathologic pattern on overall survival.[54,194,199,222] In the setting of rapid-onset ILD, surgical biopsy may not be clinically feasible and may lead to postoperative complications in a patient who will likely receive high-dose corticosteroids and other immunosuppressive agents.

Treatment

All treatment is empiric in MA-ILD, because no controlled studies exist to guide treatment decisions. MA-ILD seems responsive to corticosteroids, but high doses may be required.[192,223] Corticosteroids continue to be the most common and widely accepted therapy for MA-ILD.[224] In acute, life-threatening disease, pulse dose regimens (1 g/d) of methylprednisolone may be required. Additional therapy is often needed in MA-ILD and may be added either for either steroid-sparing effect or for additional efficacy. In particular, some forms of MA-ILD with low creatine kinase levels may respond poorly to corticosteroids alone and require treatment with other agents.[225] Choice of agent often depends on clinician familiarity as well as on the severity of illness.

Azathioprine, an inhibitor of purine synthesis, is efficacious in treating myositis in the IIMs.[224] It is a commonly used agent in many CTD-ILDs and is often used in MA-ILD, although with few reports in the literature.[54,226] Cyclophosphamide is typically chosen for rapidly progressive or severe MA-ILD, either via monthly intravenous pulse infusions or oral therapy.[227] Pulse dosage between 300 and 800 mg/m^2 has been described to improve MA-ILD in treatment-resistant disease.[228] Methotrexate has long been used in the treatment of myositis in the IIMs and has been used in the treatment of MA-ILD.[224] However, the known pulmonary toxicity that may occur with this drug can be difficult to distinguish from progressive MA-ILD, making this agent less ideal.[229] Other agents such as cyclosporine, tacrolimus, MMF, intravenous immune globulin, and rituximab have all been used in small numbers of patients with refractory disease, and may be used in select situations.[225,230–235]

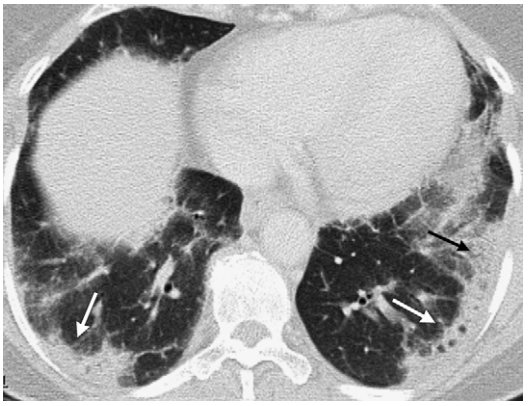

Fig. 9. A 58-year-old woman with OP secondary to PM. Axial images at the level of the lower thorax show peripheral, subpleural areas of consolidation, as indicated by the arrows.

SJÖGREN SYNDROME

Sjögren syndrome is characterized by lymphocytic infiltration of the exocrine glands and marked B-cell hyperreactivity.[236] In particular, the salivary and lacrimal glands are affected, leading to the sicca syndrome characterized by dry eye (keratoconjunctivitis sicca) and dry mouth (xerostomia), often accompanied by arthritis.[237] When Sjögren syndrome is seen in isolation, it is called primary Sjögren syndrome. Secondary Sjögren syndrome may accompany other CTDs such as RA, SSc, SLE, and PM/DM.[238] In addition to the main sicca symptoms of Sjögren syndrome, involvement of the stomach, pancreas, kidney, and peripheral nervous system may occur.[238,239] Middle-aged women are most commonly affected.[240] The diagnosis depends on a combination of ocular and oral symptoms of dryness, objective testing for xerophthalmia and xerostomia, histopathologic features on minor salivary gland biopsy, and autoantibodies to Ro (anti-SSA) and/or La (anti-SSB).[241]

Clinical Features

Like other forms of CTD-ILD, the prevalence of lung involvement in Sjögren syndrome depends on the methodology used to determine active disease and varies between 9% and 60%.[242] Although radiographic abnormalities observed on HRCT may be common, the prevalence of clinically significant pulmonary disease was 11% in a large cohort of patients with Sjögren syndrome.[243] Many patients are asymptomatic and lung involvement is mild and only slowly progressive.[242,244,245] Most commonly, lung involvement is manifested by both upper and lower airways disease, ILD, and lymphoproliferative disorders. Many patients complain of a dry cough (sicca cough), which is a result of xerosis of the airways caused by involvement of the submucosal glands.[246]

Symptoms of ILD most often include dyspnea and cough, with a minority complaining of chest pain and wheezing.[247] Sicca symptoms are present in most patients.[247] Inspiratory crackles are commonly found, although wheezing may also be present. Clubbing is rare.[247] PFTs are most often normal in patients with Sjögren syndrome but, among those with ILD, restriction and diffusion abnormalities predominate.[236,247,248] Care must be taken with interpretation, because airways obstruction is common in Sjögren syndrome and may lead to mixed obstructive and restrictive physiology.[249]

Radiographic Features

HRCT is abnormal in more than one-third of unselected patients with Sjögren syndrome.[250] Multiple abnormalities may be observed and include findings of large airways disease (bronchiectasis, bronchial wall thickening), small airways disease (air trapping, bronchiolectasis, centrilobular nodules, and tree-in-bud opacities), and interstitial disease (ground-glass opacities, air space consolidation, interlobular septal thickening, honeycombing, cysts and micronodules).[237,250,251] The presence of thin-walled cysts suggests the diagnosis of LIP, which is a lymphoproliferative disorder common in Sjögren syndrome (**Fig. 10**).[252,253] LIP is considered to be a steroid-responsive lung disease but may rarely evolve into lymphoma.[252,253] Findings that may suggest lymphoma include nonresolving air space consolidation, nodules greater than 1 cm in size, and enlarging lymph nodes.[254] If these features are present, biopsy should be considered. The presence of air trapping on expiratory films may be helpful in distinguishing small airways disease from ILD, and may be present in the absence of PFT abnormalities.[255] In general, in Sjögren syndrome–associated ILD (SS-ILD), HRCT features, and histopathology tend to correlate well, particularly for NSIP.[247,256]

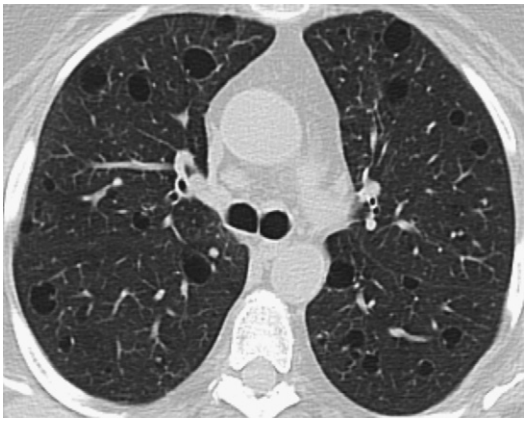

Fig. 10. A 63-year-old woman with Sjögren syndrome and lymphocytic interstitial pneumonia. Axial CT images through the upper thorax show multiple thin-walled cysts of varying sizes scattered throughout the lungs.

Pathologic Features

Older studies of histologic pattern in Sjögren syndrome reported LIP as the most common ILD.[257] More recent studies, using the newer ERS/ATS classification of ILD, describe a higher frequency of NSIP, although with UIP, OP, and LIP also observed.[247,256] Rarely, primary pulmonary lymphoma and amyloidosis are found.[247] When CT features are typical for NSIP, biopsy need not be pursued but, when features that suggest lymphoma are present, tissue sampling is advisable.

Treatment

Treatment in SS-ILD is most often initiated with corticosteroids, although little is known about the optimal treatment. In some milder cases of LIP, observation without therapy may be reasonable.[247] In more advanced fibrotic lung disease, it is less clear that immunosuppressive therapy reverses the underlying injury, and it may expose the patient to excessive risk without significant benefit. In general, SS-ILD seems to be treatment responsive. When SS-ILD is treated, symptoms can improve rapidly, although objective treatment response may occur over months and may be incomplete.[247] The addition of steroid-sparing agents, such as azathioprine, may improve lung function but has not been rigorously studied and use of these agents is largely anecdotal.[257] Early data suggest that B-cell depletion with rituximab

may play some role in the treatment of SS-ILD and deserves further study.[258,259]

SLE

SLE is an immune-mediated disease that most commonly occurs in younger women.[260] It typically presents with malar, discoid, and photosensitivity rashes, oral ulcers, nonerosive arthritis, glomerulonephritis, and hematologic abnormalities.[261] Autoantibodies including ANA, anti–double-stranded DNA (dsDNA), and anti-Smith are commonly detected and are part of the diagnostic criteria.[261] The most common form of pulmonary involvement in SLE is pleuritis, but parenchymal lung disease, pulmonary vascular disease, airways disease, and respiratory muscle dysfunction may all occur.[260] Diffuse parenchymal lung disease in SLE may have either acute or chronic presentation.

Acute Lupus Pneumonitis

One of the less common complications of SLE is acute lupus pneumonitis, which occurs in 1% to 12% of patients and may be the presenting feature of SLE.[262] Patients present with acute onset of fever, cough, dyspnea, and hypoxemia.[262] Acute respiratory failure requiring mechanical ventilatory support may occur. Physical examination may show bibasilar rales, and radiographic findings are significant for diffuse ground-glass and alveolar filling patterns on chest radiograph and HRCT.

In all forms of acute parenchymal lung disease in SLE, there is significant overlap in terms of presentation, with similar clinical history, radiographic findings, and progression. The most important piece of the clinical evaluation is to rule out infection. In particular, patients with SLE are at high risk for both bacterial and opportunistic infection. In addition to the common use of immunosuppressive medications, SLE itself is associated with innate immune dysfunction resulting from complement deficiency, immunoglobulin deficiency, defects in chemotaxis and phagocytosis, as well as functional asplenia.[263] Empiric antibiotics are typically begun in an acutely ill patient and bronchoalveolar lavage should be performed if clinically feasible, particularly in the patient already receiving immunosuppressive drugs.

Surgical lung biopsy is not always feasible or warranted in acute lupus pneumonitis, but, when performed, is nonspecific and commonly shows DAD characterized by hyaline membranes and type II pneumocyte proliferation and inflammation. Capillary inflammation and fibrin thrombi may be present, and immunofluorescence studies have shown immune complement deposition.[264]

Prognosis for acute lupus pneumonitis is generally thought to be poor, with older studies reporting mortalities of 50% and residual lung impairment among the survivors.[262] Newer data are not available to assess whether alterations in supportive care have changed these outcomes. Treatment is largely anecdotal, with emphasis on empiric antibiotics accompanied by a careful search for opportunistic infection, followed by corticosteroids. High doses are used for critically ill patients and include a 3-day pulse of methylprednisolone (1 g per day) followed by 1 to 2 mg/kg/d depending on clinical response. Additional cytotoxic therapies such as cyclophosphamide and azathioprine have been reported to improve lung function, but no well-controlled studies are available to guide practice.[265,266]

Diffuse Alveolar Hemorrhage

Diffuse alveolar hemorrhage (DAH) is also rare but, when it occurs, it contributes to high mortality and may be recurrent among survivors.[267,268] The clinical presentation is similar to that of acute lupus pneumonitis with the abrupt onset of dyspnea, cough, and hypoxemia. Fever may be present and hemoptysis may occur; however, at least half of patients may present without this feature.[267,269] Lupus nephritis or other active SLE involvement may be concomitant.

An acute drop in hematocrit may suggest the diagnosis. Radiographic findings may be initially unimpressive but can progress to diffuse ground-glass opacities and alveolar consolidation and can be indistinguishable from acute lupus pneumonitis, infectious pneumonia, or the acute respiratory distress syndrome (ARDS).[269] BAL is a crucial diagnostic step in the evaluation of these patients, both for the exclusion of infection, as well as for the diagnosis of DAH, which can be made with the observation of progressively bloody lavage fluid and hemosiderin-laden macrophages in the fluid. Among more clinically stable patients, DL_{CO} measurements obtained within the first 48 hours after the hemorrhage have been reported to show an increase of 30% more than baseline values while the erythrocytes are still within the alveoli.[269] Surgical lung biopsies are not typically performed in acutely ill patients. Histopathologic findings in DAH most commonly show bland hemorrhage, but some cases of capillaritis with immune complex deposition as well as small vessel vasculitis and microangiitis have been reported.[263,268,270]

DAH may be triggered by infection and initial treatment consists of empiric antibiotics, which may significantly improve survival.[269] High-dose corticosteroids are generally combined with intravenous cyclophosphamide.[267] Plasmapheresis may also improve survival.[271–273] MMF has been reported to be efficacious in maintaining remission from DAH episodes.[274]

Chronic ILD in SLE

Chronic ILD may be observed in SLE and has been reported as being less common than in other CTDs, with a reported prevalence of 3% to 13%.[275] However, subclinical disease is likely common, based on HRCT studies that estimate the prevalence of ILD at 38% among patients with lupus without previously diagnosed lung disease.[276] In some cases, an association is seen between ILD and anti-SSA antibodies, but it is unclear whether this is pathogenic and whether such findings describe an overlap with Sjögren syndrome.[277,278]

Like other forms of ILD, SLE-associated ILD (SLE-ILD) commonly presents with the insidious onset of dyspnea and occasional nonproductive cough. ILD may present acutely, as in acute lupus pneumonitis, and chronic lung disease may result from prior episodes of lupus pneumonitis.[262] ILD onset is associated with longer disease duration, male gender, older age, as well as later onset of SLE.[279]

HRCT findings in SLE-ILD are similar to those of other chronic ILD and show bibasilar-predominant reticulations and ground-glass with progression to traction bronchiectasis with some honeycombing. The most typical histopathologic patterns are NSIP, UIP, and LIP; however, surgical biopsy is rarely obtained.[60,280]

Treatment of SLE-ILD is not standardized and the choice to treat is an individualized decision based on clinical progression and radiographic findings. In particular, the presence of ground-glass opacities might suggest a more active alveolar inflammatory process with the possibility of treatment responsiveness. Corticosteroids are often used and, when chronic therapy is anticipated, steroid-sparing agents such as azathioprine and MMF are added. MMF has been shown to have a good safety profile in patients with CTD-ILD.[135,281] Cyclophosphamide has been used for refractory disease.[266] Rituximab has been reported to have controlled progressive and refractory ILD in 1 case.[282]

SUMMARY

Lung disease is a common manifestation of the CTDs and may be a presenting feature. Subclinical disease is common. Clinically apparent disease is often slowly progressive but may present in an acute fashion, contributing to high morbidity and mortality. Infection and drug reaction may share clinical features with CTD-ILD and should be considered when evaluating the patient with dyspnea and abnormal radiographic findings. Treatment of CTD-ILD is not well studied but typically includes corticosteroid therapy and immunosuppressive agents, as well as careful supportive care. Further study is needed for the many unanswered questions in this field.

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