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Interstitial lung disease in the patient who has connective tissue disease

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Interstitial lung disease (ILD) commonly complicates the management of connective tissue diseases (CTDs). Because the pulmonary specialist often is involved in the care of these patients, a comprehensive understanding of the CTD and the usual course of the ILD is important. Furthermore, pulmonary conditions in clinical practice, such as cough, dyspnea, or ILD, may be the first manifestations of a rheumatologic disease. It is estimated that approximately 15% of patients who present with ILD have an underlying CTD. This article reviews the most recent data on the pulmonary presentations of the common rheumatologic diseases with a focus on diffuse lung disease; appropriate treatment requires a correct diagnosis. The article also focuses on new developments and areas of controversy because a comprehensive review is beyond the scope of this paper.

Review of systems

Systemic complaints are common in many diseases; a detailed history and review of systems is critical in obtaining the correct ILD diagnosis. Box 1 is a checklist of symptoms and physical examination findings that commonly are associated with an underlying connective tissue disease. Some office practices have interstitial lung disease questionnaires so that errors of omission in symptom review do not occur.

Physical examination

Physical examination findings provide important clues to diagnosis of an underlying rheumatologic condition. A careful skin examination is an essential part of the physical examination. Skin findings in early systemic sclerosis (SSc) or scleroderma may be subtle; finger swelling (puffy fingers) often is the first specific SSc manifestation. This edematous phase is followed by sclerodactyly and thickening (sclerosis) of the skin more proximally. The term ''limited cutaneous SSc'' refers to skin thickening that does not progress proximally beyond the elbow or knee; the neck and face also may be involved in limited disease. Limited cutaneous SSc also has been called ''CREST variant'' because of the combination of Calcinosis, Raynaud's phenomenon, Esophageal dysmotility, and Telangiectasias that is seen frequently in these patients. Subcutaneous calcinosis is seen most frequently on the palmar aspects of the tips of the fingers, but also occurs over bony prominences. Telangiectatic mats most commonly are found on the face, palms, lips, and mucous membranes. Patients who have severe Raynaud's phenomenon also may have digital ulcers or pits. Most patients who have systemic lupus erythematosus (SLE) have cutaneous manifestations, which may include malar or discoid rash, alopecia, photosensitivity, and mucosal ulcers. Patients who have dermatomyositis have characteristic violaceous scaling patches that are located over bony prominences and sun-exposed areas; violaceous (heliotrope) discoloration of the eyelids and Gottron's papules are pathognomonic for this condition.

A detailed musculoskeletal examination can detect synovitis, effusions, nodules, tendon friction

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Box 1. Symptoms that are associated with connective tissue diseases

Joint and muscle symptoms
- Arthritis
- Arthralgias
- Morning stiffness
- Synovitis
- Myalgias
- Muscle weakness
- Neuropathy

Raynaud's syndrome

Gastrointestinal symptoms
- Esophageal reflux
- Dysphagia
- Abdominal bloating, diarrhea

Sicca symptoms
- Dry eyes
- Dry mouth

Skin manifestations
- Malar rash
- Photosensitivity
- Machinist's hands
- Gottron's papules
- Erythema nodosum
- Subcutaneous nodules
- Sclerodactyly
- Digital or oral ulcers
- Edema
- Telangiectasias

Chest pain
- Pleurisy
- Pericarditis

Eye abnormalities
- Corneal ulcers
- Uveitis
- Scleritis

rubs, and muscle weakness that give clues to the presence and activity of an underlying CTD.

Usually, pulmonary examination is not helpful because crackles can be found in any of the ILDs that are associated with CTD and wheezing can be seen occasionally when airways disease is present from bronchiolitis or bronchiectasis.

Nailfold capillary microscopy can detect dilated, tortuous capillary loops and avascular areas that are suggestive of SSc, polymyositis/dermatomyositis (PM/DM), and mixed connective tissue disease (MCTD). This can be performed through a dissecting microscope or with an ophthalmoscope that is set at +40 after mineral oil is applied to the nailfold (Fig. 1).

Laboratory screening

Laboratory screening commonly is used to decide if further CTD evaluation is needed. Laboratory tests that are used for screening purposes are neither sensitive nor perfectly specific for the CTD. A Westergren sedimentation rate is elevated in many infectious, malignant, and systemic diseases. Therefore, a high value is of limited benefit. Conversely, a low value may help to exclude active CTD, although normal values can be found occasionally.

Antinuclear antibodies (ANA) are found in most patients who have CTD; their prevalence ranges from approximately 30% in rheumatoid arthritis (RA) to 95% in SLE and SSc. Diseases, such as idiopathic pulmonary fibrosis (IPF) and coal workers pneumoconiosis, have a positive ANA in 15% to 34% of cases [1]; 2% to 3% of the general population has an ANA positive at a titer greater than 1:40. An extractable nuclear antigen (ENA) panel is available through most reference laboratories that measure the most common antigens that are responsible for a positive ANA. Although each ENA antigen has individual prognostic and diagnostic utility, few studies have correlated ENA positivity with important pulmonary outcomes.

Patients who have RA and a high titer rheumatoid factor (RF) are more likely to have severe extraarticular manifestations of disease. Other CTDs may have a RF that is positive; patients who have IPF can have a positive RF in the absence of RA from 13% to 49% of the time [2]. RF also is positive in more than 50% of patients who have bird fanciers' hypersensitivity pneumonitis, likely because of sensitization to avian proteins [2]. Therefore, a high titer of RF in a new patient who has ILD should prompt intensive

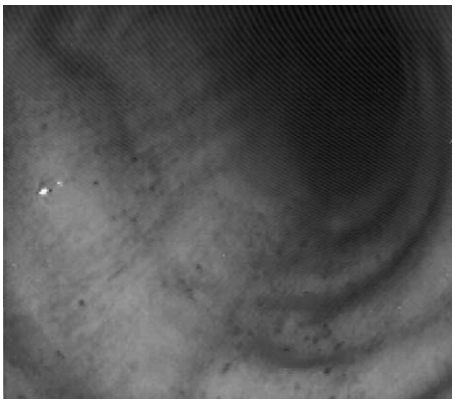

Fig. 1. Telangiectasias are seen in the bronchial mucosa of this patient who has systemic sclerosis.

questioning about hypersensitivity risk factors. The combination of a positive RF with the presence of antibodies to cyclic citrullinated peptides, however, increases the sensitivity and specificity for RA to 81.4% and 91.1%, respectively [3]. RF is present in low titers in the elderly population at a frequency of approximately 8% [4].

Measurement of muscle enzymes often is overlooked in a CTD screen. Because polymyositis and dermatomyositis can present with acute lung injury or slowly progressive ILD, creatine kinase or an aldolase measurement occasionally is helpful when screening patients who have diffuse lung disease.

Systemic lupus erythematosus

The American College of Rheumatology (ACR) publishes and updates the criteria that are necessary to establish a diagnosis of SLE. The most common pulmonary manifestations of disease are listed in Box 2. Patients who have evolving lupus may present with pulmonary manifestations without meeting formal criteria for the diagnosis. Patients who have SLE and diffuse lung disease require bronchoscopy to rule out infection or alveolar hemorrhage. Although infection is the most common cause of diffuse alveolar infiltrates in the patient who has SLE, alveolar hemorrhage is the most fatal of the manifestations and warrants review.

Alveolar hemorrhage

Alveolar hemorrhage should be suspected by the triad of hemoptysis (not required), decrease in hematocrit, and diffuse alveolar infiltrates. This rarely is a presenting manifestation of SLE and frequently is associated with SLE activity in other organs. Usually, alveolar hemorrhage is secondary to a pulmonary capillaritis and is diagnosed with progressively bloody lavage aliquots on bronchoalveolar lavage (BAL). Because BAL has been standardized by using four 60 mL-aliquots, the completion of all aliquots is important, when SLE is suspected, to detect this finding. No standards have been established to determine how many red blood cells (RBCs) are needed to establish a diagnosis of alveolar hemorrhage. Occasionally, a patient who has alveolar hemorrhage has hemorrhage because of an infectious pathogen. Therefore, SLE alveolar hemorrhage remains a provisional diagnosis until the results from cultures and cytology that look for infectious pathogens are received. Because some cases of SLE coexist with other forms of pulmonary vasculitis, an antineutrophil cytoplasmic antibody should be sent; if positive, it should be confirmed with specific testing for proteinase-3 (PR3) or myeloperoxidase antibodies.

Treatment of alveolar hemorrhage in SLE remains controversial because no randomized trials are available [12]. The experience from many case series suggests that high-dosage pulse corticosteroids (1000 mg solumedrol daily for 3 days) with plasmapheresis, cyclophosphamide, or both improves survival [13]. Correction of thrombocytopenia or coagulopathy, if present, should be considered standard of care and thrombotic thrombocytopenic purpura should be excluded. Most experts use plasmapheresis in the first 48 hours after an alveolar hemorrhage presentation because cyclophosphamide-induced neutropenia is contraindicated if an infection is present. BAL cultures usually take 48 hours to return.

Box 2. Most frequent pulmonary complications of systemic lupus erythematosus

- Lupus pleurisy [5]
- Lupus pneumonitis
- Shrinking lung syndrome [6–8]
- Bacterial pneumonia
- Immune modulating drugs
- Altered immunity
- Capillaritis with alveolar hemorrhage [9]
- Pulmonary emboli associated with lupus anticoagulants
- Pulmonary arterial hypertension [10,11]

Systemic lupus erythematosus pneumonitis

SLE pneumonitis may be the first recognized manifestation of SLE. Typically, patients present with an abrupt onset of dyspnea, fever, cough, and diffuse alveolar infiltrates that can progress to acute respiratory distress syndrome (ARDS) [14]. Rarely, a chest radiograph may be normal [15]. Although increased numbers of RBCs are present in BAL, the lavage fluid does not turn red on return; this differentiates it from alveolar hemorrhage. Lupus pleuritis and other manifestations of active SLE, such as fever, arthralgias, nephritis, and cerebritis, frequently are present. Patients usually respond to treatment with high-dose corticosteroids; immunosuppressive therapy should be delayed until the possibility of infectious disease has been excluded.

Systemic lupus erythematosus interstitial lung disease

SLE rarely has been associated with slowly progressive usual interstitial pneumonitis (UIP) [16,17] (Box 3). When a patient who has SLE presents with a CT scan that shows peripheral honeycombing, a laboratory review to reclassify the disease should be begun [18]. Many of these patients have concomitant muscle disease, Sjögren's syndrome (SS), RA, or SSc that prompts reassessment of the diagnosis. Treatment success with immunosuppressive medications depends on the stage of disease.

Box 3. Connective tissue diseases that are associated with usual interstitial pneumonitis

- Rheumatoid arthritis
- Systemic sclerosis (scleroderma)
- Polymyositis/ dermatomyositis
- Mixed connective tissue disease
- Undifferentiated connective tissue disease
- Systemic lupus erythematosus (rare)
- Primary Sjögren's syndrome (rare)

Rheumatoid arthritis

RA is characterized by a symmetrical inflammatory arthritis and has a high prevalence of extra-articular manifestations. RA-associated pulmonary abnormalities are listed in Box 4. Although ILD is common in autopsy series, the frequency of clinically-significant ILD seems to be declining because disease-modifying antirheumatologic drugs are used with higher frequency. In the recent Spanish Registry of RA, ILD had a prevalence of 3.7% when diagnosed by chest radiography [12,19]. Most patients had evidence of ILD when high-resolution chest CT (HRCT) was used for diagnosis.

Rheumatoid interstitial lung disease

Histologically, rheumatoid ILD (RA-ILD) has not been characterized carefully using new classification schemes [21]. RA-ILD often begins as a patchy alveolar infiltrate that progresses in more severe cases to a prominence of reticular or nodular infiltrates on HRCT [22]. Traction bronchiectasis and peripheral honeycombing is common in more advanced disease. With exacerbations, new alveolar opacities occur. No specific HRCT findings distinguish RA from IPF [23].

Box 4. Lung diseases that are associated with rheumatoid arthritis

- Rheumatoid interstitial lung disease
- Non-specific interstitial pneumonitis
- Usual interstitial pneumonitis
- Cryptogenic organizing pneumonia
- Diffuse alveolar damage
- Exudative pleural effusions
- Rheumatoid nodules
- Bronchiolitis
- Follicular bronchiolitis
- Constrictive bronchiolitis
- Bronchiolitis obliterans
- Bronchiectasis
- Methotrexate pneumonitis
- Gold pneumonitis [20]
- Cricoarytenoid arthritis with upper airway obstruction

Because arthritic symptoms can occur up to 2 years after the onset of lung disease, any patient who has UIP pathology or a suggestive CT scan should be screened with a RF and monitored for the development of RA. Although there is no difference in the frequency of RA-ILD between patients who do and do not have RF, disease severity and progression is most severe in patients who are RF positive and correlates with the titer of RF [24].

BAL seems to be less helpful in RA than in other CTDs because the presence of neutrophils and activated populations of alveolar macrophages do not correlate well with disease activity or HRCT findings [25]. Patients who have RA who do not have clinical lung disease can have a BAL lymphocytosis.

Other rheumatoid-associated lung diseases

Rapidly progressive ILD has been described in RA. Cryptogenic organizing pneumonia (COP) can be particularly rapid in onset and can look like ARDS [26]. This patchy lung disease usually responds to steroids but portends a poor long-term prognosis because of its tendency to recur when high-dosage steroids are withdrawn [27].

Another presentation of rheumatoid disease in the lung is rheumatoid bronchiolitis. This lymphocytic

inflammatory disease of the small airways may present with cough, wheezing, or dyspnea and obstructive spirometry. HRCT is useful in differentiating between the manifestations of rheumatoid airways disease: follicular bronchiolitis, bronchiolitis obliterans, and bronchiectasis [28].

Although there are no studies that describe the best treatment for bronchiectasis that is secondary to CTD, management principles are the same as for patients who do not have CTD. These include therapies to optimize airway clearance, treat infecting but not colonizing microorganisms, and the use of low-dosage corticosteroids to treat airways inflammation, if present.

Rheumatoid nodules rarely occur without skin nodules. Nevertheless, the challenge is to assure that new nodules are not lung cancers because all ILDs seem to be associated with an increased cancer incidence.

Therapy for rheumatoid-associated lung diseases

Therapy for rheumatoid lung disease depends on the individual presentation. Corticosteroids are effective short-term monotherapy for airways disease and at high dosages may improve COP. Induction of disease remission is important and historically has required methotrexate, azathioprine [29], or cyclosporine [30]. Response to the newer therapies of leflunomide (arava) or the tumor necrosis factor inhibitors [31] has not been studied, although no information suggests that treatment response differs between joint and lung inflammation.

Box 5. Pulmonary diseases that are associated with systemic sclerosis

- Interstitial lung disease
- Fibrotic nonspecific interstitial pneumonitis most commonly
- Usual interstitial pneumonitis
- Diffuse alveolar damage (rare)
- Cryptogenic organizing pneumonia
- Pulmonary hypertension (PH)
- Pulmonary arterial hypertension most common in lcSSc
- Secondary PH from ILD most common in dcSSc
- Lung cancer
- Aspiration pneumonia
- Pleuritis and pericarditis
- Alveolar hemorrhage (rare)
- Spontaneous pneumothorax (rare)

Systemic sclerosis

SSc (scleroderma) is a systemic fibrotic disease of unknown etiology that presents with two clinical phenotypes: ILD occurs with the limited (CREST variant, lcSSc) and diffuse (dcSSc) variants and is now a leading cause of morbidity and mortality (Box 5). Usually, ANA is positive in both subsets of disease: anticentromere or antibodies to T0/TH are predominant in limited disease [32] and an anti-SCl-70 antibody that is present on ENA panel is found more commonly in diffuse disease and is associated with a high prevalence of ILD. TO/TH antibodies are not measured routinely in many laboratories but their presence in lcSSc has suggested a clinical phenotype that is more in keeping with dcSSc with a high prevalence of ILD and SSc renal crisis.

A disease entity that is called "SSc sine scleroderma" has been described in which most features of systemic sclerosis are present, except for skin thickening [33]. These patients have a high prevalence of esophageal motility and reflux, abnormal nailfold capillaries, and lung disease that is typical for nonspecific interstitial pneumonitis (NSIP). The challenge to find these individuals in a clinic full of patients who have "idiopathic" pulmonary fibrosis requires routine ANA screening, nailfold capillaroscopy of patients who have positive ANA titers, and objective study of patients who have IPF and reflux.

Pulmonary fibrosis, usually of the NSIP type [34–36], occurs in most patients who have scleroderma, with an average prevalence of 70%. It progresses to severe restrictive lung disease in about 15% of patients who usually have diffuse cutaneous scleroderma. Because a subset of patients who has SSc develops rapidly progressive ILD during the first 2 years of their disease [37], spirometry and diffusion testing should be considered mandatory for all patients at the time of diagnosis and should be performed at regular intervals early in disease.

One of the most difficult decisions in patients who have SSc is to determine disease activity that requires therapy; many patients may have quiescent and stable pulmonary fibrosis for years [35]. Patients who have progressive ILD usually are within the first 2 years of their disease and have ground-glass opacities on HRCT, a neutrophilic or eosinophilic BAL, and declining spirometry or diffusion.

HRCT is being performed increasingly to determine SSc lung disease activity [38]. Correlation between pathology and HRCT shows that most, but not all, patients have NSIP [34]; the degree of cellular

versus fibrotic NSIP determines the subsequent clinical course [35]. A few patients who have SSc have UIP histology that is characterized by honeycomb change on HRCT. CT fibrosis scores correlate with forced vital capacity (FVC), DLCO, and total lung capacity. Ground-glass opacity can represent reversible alveolar inflammation (alveolitis) or irreversible homogeneous NSIP fibrosis. Therefore, the usefulness of BAL to determine more specifically an inflammatory alveolitis has been promoted in SSc. Whether BAL adds to the usefulness of HRCT in determining disease activity remains controversial and is the focus of several clinical studies.

Cyclophosphamide

The treatment of systemic sclerosis–associated ILD (SScILD) remains controversial. Although some investigators noted a population of patients who had active lung disease that responded to corticosteroids [39], most investigators have found limited long-term benefit to corticosteroids in SScILD [40]. Many therapies have been tried for SScILD. The best anecdotal clinical improvement has been seen with cyclophosphamide. Although randomized clinical trials are in progress with daily oral cyclophosphamide, the optimal end points to follow medication response remain controversial. The toxicity of this medication requires monthly monitoring for hematuria and neutropenia and yearly urine cytologies. When toxicity develops, cyclophosphamide should be stopped.

Some experience suggests that intravenous cyclophosphamide pulses, with or without corticosteroid pulses, may be tolerated better [41]. Additionally, this regimen is tolerated in some patients who had previous toxicity to oral medication. Intravenous dosing allows prophylaxis for hemorrhagic cystitis by administration of sodium 2-mercaptoethane sulfonate (MESNA) that binds to acrolein, the toxic metabolite that is responsible for bladder toxicity. No randomized comparative trials of intravenous versus oral cyclophosphamide for lung disease have been performed. One recent trial compared pulse cyclophosphamide plus high-dose or low-dose corticosteroids; improved outcomes occurred when it was combined with high-dose corticosteroids [42]. It seems that intravenous cyclophosphamide may be less effective than daily oral cyclophosphamide, unless high-dose corticosteroids also are used.

Pulmonary hypertension

Patients who have SScILD have a higher likelihood than patients who have other ILDs to develop pulmonary hypertension; therefore, all patients who have SSc should have baseline and periodic echocardiograms. Although pulmonary hypertension occurs in limited and diffuse cutaneous disease, pulmonary arterial hypertension (PAH) is more common in lcSSc. In dcSSc, more significant ILD is common at the time of presentation with pulmonary hypertension. In these patients, pulmonary vascular vasoreactivity nearly is universal and clinical improvement in symptoms can be obtained by using agents, such as epoprostenol and bosentan, that are reserved more typically for pure presentations of PAH [43].

Polymyositis/dermatomyositis

PM is a rare muscle disease that is characterized by proximal muscle weakness. Skin lesions that consist of violaceous scaling patches, Gottron's papules, facial heliotrope rash, or mechanic's hands characterize DM. Some patients who have DM without muscle disease (amyotrophic DM) also can have lung disease [44,45]. The presentation of PM/DM diffuse lung disease was present in 65% of new diagnoses in one recent clinical series and was clinically silent in some individuals [46]. Lung disease is a common presenting manifestation [47]. PM/DM also can have an acute pulmonary presentation that causes the ARDS [48]. Because many diseases present with neuromuscular weakness in the ICU, a screening ANA is recommended for patients who have ARDS of unknown cause. In DM/PM, an ANA is positive in only 30% of patients, Raynaud's phenomenon is present in only 10% of patients, and arthralgias are present in only 40% of patients [49]. Therefore, looking carefully for a DM skin rash or elevated muscle enzymes is necessary in all patients who have diffuse lung disease of unknown cause.

Approximately 30% of patients who have PM/DM and diffuse lung disease have an extractable nuclear antigen to RNA synthetase that is called the Jo-1 antibody [50]. Patients who have the antisynthetase syndrome (arthritis, Raynaud's phenomenon, mechanic's hands, and ILD with anti–Jo-1 autoantibody) have a higher incidence of lung disease than patients who have PM/DM without the Jo-1 antibody.

Usually, the histology of the diffuse lung disease of PM/DM is NSIP, although UIP, COP, and diffuse alveolar damage have been described. Typically, HRCT scans show ground-glass opacities and alveolar infiltrates that usually are concordant with FVC and DLCO [51]. Rare presentations with UIP histology and honeycombing on CT tend to progress, whereas most patients who have NSIP stabilize on

therapy for their muscle disease [52]. Patients who have an ARDS presentation sometimes respond sufficiently to therapy to allow for ventilator weaning, although complete resolution of infiltrates and normalization of physiology is rare. In a recent series, the overall mortality of PM/DM with associated lung disease was 50% at 5 years [53]; this suggests that all patients who have PM/DM should be screened for pulmonary abnormalities at the time of diagnosis [46].

Clinical outcome is dependent on strong muscles of respiration, intact pulmonary physiology, and normal pharyngeal function; therefore, small changes in disease activity can produce significant changes in dyspnea. Although there is a lack of correlation between the severity of pulmonary disease and the severity and progression of myositis, to date no clinical trial has demonstrated a benefit from treating the lung disease of PM/DM independently from following muscle strength and muscle enzymes (creatine kinase and aldolase) [54]. One trial studied an aggressive approach to treatment of any active lung disease in patients who had PM/DM. A neutrophilic BAL or ground glass on CT in the presence of progressive lung disease was treated with intravenous pulse cyclophosphamide with prednisone. All 10 patients stabilized or improved as did another 10 patients who had more indolent pulmonary progression that was treated with weaker immunosuppressive regimens [55].

Methotrexate

Few comparative trials have been performed to determine which steroid-sparing agent to use for continuing disease; however, methotrexate has gained popularity because of its ease of use and safe side-effect profile. Methotrexate is dosed weekly at 5 to 20 mg orally. Liver function tests should be performed at least five times yearly and any abnormalities should prompt a liver biopsy because the hepatic fibrosis that is associated with methotrexate usually is clinically silent. Rare idiosyncratic decreases in white blood cell counts or platelet counts should prompt a complete blood cell count as part of routine laboratory follow-up care for patients who are on methotrexate. Lastly, a granulomatous pneumonitis was reported in approximately 1% of patients who were on methotrexate. There is no conclusive evidence that methotrexate has any low-grade pulmonary toxicity independent of this idiosyncratic reaction [56,57]. Nevertheless, patients who have positive Jo-1 antibodies who are at high risk for ILD or those who have existing ILD often are treated with azathioprine instead. Poor response to azathioprine or methotrexate in patients who are nonresponsive to steroids occasionally is treated with cyclosporine [54] or intravenous immunoglobulin.

Sjögren's syndrome

SS is an autoimmune exocrinopathy and an autoimmune epithelitis that is characterized by lymphoproliferation and lymphocytic infiltration of glandular and nonglandular tissue. Typically, patients present with dry mouth (xerostomia), dry eyes (keratoconjunctivitis), and arthritis. SS is a complicating factor of many CTDs (secondary Sjögren's syndrome), but also may present without other CTDs (primary Sjögren's syndrome). Pulmonary symptoms of SS include cough and dyspnea. Usually, cough is from xerotrachea (dry trachea), although small airways inflammation often is present, which causes obstructive physiology. The lymphocytic bronchiolitis that is associated with SS can advance to bronchiectasis.

ILD is common in patients who have Sjögren's syndrome; the histopathologic finding that is seen most frequently is lymphocytic interstitial pneumonitis, which can arise from the airways disease. UIP and COP are less frequent and should prompt consideration that an underlying disease, such as RA or SSc, is being missed.

Rarely, patients may develop a non-Hodgkin lymphoma, occasionally of the mucosa-associated lymphoid tissue type [58]. Other rare manifestations of SS in the lung include lung cysts [59,60] and amyloidosis [61]. The pathogenesis of lung cysts in SS remains unknown; however, there is a theory that thick mucus acts as a one-way valve, which results in airway obstruction. These cysts can be large—up to 10 cm^3—and can become infected secondarily.

Although corticosteroid and immunosuppressant therapy can limit the lymphocytic inflammation, it does little to help airway dryness or inspissated mucus in bronchiectatic airways. Occasionally, this can be helped with nebulized saline or N-acetyl cysteine.

Mixed connective tissue disease

MCTD is an overlap syndrome that combines features of SLE, SSc, RA, and PM/DM, that is combined with the presence of ribonucleoprotein (RNP) antibodies on ENA testing. Patients who have MCTD do not meet specific criteria for another CTD, but long-term follow-up of patients showed that most

developed one of the more recognized CTD entities—usually scleroderma—over the next 5 years. Undifferentiated CTD differs from MCTD because MCTD requires the presence of an antibody to RNP. If the anti-RNP is positive in patients who meet diagnostic criteria for a more specific CTD, its presence increases the likelihood that atypical features or "overlap" manifestations will emerge.

Pulmonary disease is common in patients who have MCTD; however, it often is subclinical and only is identified radiographically. The ILD of MCTD has been compared on HRCT with other CTDs [62]. Usually, there is less honeycomb change than is found in SSc and less ground-glass opacity than is found in PM/DM. More septal thickening has been reported. These HRCT findings certainly are not specific for MCTD, however.

Because of the lack of randomized clinical trials, treatment regimens largely are anecdotal and may include prednisone with or without other immunosuppressant medications, such as azathioprine, methotrexate, or cyclophosphamide.

Undifferentiated connective tissue disease

Occasionally, patients present with individual features of a CTD but fail to meet ACR entry criteria for any single disease. These patients are classified as having undifferentiated connective tissue disease (UCTD). These individuals, like those who have MCTD, usually transition to other disease entities over time [63].

There are no studies that describe adequately the appropriate treatment of ILD in this population; most experts treat according to recommendations for the CTD that is most closely aligned with the patient's presentation.

Cryptogenic organizing pneumonia in the connective tissue diseases

Many of the CTDs have a bronchiolar and alveolar injury pattern on biopsy that heals with a loose connective tissue matrix that fills airways and airspaces (Fig. 2). Bronchiolar manifestations are more commonly seen in RA and SS; however, any of the CTDs can have an associated bronchiolitis. An organizing pneumonia that histologically contains loose connective tissue without recognizable infection also is seen in these same diseases with bronchiolar injury. The American Thoracic Society/European Respiratory Society classification scheme has called this entity COP. Previously, COP was called bronchiolitis obliterans with organizing pneumonia in the United States. The European nomenclature is preferred because of the heterogeneity of bronchiolar as compared with pneumonic infiltrates.

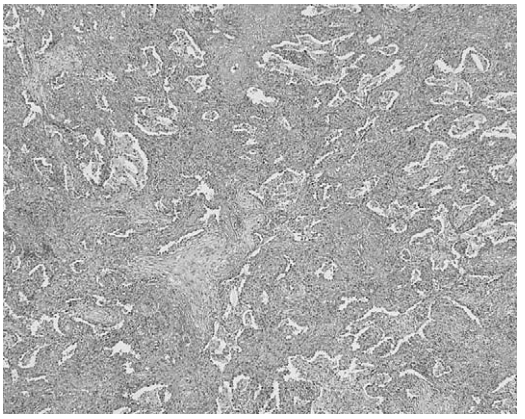

Fig. 2. Cryptogenic organizing pneumonia in an open lung biopsy from a patient who has mixed connective tissue disease (hematoxylin-eosin, original magnification ×10). Note the filling of airspaces and small airways with loose connective tissue.

COP frequently responds to corticosteroids in the CTD patient; although, the degree of improvement sometimes is less than in patients with viral respiratory illness associated COP. Additionally, the CTD patient with COP will almost always relapse when corticosteroids are withdrawn. Therefore, CTD-associated COP usually is treated with combination regimens that contain corticosteroids and an immunosuppressant medication, such as azathioprine, cyclophosphamide, cyclosporine, mycophenolate, or methotrexate, although no randomized trials are available [22,27].

Summary

Although rheumatologists often assume primary care for patients who have CTDs, their training in lung disease physiology, determining lung disease stability, and treatment of complications of ILDs, such as bronchiectasis, hypoxemia, pulmonary hypertension, and cough, require the assistance of a pulmonary physician for optimal management. Therefore, the successful and optimal management of these complicated patients is best achieved by a collaborative approach between the pulmonary physician and rheumatologist.

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