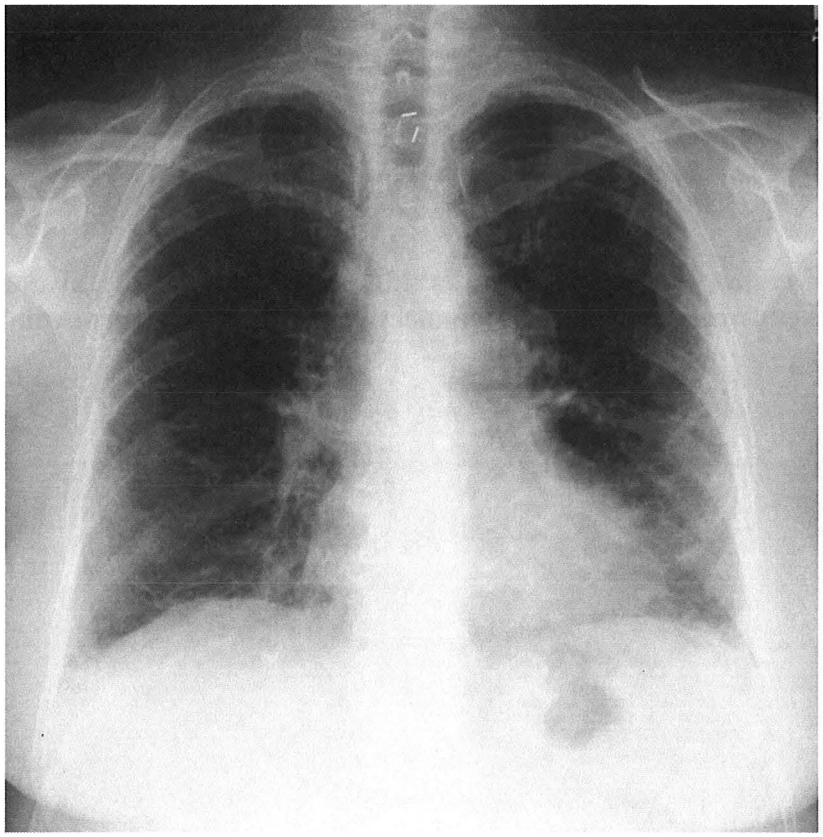

ILD in Patients with Connective Tissue Disease

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Medical Grand Rounds
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Idiopathic pulmonary fibrosis, interstitial lung disease, vasculitis, alveolar hemorrhage syndromes, sarcoidosis, connective tissue disease, bronchiolitis.

Introduction

Collagen vascular disease (CVD) encompasses a group of related autoimmune disorders characterized by inflammation and fibrosis within many organ systems. Pulmonary involvement is a major driver of morbidity and mortality in patients with connective tissue disease.(1, 2) It may manifest as pleural or diffuse parenchymal (interstitial) disease, or as pathology involving the airways, respiratory bellows or pulmonary vasculature.(1, 3) Even treatments meant to assuage the underlying immunological assault may result in opportunistic infection or direct pulmonary drug toxicity.(4) This review will focus on key issues related to the recognition and treatment of interstitial lung disease (ILD) in subjects with connective tissue disorders. ILD is prevalent in these patients.(5) It is most often identified in persons with established collagen vascular disease diagnoses, but may be a part of the original presentation. Occasionally, it develops months or even years prior to the onset of any other features of systemic illness. In some cases, it appears that ILD may be the dominant clinical feature of an otherwise undifferentiated connective tissue disorder.(6, 7) The most common CVDs associated with interstitial lung disease include systemic sclerosis and its variants (SSc), rheumatoid arthritis (RA), polymyositis/dermatomyositis (PM/DM), the antisynthetase antibody syndrome (ASA), Sjögren's syndrome (SS), systemic lupus erythematosus (SLE), and mixed connective tissue disease (MCTD). Early detection of interstitial lung disease with objective testing at regular intervals is essential. When patients present to respiratory specialists for evaluation of dyspnea, they may already have advanced, irreversible disease. Optimal management of these conditions requires a close partnership between the patient, pulmonologist, and rheumatologist.

Epidemiology of Connective Tissue Disease-Associated Interstitial Lung Disease (CTD-ILD)

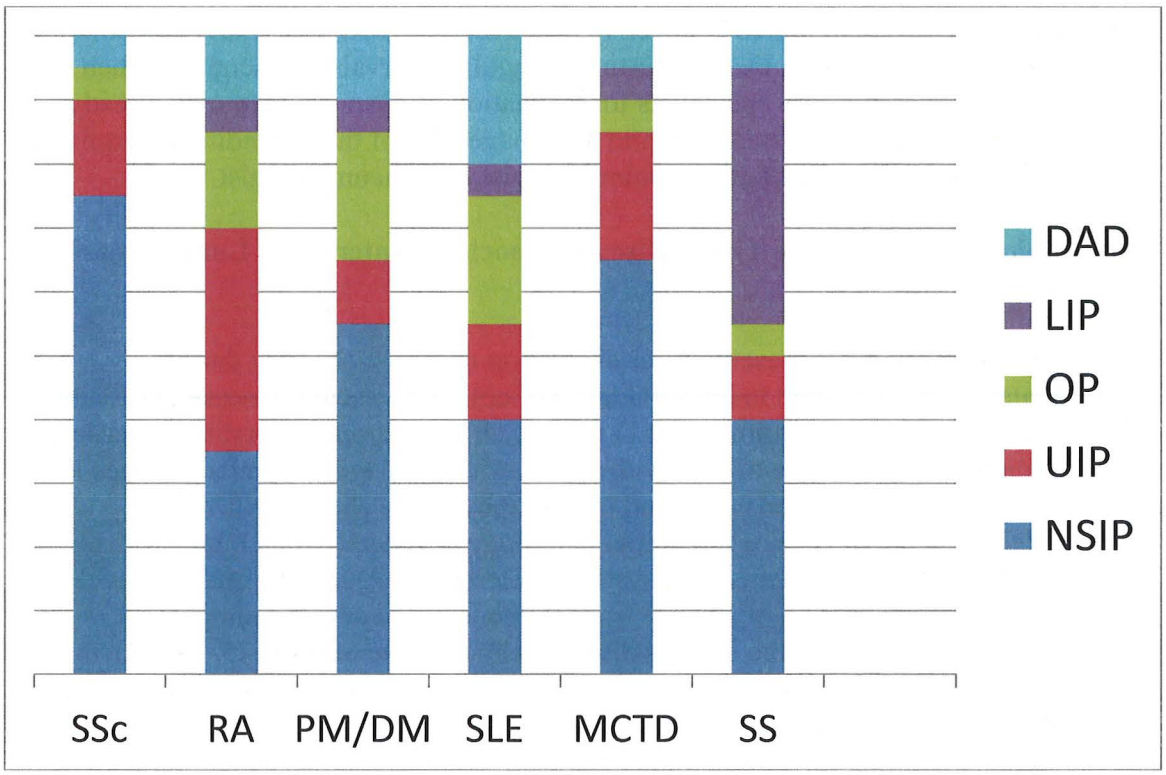
Among individuals presenting for evaluation of interstitial lung disease, approximately 15% are found to have evidence of collagen vascular disease.(8) Acute, subacute and chronic presentations of ILD may occur, but chronic interstitial disease is most common. The incidence of ILD within the various collagen vascular diseases is quite variable. High resolution computed tomography of the chest (HRCT) has confirmed that the prevalence of interstitial pathology is generally much higher than previously thought.(9) In patients with systemic sclerosis, ILD may ultimately develop in more than 70% of patients.(3, 10, 11) It leads to moderate or severe pulmonary restriction in 15-40%, and is the leading disease-related cause of death.(5, 12, 13) Conversely, patients with systemic lupus erythematosus develop chronic ILD less than 10% of the time by most reports.(10, 14, 15) Polymyositis/dermatomyositis, Sjögren's syndrome, rheumatoid arthritis and mixed connective tissue disease show intermediate prevalence rates.(9, 16-18) Rheumatoid arthritis is the most common CVD seen in clinical practice. It affects 1-2% of the general population. In this disorder, 15-20% of patients develop clinically significant interstitial lung disease.(19-21) ILD is more prevalent in older, male patients with more severe arthritis and a history of smoking.(21, 22) By contrast, the other CTD-ILD patients tend to be younger (middle aged) and

female. Indeed, interstitial lung disease occurring in that demographic should always raise concern for an underlying connective tissue disorder.

The Diversity of Radiologic and Pathologic Findings in CTD-ILD

Nonspecific interstitial pneumonia (NSIP) is the most common type of interstitial lung disease seen in subjects with CVD, except for rheumatoid arthritis, where usual interstitial pneumonia (UIP) predominates (see Figure 1).(3, 23) Even in RA, though, NSIP is a close second with regard to histopathology.(24) There are several potential causes of NSIP, including hypersensitivity pneumonitis, HIV infection, pulmonary drug toxicity, and the idiopathic version of the disease, but finding NSIP on a lung biopsy should always prompt a careful evaluation for the presence of an underlying connective tissue disorder. Other common ILD patterns seen in CVD patients include organizing pneumonia (OP), lymphocytic interstitial pneumonia (LIP) and diffuse alveolar damage (DAD).(25)

Figure 1. Relative frequency of the various ILDs in patients with collagen vascular disease.



NSIP is the most prevalent interstitial pneumonia seen in patients with connective tissue disease. UIP may be slightly more common than NSIP in rheumatoid arthritis. OP is most common in subjects with RA, PM/DM and SLE. DAD is most often associated with SLE, PM/DM and RA. LIP is uncommon except in Sjögren's syndrome.

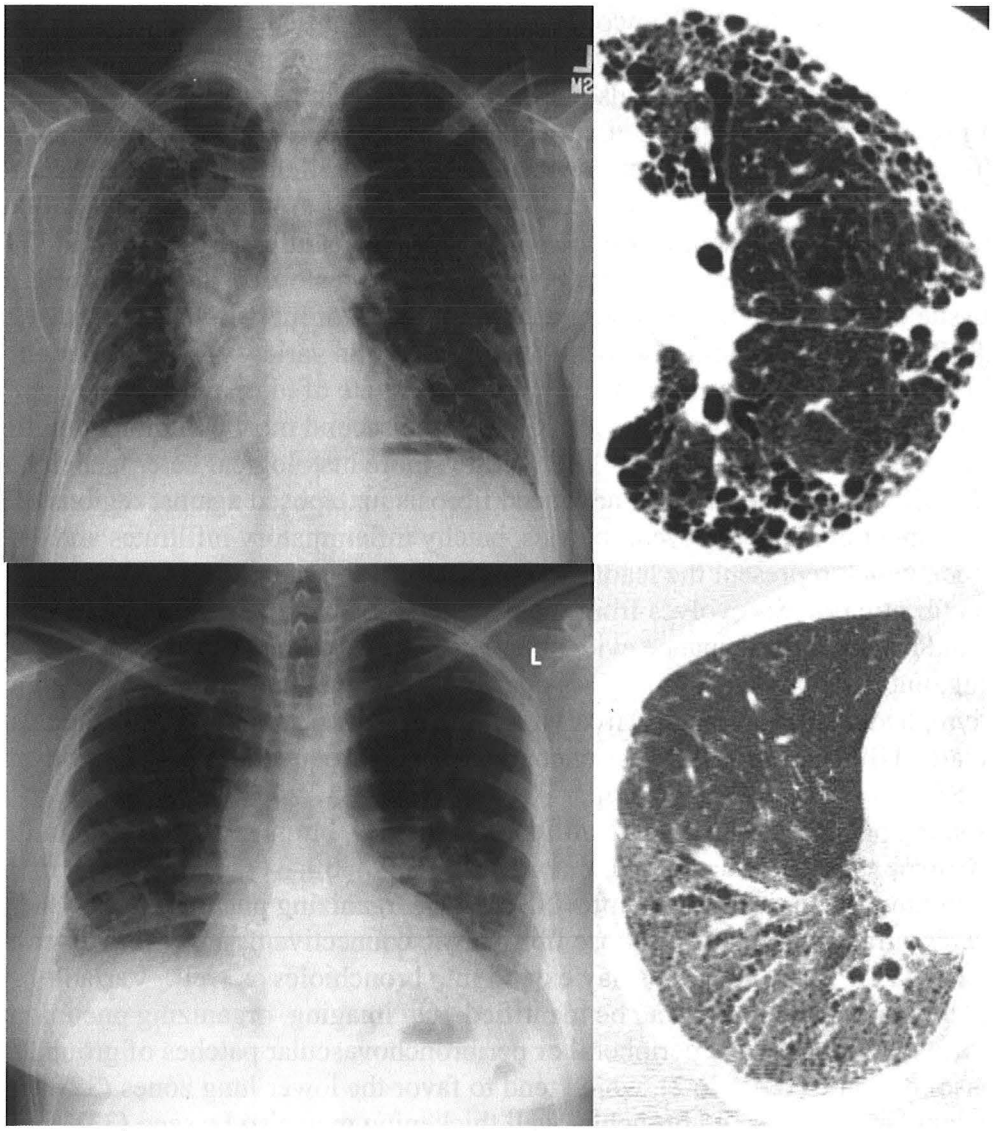
NSIP is characterized by a homogeneous histologic appearance wherein all affected regions look similar to the microscopist. There are cellular and fibrotic types of NSIP. In the cellular form, chronic interstitial inflammation is primarily responsible for the uniform widening of alveolar septae, while in fibrotic NSIP, collagen deposition predominates.(26) Honeycombing is uncommon, and mild if present. High resolution computed tomography indicates mainly ground glass opacification in the cellular form of the disease. Patchy consolidation may also be seen, and frequently reflects the concomitant presence of organizing pneumonia.(9) Superimposed intralobular interstitial thickening (reticulation) is often evident, especially in mixed cellular-fibrotic disease. Traction bronchiectasis and bronchioloectasis within regions of ground glass attenuation and intralobular interstitial thickening are the major imaging features of fibrotic NSIP.(9) NSIP is especially common in scleroderma, polymyositis/dermatomyositis and mixed connective tissue disease.(27) In scleroderma, about 75-80% of lung biopsies reveal NSIP.(23, 28) Regrettably, the less treatment-sensitive fibrotic variety is most common.

Usual interstitial pneumonia is the pathologic correlate of idiopathic pulmonary fibrosis, but it is not specific to that disorder. CVD is the second most common condition associated with the development of UIP. UIP features more histological heterogeneity than NSIP. In UIP, there are regions of advanced fibrosis juxtaposed against regions of normal lung architecture, plus honeycomb cysts, patchy inflammatory infiltrates and fibroblastic foci, which represent the leading edge of injury and repair within the lung.(29) The fibrotic process evolves from the pleural edge inward, and there is typically a subpleural and basilar predominance evident on HRCT with reticular change and honeycombing, but a paucity of ground glass opacity.(3) It is not uncommon to see some mediastinal lymphadenopathy (usually involving just one or two stations) in individuals with CTD-related UIP or NSIP.(3) UIP is encountered most frequently in association with RA and SSc.

Organizing pneumonia may be identified in any CVD, but is most common in the inflammatory myopathies, lupus and rheumatoid arthritis.(24, 30, 31) In PM/DM, it is the second most common type of ILD seen after NSIP.(24) Organizing pneumonia is characterized by intraluminal plugs of loose fibroblastic connective tissue within alveolar ducts and alveoli.(25) These "polyps" may extend into bronchioles as well. Variable degrees of interstitial inflammation can be identified. On imaging, organizing pneumonia typically presents with multifocal peripheral or peribronchovascular patches of ground glass and consolidation (see figure 2), which tend to favor the lower lung zones.(32) Nodules, perilobular opacities and bronchial wall thickening may also be seen.(33)

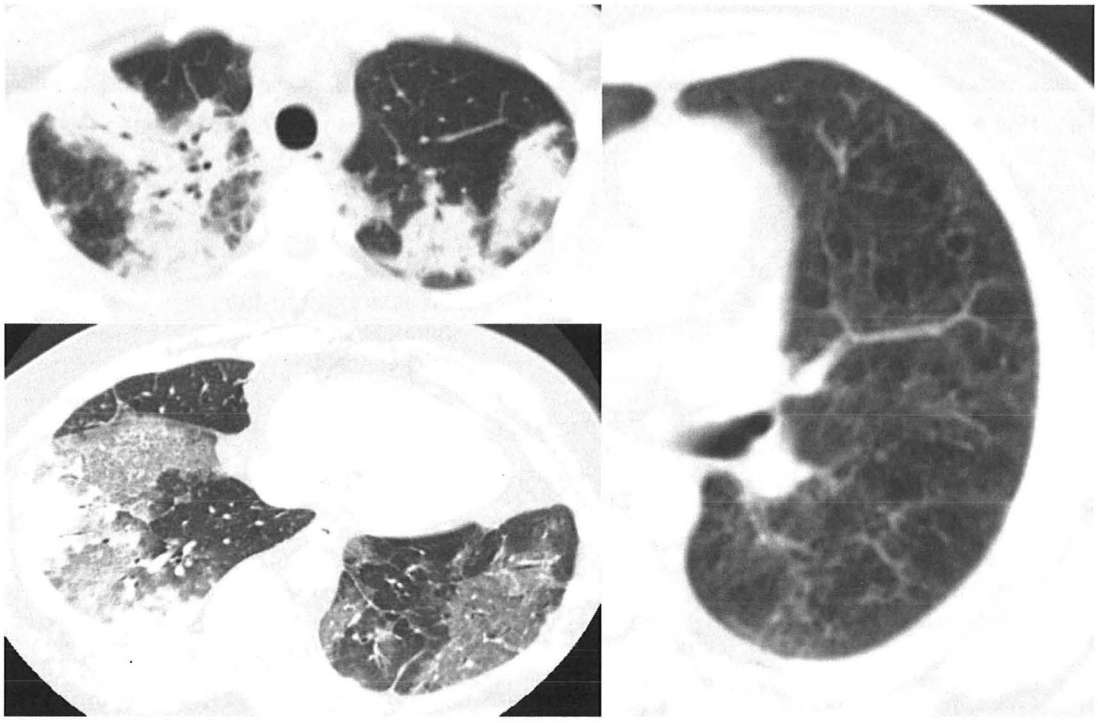
Lymphocytic interstitial pneumonia is an uncommon form of ILD which is usually associated with autoimmune disease or immunodeficiency states, and rarely is idiopathic. It is often recognized in association with Sjögren's syndrome, where up to 25% of patients will develop interstitial lung disease.(1, 34, 35) NSIP and LIP are the most common forms of ILD seen in Sjögren's syndrome. LIP is occasionally identified in patients with RA or SLE as well.(3, 24) This condition features prominent widening of the alveolar septae with polyclonal lymphocytes and variable numbers of plasma cells and histiocytes. Fibrosis develops occasionally. The HRCT patterns associated with LIP are remarkably diverse. Some patients show predominant ground glass opacities, while others have reticular infiltrates, centrilobular nodules, patches of consolidation, or thin-walled cysts which are typically few in number (see Figure 2).(3, 36)

Figure 2. Top: CXR and CT of a patient with rheumatoid arthritis and usual interstitial pneumonia featuring coarse reticular changes and prominent subpleural honeycombing. Bottom: Nonspecific interstitial pneumonia in a patient with dermatomyositis featuring basilar predominant ground glass opacities and traction bronchiectasis.



Diffuse alveolar damage, the clinical correlate of the acute respiratory distress syndrome, is the most ominous histopathologic pattern seen in subjects with CVD. The relevant clinical correlates include acute interstitial pneumonia (organizing DAD) and acute lupus pneumonitis (acute, exudative DAD). It occurs most often in association with PM/DM, the anti-synthetase antibody syndrome, RA and SLE.(3, 24, 27, 37, 38) DAD is sometimes the first manifestation of pulmonary involvement in a patient with CVD. Other times, its presence reflects an acute exacerbation of a chronic underlying interstitial disorder (e.g., NSIP or UIP).(39, 40) Widespread "geographic" ground glass opacification, with or without consolidation, is usually seen (see Figure 3).(3) Traction bronchiectasis and other evidence of architectural distortion may develop later on.

Figure 3. Top left: organizing pneumonia in a patient with systemic lupus erythematosus featuring peribronchial and peripheral consolidation. Bottom left: Diffuse alveolar damage in a patient with polymyositis demonstrating geographic ground glass opacification and areas of consolidation. Right: lymphocytic interstitial pneumonia in a patient with mixed connective tissue disease and secondary Sjögren's syndrome demonstrating mild, widespread ground glass with scattered cystic changes and some reticular infiltrates.



The Clinical Presentation of CTD-ILD

The respiratory presentation of CTD-ILD is indistinguishable from that of the idiopathic interstitial pneumonias.(41) Fibrotic NSIP and UIP are chronic, fibrosing conditions which present with the insidious onset of cough and dyspnea. In most cases, the cough is nonproductive. Pulmonary function tests reveal restriction with reduced lung volumes and often prominent impairment in diffusing capacity.(16, 25) The diffusing capacity, a measure of gas transfer across the alveolar-capillary interface, may also be reduced by the presence of anemia or pulmonary vascular disease, both of which may be present in subjects with connective tissue disease. Dry inspiratory crackles are usual on pulmonary auscultation. Clubbing is not uncommon in the subset with usual interstitial pneumonia. Look for reticular changes and honeycombing, or ground glass with traction bronchiectasis on HRCT to identify these patients (see Table 1).(9)

Individuals with organizing pneumonia, cellular NSIP and LIP often present with more subacute symptoms (2-12 weeks).(25) In addition to cough and breathlessness, these patients are more likely to note systemic complaints, such as fever or flu-like symptoms, at the onset of the respiratory illness. Fatigue and weight loss are common. Restriction is again the rule on pulmonary function testing, and crackles are expected on

pulmonary auscultation. These patients will have imaging that features predominantly ground glass opacification (patchy or widespread) and/or zones of consolidation.(9)

Table 1. Types of ILD seen in patients with collagen vascular disease: pathologic and radiologic features.

ILD	Pathologic Features	Presentation	Imaging	Main CTDs Associated
Cellular NSIP	Homogeneous mild-moderate expansion of alveolar septae with a lymphoplasmacytic infiltrate	Subacute-chronic	Predominant GGO, may see patches of consolidation	All
Fibrotic NSIP	Homogeneous widening of alveolar septae with mature collagen-type fibrosis	Chronic	GGO with traction bronchiectasis and/or intralobular interstitial thickening	All
UIP	Honeycombing, fibroblastic foci, temporal heterogeneity	Chronic	Subpleural honeycombing, predominant reticular opacities	RA, SSc, MCTD
LIP	Marked widening of alveolar septae by small, polyclonal lymphocytes	Subacute-chronic	Predominant GGO, reticular opacity, consolidation, nodules or cysts	Sjögren's syndrome
OP	Loose, fibroblastic connective tissue plugs within alveolar ducts and alveoli. Variable amounts of chronic interstitial inflammation	Acute-subacute	Peribronchial or subpleural consolidation and GGO	RA, SLE, PM/DM
DAD	Extensive proliferation of fibroblasts within the interstitial space +/– hyaline membranes	Acute	Widespread geographic GGO and/or consolidation, reticular and traction changes may be seen late	SLE, RA, PM/DM, ASA
DAH	Pulmonary capillaritis	Acute	Widespread GGO or consolidation	SLE

NSIP = nonspecific interstitial pneumonia, UIP = usual interstitial pneumonia, LIP = lymphocytic interstitial pneumonia, OP = organizing pneumonia, DAD = diffuse alveolar damage, DAH = diffuse alveolar hemorrhage

When patients with known or suspected connective tissue disease present with the rapid onset of cough, dyspnea, hypoxemia and widespread ground glass or alveolar infiltrates, the differential diagnosis should include acute or organizing DAD, acute, diffuse organizing pneumonia, diffuse alveolar hemorrhage (DAH), infection (including opportunistic pneumonias), and pulmonary drug toxicity. Acute exacerbations of

preexisting chronic ILD should also be considered.(42) Patients with PM/DM, the anti-synthetase antibody syndrome, and RA are the most prone to develop acute interstitial pneumonia, but it may occur in any CVD.(24, 27, 37, 40, 43) This features the rapid onset of shortness of breath and hypoxemia developing over days to a few weeks, and frequently culminates in the development of acute hypoxemic respiratory failure. Multifocal or diffuse ground glass opacification or consolidation is seen on chest imaging. Histology usually shows organizing DAD with extensive evidence of interstitial fibroproliferation and often remnants of hyaline membranes, a hallmark of acute lung injury. Widespread organizing pneumonia, or just very extensive fibroblastic foci, are sometimes seen instead.(39, 42) Mortality in this setting is on the order of 60-100% over 1-12 months.(37, 39) 1-5% of patients with chronic fibrotic CTD-ILD may develop acute exacerbations each year.(40, 44) These are also characterized by superimposed diffuse alveolar damage. Occasionally, thoracoscopic lung biopsy is actually a trigger for the development of these often fatal acute exacerbations.(45-48)

Patients with collagen vascular disease have an increased incidence of infectious pneumonia with routine and unusual pathogens due to both endogenous and exogenous immunosuppression.(3) In addition, these patients may have impaired cough and mucus clearance due to bellows weakness (PM/DM), or a greater risk of aspiration due to oropharyngeal dysphagia, esophageal dysmotility and severe gastroesophageal reflux disease (PM/DM, scleroderma). Subjects with CVD who are treated with corticosteroids and/or mycophenolate may be especially susceptible to the development of *Pneumocystis jiroveci* pneumonia.(49-51) Pneumocystis should always be considered and ruled out when new, widespread ground glass opacities appear in these patients.

The presence of hemoptysis, anemia or a falling hematocrit should alert the physician to the possibility of diffuse alveolar hemorrhage. DAH occurs almost exclusively in the setting of systemic lupus erythematosus, but only 1-2% of SLE patients develop pulmonary hemorrhage over the course of their illness.(52, 53) The diagnosis is confirmed by bronchoscopy and bronchoalveolar lavage (BAL). In the setting of DAH, serial aliquots of saline instilled through a wedged bronchoscope return an increasingly bloody effluent. Pulmonary capillaritis is the usual histologic finding in these patients.(54)

Clues that an ILD Patient Has an Underlying Collagen Vascular Disorder

Once the pulmonologist has excluded other common causes of interstitial lung disease with a careful occupational, environmental, medication and family history, he or she is frequently tasked with determining whether a patient with ILD has an idiopathic interstitial pneumonia (IIP) or an underlying connective tissue disease. Distinguishing the two depends on a careful history and physical examination, and attention to subtle differences that are sometimes present on imaging studies or histopathology.(55) All too often, the work-up is limited to a brief inquiry about arthritis or skin rashes, and an order to obtain an antinuclear antibody (ANA) and rheumatoid factor (RF) level. This approach is entirely inadequate. The ILD history must include a comprehensive survey of potential CTD-related complaints and include questioning about the presence of nonandrogenic alopecia, oral ulcers, dry eyes, dry mouth, skin rashes, photosensitivity, skin thickening or tightening, arthralgias, arthritis, morning stiffness, myalgias, muscle

weakness, constitutional complaints, serositis, renal disease, central nervous system complaints, Raynaud's phenomenon, dysphagia and GERD (see Table 2).

Table 2. Symptoms and signs which may indicate that a patient's interstitial lung disease is driven by an underlying connective tissue disorder.

Symptoms	Physical Exam Clues
• Skin rashes • Skin thickening or tightening • Thinning hair • Oral ulcers • Dry eyes • Dry mouth • Photosensitivity • Arthralgias • Arthritis • Morning stiffness • Myalgias • Muscle weakness • Pleurisy • Pericarditis • Neurological symptoms • Fever, malaise, weight loss • Dysphagia • GERD • Change in urine color or reduced output • Sudden onset of pallor or cyanosis in digits after cold exposure with blushing upon recovery	• Malar rash • Nonandrogenic alopecia • Heliotrope periorbital rash • Shawl sign or V-neck rash • Gottron's sign • Mechanic's hands • Telangiectasias • Oral ulcers • Cutaneous sclerosis • Sclerodactyly • Digital ulcerations • Periungual erythema • Abnormal nailfold capillaroscopy • Active Raynaud's phenomenon • Muscle tenderness • Proximal muscle weakness • Combined inspiratory squeaks and crackles on auscultation • Pleural or pericardial rubs • Synovitis or synovial thickening • Joint destruction • Ulnar deviation of digits

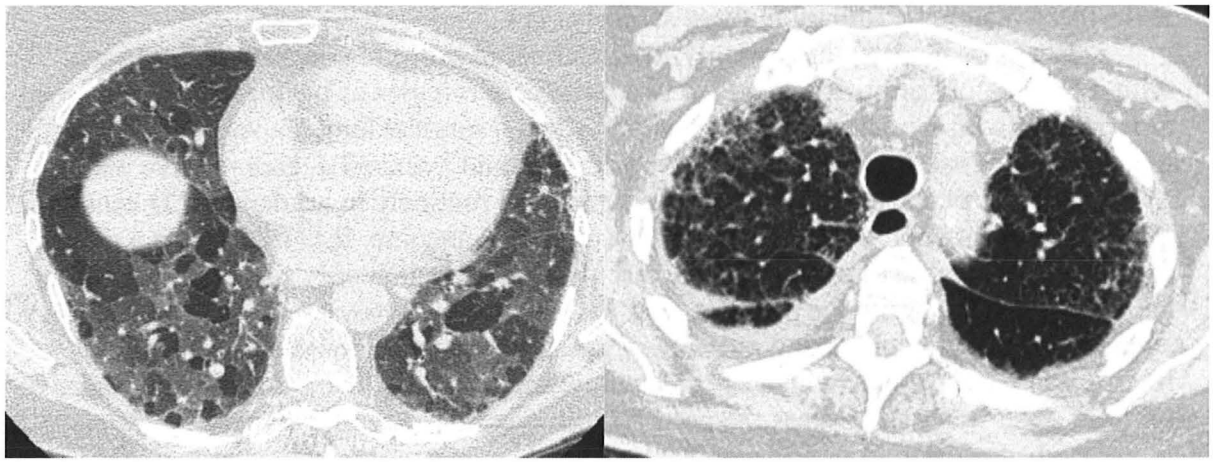
Similarly, the physical examination in ILD patients requires specific attention to sometimes subtle clinical clues. Some findings are obvious, such as widespread cutaneous sclerosis, Raynaud's phenomenon, or a malar rash. It is important to note more subtle psoriaciform lesions on the scalp, telangiectasias over the palms, face or upper chest, digital or oral ulcerations, sclerodactyly, Gottron's papules, a periorbital heliotrope rash or mechanic's hands. Nailfold capillaroscopy can be very helpful to identify the capillary dropout, giant capillaries and microhemorrhages seen in certain connective tissue disorders.(56-58) On auscultation of the chest, listen for inspiratory squeaks in conjunction with inspiratory crackles. This suggests concomitant small airways disease and ILD, which is seen in the setting of collagen vascular disease and hypersensitivity pneumonitis, but not the IIPs. Occasionally, one may identify other findings like pleural or pericardial friction rubs, a consequence of CVD-related serositis. Even though overt synovitis may be lacking, look for evidence of synovial thickening, ulnar deviation of the digits, or prior joint destruction.

A positive ANA and/or RF are nonspecific, and may be seen in the presence of idiopathic ILD. High titers of antinuclear antibodies (>1:320), or certain ANA patterns (i.e., nucleolar) are more suggestive of an underlying connective tissue disorder. Some

antibodies are more specific than others, and we recommend checking a complete extractable nuclear antigen (ENA) panel as well as creatine phosphokinase and aldolase levels, anti-cyclic citrullinated peptide (anti-CCP) and myositis (anti-synthetase) antibody panel on individuals with ILD of unclear etiology. The anti-CCP antibody is highly specific for rheumatoid arthritis.(59) The anti-Jo1 antibody and other myositis antibodies like PL-7 or PL-12 (and others) are specific for PM/DM or the anti-synthetase antibody syndrome.(60-62) Scl-70 is specific for systemic sclerosis and predictive of the development of interstitial lung disease.(63) High titer SSA (anti-Ro) or SSB (anti-La) antibodies are suggestive of Sjögren's syndrome. Double-stranded DNA antibodies would favor systemic lupus erythematosus, and anti-ribonuclear protein (RNP) antibodies are seen in patients with MCTD.

On HRCT, it is important to look for clues apart from the ILD pattern alone, as the patterns of IIP and CTD-ILD are frequently indistinguishable.(9) A dilated, patulous esophagus is common in individuals with scleroderma/CREST-related ILD. Pleural or pericardial thickening or effusion may signal past or current serositis, and is decidedly uncommon in the idiopathic interstitial pneumonias. Enlargement of the central pulmonary arteries, if disproportionate to the extent of parenchymal damage, might signal the presence of concomitant pulmonary vascular disease, which is especially common in patients with SSc or MCTD. ILD plus lobular air-trapping, which suggests simultaneous pathology within the small airways, is often identified in patients with RA and Sjögren's syndrome.

Figure 4. Left: expiratory HRCT in a patient with Sjögren's syndrome and ILD demonstrating ground glass opacities and prominent lobular air trapping indicative of concomitant bronchiolitis; Right: subpleural reticulation, prominent pleural thickening and a dilated esophagus in a patient with a PM-SSc overlap syndrome.



At times, the pathologist reviewing the surgical lung biopsy specimen is helpful in distinguishing idiopathic interstitial pneumonia from CTD-ILD. With regard to the essential diagnostic features of each interstitial pneumonia (NSIP, UIP, etc.), there is no difference histopathologically between the IIPs and CTD-ILDs. The difference comes in the additional features which may or may not be present in subjects with connective tissue disease. These features include the presence of prominent lymphoid follicles with germinal centers, extensive pleuritis, constrictive or lymphocytic bronchiolitis, prominent

lymphoplasmacytic interstitial infiltrates, and dense perivascular collagen deposition.(41, 64-66)

Does the Patient Have an IIP or a Lung-Dominant Connective Tissue Disorder?

There are many subjects with ILD who present for evaluation demonstrating some limited clinical and serological evidence of an underlying autoimmune disease, but they fail to meet defined criteria for a connective tissue disorder according to American College of Rheumatology standards.(7, 67) Should these patients be classified as idiopathic interstitial pneumonia or CTD-ILD? Rheumatologists recently established a new category called "undifferentiated connective tissue disease (UCTD)" to describe individuals who have features of a systemic autoimmune disease, but who do not meet established standards for diagnosis of a specific CVD. These patients generally have milder disease with an absence of major organ involvement, simplified clinical and serological presentations (e.g., at least one positive autoantibody), and a good prognosis.(68) When followed longitudinally, most of these subjects (about 70%) do not evolve into defined collagen vascular diseases, so UCTD is not simply an early phase of another disorder.(68, 69) Some have suggested that most patients with idiopathic NSIP may actually have an occult connective tissue disorder.(70) Kinder et al. studied 28 consecutive IIP patients and found that 88% of the idiopathic NSIP patients met criteria for an undifferentiated connective tissue disorder.(70) A positive ANA was the most common serologic abnormality in these patients with a median titer of only 1:320. Patients were only required to have one potential symptom of a CVD, but 86% had two, and 67% had three. In another study of 47 consecutive patients with idiopathic NSIP, Suda and colleagues found that 47% met criteria for UCTD.(71) The most common extrapulmonary symptoms were skin change or Raynaud's phenomenon. Fibrotic NSIP is the usual histologic finding in these subjects.(71)

Rheumatologists, interestingly, are much more prone to consider an individual with inflammatory arthritis and one or two positive serologies as having UCTD than they are a patient with the same serologies and NSIP on a surgical lung biopsy.(63) What if the patient also had a first degree relative with RA, and a second degree relative with Sjögren's syndrome? Such patients are encountered routinely in academic ILD centers. Yet despite its high prevalence and impact on patient outcome, ILD is not even a part of the diagnostic criteria of most collagen vascular diseases. It is only a minor criterion for patients with SSc, where the prevalence of ILD is over 70% based on HRCT and autopsy studies. The rheumatology and pulmonary group at National Jewish Health suggest referring to these patients with suspected autoimmune ILD as "lung-dominant connective tissue disease".(67) They stress the need for utilizing more specific autoantibody panels in our evaluation of ILD patients, and recommend incorporating histopathologic findings supportive of an underlying rheumatic disease into the diagnostic equation.(67) I believe we should also include histopathology from minor salivary gland biopsies (in subjects with sicca symptoms), and a family history of defined CVD among first and second degree relatives in our definition "lung-limited" or "lung-dominant" connective tissue disorders.

Table 3. Proposed criteria for the diagnosis of lung dominant connective tissue disease (modified from Fischer et al, Chest 2010(67)).

Evidence of interstitial lung disease (NSIP, UIP, OP, LIP, DAD or DIP if no smoking history) by high resolution chest CT or surgical lung biopsy with no alternate etiology evident *and*

Any one of the following "specific" autoantibodies:
ANA > 1:320
Nucleolar ANA pattern
Anti-CCP
Anti-SSA or SSB
Anti-Scl 70
Anti-centromere
Anti-dsDNA
Anti-Smith
Anti-RNP
Anti-tRNA synthetase antibodies (Jo-1, PL-7, PL-12, MI-2, SRP, KU, U2 SN RNP, EJ, OJ)
Anti-PM-Scl

or

symptoms suggestive of a possible underlying connective tissue disorder

- sicca symptoms, inflammatory arthritis, typical CTD-related skin findings, Raynaud's phenomenon (especially with abnormal nailfold capillaroscopy)

and either

- a 1st or 2nd degree relative with a defined connective tissue disease

or

- a minor salivary gland biopsy indicating grade 2-4 chronic sialadenitis

or

- at least two of these histopathologic features on lung biopsy
  - prominent lymphoplasmacytic interstitial infiltrate
  - prominent lymphoid follicles with germinal centers
  - constrictive or lymphocytic bronchiolitis
  - extensive pleuritis
  - dense perivascular collagen

or

- an HRCT demonstrating interstitial lung disease and additional features suggestive of CTD-ILD:
  - lobular air-trapping indicative of concomitant bronchiolitis
  - a dilated, patulous esophagus
  - significant pleural or pericardial thickening or effusion

Value of Bronchoscopy and Surgical Lung Biopsy in CTD-ILD

Bronchoscopy is generally not useful for determining the histologic subtype of interstitial lung disease in patients with collagen vascular disease. The small biopsies obtained transbronchially offer an insufficient sampling of the lung's architecture. Bronchoalveolar lavage may be useful for excluding infection in these patients. Infection is especially common in SLE and PM/DM.(72, 73) Most infections are bacterial, but mycobacteria, fungi, viruses and opportunists like pneumocystis, nocardia and CMV must be considered.(74)

Bronchoalveolar lavage (BAL) is the best test for confirming the presence of diffuse alveolar hemorrhage.(52, 75) This occurs almost exclusively in SLE, but

occasionally is identified in other CVDs. Infection is commonly identified in SLE patients with DAH, and may actually be a trigger for developing capillaritis. In one study, evidence of infection was found in 57% of SLE patients within 48 hours of admission for pulmonary hemorrhage.(76) BAL and transbronchial biopsy may assist in excluding concomitant malignancy in some patients as well (e.g., lymphoma complicating Sjögren's syndrome with LIP, or a "scar carcinoma" in a patient with fibrosis).

In the appropriate clinical setting, high percentages of lymphocytes or eosinophils in BAL fluid may help support a diagnosis of drug-induced lung disease in CTD patients.(74) This is most frequently encountered in RA patients taking methotrexate.(77, 78) In some CVDs, especially Sjögren's syndrome and rheumatoid arthritis, high percentages of lymphocytes are common on analysis of BAL fluid, even in the absence of respiratory symptoms, abnormal chest radiographs or abnormal PFTs.(79, 80) Thus, this should not be considered evidence of disease activity. In general, BAL granulocytosis (>3% neutrophils or eosinophils) is indicative of more severe interstitial disease.(74) It remains unclear whether such an "alveolitis" has any independent prognostic value.

The other value of BAL is as a tool of research to expand our understanding of the pathogenesis of ILD in these patients. BAL allows for sampling of cellular and biochemical elements within the lung. Inflammatory cell differentials and products (cytokines, growth factors, etc.) can be analyzed, and myofibroblasts can be cultured from BAL fluid. The ultimate goal is to identify reliable biomarkers that track disease activity, predict outcome of response to specific treatments, and gauge global prognosis. Insights garnered from such research have already suggested a number of novel therapeutic targets.

Surgical (thoracoscopic) lung biopsy is a routine and essential part of the evaluation of interstitial lung disease when the etiology of the parenchymal disorder is unknown. Prognosis in the idiopathic interstitial pneumonias is closely tied to the histopathologic pattern.(81, 82) That is to say, the prognosis of idiopathic cellular NSIP, fibrotic NSIP and UIP are substantially different. The same cannot be said of those patterns occurring in CTD-ILD patients.(83) Thoracoscopic lung biopsy is also known to be a potential trigger for an acute exacerbation of ILD with the development of often life-threatening diffuse alveolar damage in 2%.(45, 48) The fact that the damage is often worse in the non-operated lung suggests that alveolar overdistention and/or toxicity from high inspired concentrations of oxygen intraoperatively may contribute to this complication. When biopsies are done in this population, care should be taken to use very small tidal volumes during single lung ventilation of these intrinsically damaged lungs, and to use only enough supplemental oxygen to ensure adequate systemic delivery during the procedure (not the 100% FiO2 which is frequently employed by anesthesiologists). Surgical lung biopsy in the setting of collagen vascular disease should generally be reserved for atypical clinical or imaging presentations, or for suspicion of malignancy (e.g., lymphoma in Sjögren's syndrome).

Pathogenesis and Treatment of CTD-ILD

Formulating effective treatment plans for CTD-ILD requires an understanding of the pathogenesis underlying these complex illnesses.(84) Unfortunately, there is not just

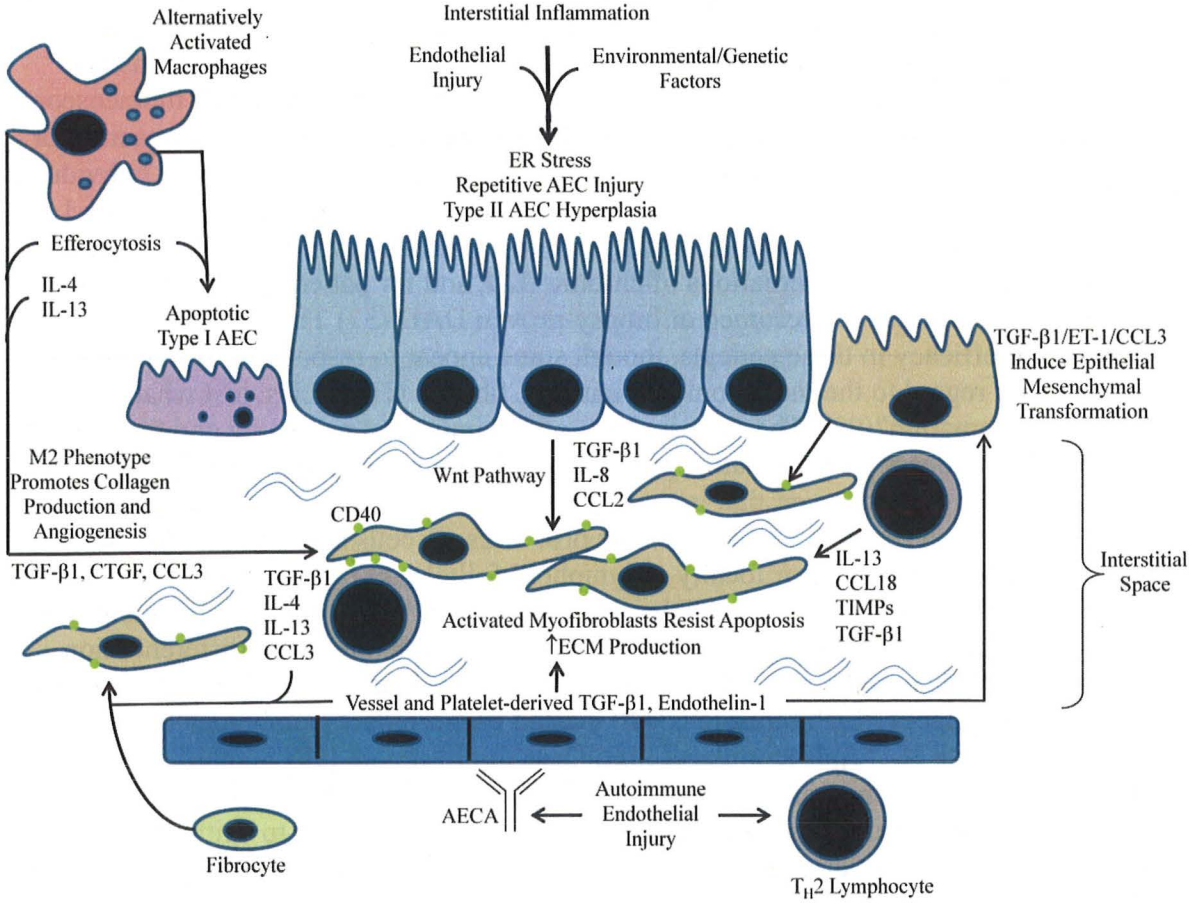
one lung injury and repair process to consider, as evidenced by the numerous distinct histopathologies seen in these patients. Furthermore, the individual collagen vascular diseases are themselves quite phenotypically diverse. At this point, there is much to learn about how environment and genetics interact to produce autoimmunity. What is the role of specific autoantibodies in the pathogenesis of these disorders? Is inflammation a primary or secondary event in CTD-ILD? To what degree does autoimmune inflammation cause the endothelial or epithelial injuries which incite the cascade of cellular and molecular events that culminate in the development of pulmonary fibrosis? What self-antigens are targeted? We now know that repeated injury, along with abrogation of normal reepithelialization and reendothelialization responses, leads to a loss of basement membrane integrity at the alveolar-capillary interface.(85) When combined with a milieu of particular cytokines and chemokines, these events result dysregulated wound repair, abnormal extracellular matrix deposition and pathologic fibrosis (see figure 5).

Current therapies directed at CTD-ILD target the inflammatory response and include corticosteroids, azathioprine, mycophenolate and cyclophosphamide. Controlled trials demonstrating the efficacy of corticosteroids in CTD-ILD are lacking, yet there are certain types of ILD that clearly demonstrate favorable treatment responses. These include organizing pneumonia, diffuse alveolar hemorrhage, the cellular form of NSIP and LIP. Patients with these pulmonary manifestations may require the concomitant use of other immunomodulating agents for systemic disease control, as steroid-sparing agents, or because of glucocorticoid-resistant ILD.(86-90) These steroid-responsive subsets of CTD-ILD are generally easy to recognize even in the absence of thoracoscopic lung biopsies because they have predominantly or exclusively ground glass opacities or consolidation on HRCT imaging.(9) Steroids alone are generally unhelpful in individuals with UIP.(91) High dose "pulse" corticosteroid treatment (e.g., methylprednisolone 1 gram intravenously for 3-5 days) is usually employed in subjects with diffuse alveolar hemorrhage, for acute exacerbations of chronic ILD, and for patients with acute respiratory failure due to presumed or biopsy-proven DAD.(37) There is no clear evidence of efficacy in these patients, though some appear to respond to this approach.

With regard to the more common chronic, fibrotic CTD-ILDs, just what is the role of inflammation?(92) The old paradigm of inflammation preceding and then leading to fibrosis in patients with idiopathic pulmonary fibrosis has been debunked. It is tempting to believe, however, that in these CVDs, autoimmune inflammation at least plays a key role in regulation of the fibrotic processes. T cells may be seen diffusely within the interstitial space or focally as lymphoid follicles in biopsy specimens of fibrotic CTD-ILD patients.(93, 94) T lymphocyte-derived cytokines and chemokines, in a non-antigen-directed fashion, may activate fibroblast proliferation and differentiation leading to collagen production.(92) Activated T cells are known to express CD40 ligand on their cell surface, which binds to CD40 located on fibroblast membranes. In combination with IL-4, this stimulates fibroblasts to proliferate.(95) Signaling molecules like chemoattractant chemokine ligand 3 (CCL3) released by polyclonal lymphocytes in the lung may also recruit marrow-derived fibrocytes and contribute to epithelial mesenchymal transformation.(85, 96-99) Lymphocyte chemoattractant chemokine ligand 18 (CCL18) is upregulated in the lungs of patients with pulmonary fibrosis, and CCL18 levels have been shown to correlate negatively with total lung capacity and diffusing

capacity changes in patients with IPF and systemic sclerosis.(100) Furthermore, the delivery of human CCL18 into the mouse lung by an adenoviral vector was sufficient to produce pulmonary lymphocyte infiltration and fibrosis.(101)

Figure 5. Pathogenesis of inflammation and fibrosis in CTD-ILD. Anti-endothelial cell antibodies and self-reactive T cell clones induce endothelial injury leading to vessel and platelet-derived release of TGF-β and endothelin-1. These substances promote myofibroblast activation within the interstitial space. Activated myofibroblasts proliferate, resist apoptosis and release more extracellular matrix components. Endothelial injury, interstitial inflammation and environmental and genetic factors (e.g., smoking, short telomeres, surfactant protein mutations, Fas gene polymorphisms) combine to induce endoplasmic reticulum stress and alveolar epithelial cell injury leading to type II cell hyperplasia and the release of profibrotic cytokines and chemokines. Apoptosis of injured type I alveolar epithelial cells combined with lymphocyte-derived IL-4/IL-13 exposure causes macrophages to become alternatively activated (M2 phenotype). These cells release substances that further promote collagen production and angiogenesis. Fibrosis is not dependent solely on the proliferation of resident interstitial fibroblasts. Exposure of type II alveolar epithelial cells to TGF-β, CCL3 and endothelin-1 results in epithelial mesenchymal transformation, and circulating bone marrow-derived fibrocytes provide another important source of fibroblasts within the interstitial space.



T lymphocytes may produce profibrotic (TGF-β, IL-4, IL-13) or antifibrotic (TNF-α, IFN-γ) cytokines. Rather than looking to deplete all T lymphocytes in these patients, which may increase the risk of infectious complications while also potentially eliminating T cells with an antifibrotic phenotype, we perhaps should be trying to change the balance of T cell and macrophage phenotypes in order to temper the profibrotic characteristics that some leukocytes express.(92) Self-reactive T lymphocytes may not be the underlying cause of fibrosis in CVD patients, but T cells may well play a key role in modulating the fibrotic process.

It is well-established that the use of lymphocyte-modulating agents like azathioprine, mycophenolate, cyclophosphamide, tacrolimus and rituximab can affect the clinical course of fibrotic CTD-ILDs.(84, 102-107) For instance, several studies, some uncontrolled, have demonstrated the beneficial effects of cyclophosphamide in SSc patients with respect to lung function, symptoms and imaging.(108-110) The Scleroderma Lung Study was the first multicenter, randomized placebo-controlled trial in 158 patients with symptomatic ILD and CT or BAL evidence of "inflammation".(111) This showed a modest, but statistically significant benefit in vital capacity measurements (2.5%) favoring the cyclophosphamide arm, along with improved skin scores and dyspnea. The toxicities associated with cyclophosphamide use, however, are many, and prolonged therapy (> 6 months) with this agent is generally unattractive. We tend to favor this drug in patients with severe and rapidly progressing CTD-ILD, especially when other less toxic immunosuppressive agents have failed. The role of this drug in systemic sclerosis patients is better defined compared to other rheumatic diseases. Indeed, there is a striking lack of large, controlled studies of the treatment of CTD-ILD in patients with other collagen vascular diseases.

Most patients with chronic CTD-ILD who have a HRCT pattern indicative of fibrotic or mixed cellular/fibrotic NSIP or honeycombing plus symptomatic, physiologic or radiographic evidence of recent disease progression will be offered therapy with either azathioprine or mycophenolate, usually in conjunction with low dose steroids. Thiopurine methyltransferase levels should be checked prior to choosing azathioprine, as low levels of that enzyme would mean the risk of drug toxicity may be unacceptably high. Generally, these drugs are better tolerated than cyclophosphamide, and may be used for longer treatment periods. In one study of 13 SSc-ILD patients who demonstrated worsening pulmonary function trends in the 12 months prior to initiation of treatment (negative 5% vital capacity, negative 5% diffusing capacity), mycophenolate led to a significant improvement in vital capacity (+4% of predicted normal VC), and stabilization in diffusing capacity (+1% of predicted normal DLCO).(112) In another retrospective trial of mycophenolate in SSc-ILD patients treated for at least a year, the radiologic extent of disease was stable in eleven, worse in three, and improved in one.(113) The Scleroderma Lung Study II will compare the effects of daily oral cyclophosphamide vs. mycophenolate and is presently enrolling.

A mixed cohort of 28 CTD-ILD patients treated with mycophenolate showed improvements in average percentage predicted FVC and DLCO of 2.3% and 2.6%, respectively.(114) In another mixed cohort of 10 subjects, all 10 had improvements in alveolitis, respiratory symptoms and quality of life scores.(115) Four of five patients requiring oxygen were able to discontinue it. Two of eight repeat HRCT scans showed improvement, and none worsened while on therapy. Three of nine with pulmonary

function data showed improvement, and 5 were stable.(115) In addition to targeting lymphocytes, mycophenolate has antifibrotic effects related to effects on the proliferation of non-immune cells including fibroblasts and smooth muscle cells.(116, 117) It also reduces the synthesis of type I collagen and increases the synthesis of interstitial collagenase (matrix metalloproteinase-1).(117) Our experience also suggests that mycophenolate is the most effective and generally well tolerated cytotoxic agent for use in patients with progressive, fibrotic forms of CTD-ILD, particularly in PM/DM, SSc, "lung dominant" CTD and Sjögren's syndrome.

Pirfenidone, a novel anti-fibrotic and anti-inflammatory molecule, has demonstrated some efficacy in patients with IPF.(118, 119) It has not yet been approved for use in IPF in the United States, though it has been approved in Europe and Japan. Studies in patients with CTD-ILD have not yet been performed.

Tacrolimus, an inhibitor of T cell activation, has produced favorable pulmonary responses in small studies of patients with refractory myositis and the anti-synthetase antibody syndrome.(107, 120) Randomized, controlled trials with this agent need to be conducted.

Major advances have been made in the last decade with respect to the pathogenesis of idiopathic pulmonary fibrosis. At least some of these lessons are sure to be applicable to the chronic, fibrotic types of ILD seen commonly in patients with connective tissue disease.(84) The hope is that this science will help us identify subsets of CVD patients who are likely to develop ILD in the future, while also leading to new and more effective therapeutic approaches.

There is evidence in mice that the targeted deletion of type II alveolar epithelial cells can lead directly to remodeling and fibrosis in the lung without other external factors being present.(121) In humans, mutations in surfactant proteins C and A2 promote endoplasmic reticulum stress in type II cells and the development of pulmonary fibrosis.(122) Hermansky-Pudlak syndrome, an inherited disorder of lysosome function, is also linked to type II alveolar epithelial cell stress, apoptosis and pulmonary fibrosis.(123)

Mutations in telomerase, short telomere lengths and premature cellular senescence play a key role in some cases of familial pulmonary fibrosis.(124-126) Interestingly, telomerase activity was noted to be markedly decreased in one study of systemic sclerosis patients also.(127) SSc is the CVD most strongly associated with pulmonary fibrosis, and telomere shortening has been noted previously in scleroderma patients.(128) Defective apoptosis related to certain Fas gene polymorphisms has been associated with autoimmune disease.(129-133) Apoptosis and efferocytosis have important immunologic consequences including macrophage activation leading to the secretion of key profibrotic cytokines like transforming growth factor-beta (TGF-β) and its downstream mediator, connective tissue growth factor (CTGF), which stimulate extracellular matrix production and myofibroblast differentiation.(5, 134, 135) TGF-β signal transduction involves the phosphorylation of Smad proteins, which then effect the transcription of collagen, other matrix elements, and CTGF. Monoclonal antibodies against TGF-β and CTGF, or molecules capable of blocking of Smad phosphorylation or further downstream signaling are promising candidates for disrupting the fibrotic machinery in interstitial lung disease.(5)

In connective tissue disease, autoimmune microvascular injury may lead to endothelial and epithelial damage and activation, the release of profibrotic endothelin-1, local myofibroblast activation, and the development of additional profibrotic cellular activity related to epithelial-mesenchymal transformation and fibrocyte recruitment.(84, 136-139) Bosentan is an endothelin-1 receptor antagonist used in the treatment of pulmonary arterial hypertension. However, it has thus far failed to demonstrate efficacy in the treatment of IPF or SSc-ILD.(140-142)

Imatinib, a tyrosine kinase inhibitor, binds to c-abl and impairs downstream signaling of TGF-β, while also blocking the tyrosine kinase activity of platelet derived growth factor (PDGF).(143, 144) Thirty patients with diffuse cutaneous systemic sclerosis were recently treated with imatinib in an open-label study.(145) Improvements in skin thickening and FVC (6.4% predicted) were seen, while DLCO measurements remained stable. The FVC improvements were actually greater in patients without interstitial lung disease. Imatinib did not affect lung function or survival in a randomized, placebo-controlled trial of mild-moderate IPF patients who were followed for 96 weeks.(146)

Peroxisome proliferator-activated receptor gamma (PPARγ) is a nuclear hormone receptor that may have important effects on inflammation, fibrogenesis and vascular remodeling.(147) Its antifibrotic function relates to blockade of the effects of TGF-β on collagen gene expression and myofibroblast differentiation.(148) PPARγ is markedly reduced in lung biopsies from SSc-ILD patients.(149) Interestingly, activators of PPARγ include rosiglitazone and pioglitazone, which are currently approved for use in patients with type II diabetes mellitus. Treatment of lung myofibroblasts with PPARγ agonists like rosiglitazone induces cell cycle arrest and inhibits fibroblast migration. The drug also prevents alveolar epithelial mesenchymal transition, and inhibits the development of fibrosis in the murine bleomycin model.(150) PPARγ agonists have not yet been evaluated in any human fibrosis trials.

Immunoneutralization of the profibrotic cytokine, IL-13, is also being studied in patients with idiopathic pulmonary fibrosis and systemic sclerosis.(103) IL-13 triggers fibroblast proliferation and collagen synthesis, and is elevated in patients with IPF and SSc.(151-153) No results are yet available from these trials.

What, then, is the role of currently approved biologics in the treatment of CTD-ILD? There is limited and conflicting evidence at this point. Rituximab has been reported to produce favorable pulmonary and systemic responses in patients with systemic lupus, the inflammatory myopathies, and systemic sclerosis.(154-160) It has also, however, been reported to cause new onset ILD in isolated cases.(157, 161) The vast majority of drug-induced or drug-exacerbated interstitial lung disease linked to biologics, however, has been with the use of tumor necrosis factor-α blocking agents.(157, 162, 163) Although there are sporadic reports of a beneficial impact from anti-TNF therapies on CTD-ILD, there have been 144 reports of new or worsening ILD in RA patients following treatment with these drugs, and mortality rates have been high.(157) The presence of ILD is not considered a contraindication to the use of these otherwise very helpful biological agents, but the development of new respiratory symptoms in this setting should prompt immediate discontinuation of the drug and prompt pulmonary consultation.

The potential role of microaspiration of acidic gastroesophageal reflux in the development or worsening of pulmonary fibrosis remains a topic of debate.(164, 165) Therapy of even asymptomatic GERD is now recommended as part of the new IPF treatment guidelines.(166) GERD is even more prevalent in subjects with secondary forms of pulmonary fibrosis, especially scleroderma and its variants, and it should be managed with proton pump inhibition and additional reflux precautions as a matter of routine.(165, 167, 168)

Antioxidant therapy with oral N-acetyl cysteine (NAC), a glutathione precursor, may also be beneficial in subjects with pulmonary fibrosis.(169-171) A specific role for NAC in the setting of collagen vascular disease has not yet been established on the basis of clinical trials, but the safety profile of the drug is good, and it has several putative antifibrotic effects.(172-175) Adjunctive measures such as influenza and pneumococcal vaccination should not be overlooked.

Lung transplantation remains an option for some patients with advanced fibrosis and collagen vascular disease. Careful patient selection is important. Severe reflux disease and oropharyngeal dysphagia (aspiration risk), neuropsychiatric issues, significant renal pathology, non-healing wounds or advanced sclerosis of the chest wall may preclude consideration of transplantation. Notwithstanding, in a recent study comparing post-transplant outcomes in IPF, SSc and idiopathic pulmonary arterial hypertension, no significant differences in mortality were noted at 24 months (64% survival).(176) Another retrospective analysis of 47 SSc patients undergoing transplantation at 23 centers between 1987 and 2004 indicated a one and three-year survival rate of 68% and 46%, respectively.(177) These values were not significantly different compared to the outcomes of the 10,000 other patients undergoing lung transplantation during this interval for other indications.

Prognosis of CTD-ILD

Interstitial lung disease is clearly a negative prognostic factor in patients with connective tissue disorders.(12, 178, 179) The prognosis of CTD-ILD is, however, extremely variable. Certainly some histologic subgroups have distinct prognoses in the setting of CTD-ILD.(180) For instance, organizing pneumonia has a much better prognosis than usual interstitial pneumonia, which has a much better prognosis than diffuse alveolar damage. However, those entities can be reliably distinguished from one another on the basis of clinical and radiographic findings alone. Establishing specific histopathologic patterns by way of surgical lung biopsy in CTD-ILD is not particularly useful from a prognostic standpoint. In this way, CTD-ILD differs from the idiopathic interstitial pneumonias. Distinguishing UIP from fibrotic (or even cellular) NSIP among collagen vascular disease patients does not seem to confer the same important prognostic information that it does in the setting of the idiopathic interstitial pneumonias.(23) In systemic sclerosis, the prognosis of UIP and NSIP is similar. In the largest study to date, the 5-year survival for SSc patients with NSIP was 91% versus 82% in the UIP group, and there was no difference in outcomes between subjects with cellular NSIP and those with fibrotic NSIP.(23) Instead, disease severity at presentation and trends in functional parameters (diffusing capacity and vital capacity) were more important predictors of

outcome. Higher fibrosis scores on HRCT also indicate a worse prognosis in CTD-ILD, as does the presence of pulmonary hypertension.(181-183)

Why would UIP in the setting of collagen vascular disease have a different prognosis than idiopathic UIP, even accounting for differences in age and controlling for severity of functional impairment.(184)? CTD-UIP and idiopathic UIP are, for the most part, indistinguishable to the pathologist. The outcome difference may relate to finding fewer fibroblastic foci (active zones of injury and repair within the lung) in CTD-UIP patients compared to those with idiopathic pulmonary fibrosis.(185, 186)

In a study of 362 ILD patients (269 with IIP and 93 with CTD-ILD), the mean survival in the CVD group was 130 months compared to 81 months in the IIP group even though baseline lung functions were similar.(184) Patients with idiopathic NSIP and collagen vascular disease-related NSIP appear to have a similar prognosis.(184, 187) This may not be true for patients with UCTD-related NSIP, where one study suggested a significantly better prognosis relative to idiopathic NSIP.(7, 71)The prognosis and treatment responsiveness of collagen vascular disease-related OP is similar to that of cryptogenic organizing pneumonia.(188) Diffuse alveolar damage is the most severe and life-threatening interstitial complication of collagen vascular disease. The reported mortality rates for this complication are 60-100%, and may be highest when DAD occurs on top of preexisting chronic interstitial disease.(3, 37, 39)

The clinical course of the interstitial lung disease does not necessarily parallel other global (i.e., skin, joint, muscle) evidence of disease activity. Interstitial lung disease can be an early or late complication.(12) In some cases, the ILD may effectively "burn out" and stop progressing even though the systemic illness remains active. SSc patients, for example, often progress fastest over the first few years, but then the pace of physiological deterioration slows and may even stop.(11, 13, 110) It is crucially important to consider not just the HRCT appearance (i.e., disease extent), but serial pulmonary function and symptom trends over time when deciding which patients require treatment directed at their ILD. Therapeutic decisions are also frequently driven by other systemic features of the disease. This reinforces the need for close cooperation between the rheumatologist and pulmonologist in optimizing management of these patients.

Conclusions

- Interstitial lung disease is an important cause of morbidity and mortality among patients with collagen vascular disease.
- When evaluating patients with interstitial lung disease of unknown etiology, it is essential to include a complete connective tissue disease-specific review of symptoms, family history, serological work-up and CTD-focused physical examination.
- NSIP is the most common type of interstitial lung disease seen in subjects with collagen vascular disease.
- Many patients currently classified as having "idiopathic" interstitial pneumonias may actually have a *forme fruste* of connective tissue disease with the lung as the primary or sole target. There are not yet well established criteria for the diagnosis of these apparent autoimmune interstitial disorders.

- Bronchoscopy in patients with collagen vascular disease is mainly useful for excluding complicating infections and specific complications like diffuse alveolar hemorrhage.
- Surgical lung biopsy is uncommonly required in CTD-related ILD. HRCT patterns combined with basic clinical information, like the acuity of the presentation, are generally enough to separate the major types of interstitial pathology and to make the necessary treatment decisions.
- The prognosis of CTD-ILD is quite variable. Diffuse alveolar damage and diffuse alveolar hemorrhage may be rapidly fatal. Subacute forms of ILD like organizing pneumonia and cellular NSIP generally have a good prognosis and response to steroids. Most patients with CTD-ILD have chronic, fibrotic conditions (fibrotic NSIP or UIP), which can often be stabilized, and sometimes improved, with immunosuppressive therapy.
- Anti-inflammatory drugs constitute the backbone of present CTD-ILD therapy. Major developments in our understanding of the pathogenesis of pulmonary fibrosis and autoimmune disease over the last decade have, however, led to the identification of a number of potentially exciting biologic targets.
- Not all patients with CTD-ILD require treatment of their pulmonary condition.
- Patients with CTD-ILD are best managed in multidisciplinary clinics including both rheumatologists and pulmonologists.

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