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Management of Connective Tissue Diseases Associated Interstitial Lung Disease: A Review of the Published Literature

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Abstract

Purpose of review—Interstitial lung disease (ILD), though a common and often a severe manifestation of many connective tissue diseases (CTD), is challenging to manage due to its variable presentation and the relative lack of guidelines to assist the clinician. In this review, we discuss the approach to diagnosis, treatment, and monitoring patients with CTD-associated ILD, with a focus on systemic sclerosis (SSc), rheumatoid arthritis (RA), and idiopathic inflammatory myopathy (IIM).

Recent findings—High-resolution CT scan and pulmonary function testing can be reliably used to diagnose ILD and monitor progression, and often to determine its likely histologic subtype and severity. In SSc-ILD, randomized controlled trials show ILD stabilization with cyclophosphamide treatment; preliminary data from another randomized controlled trial demonstrates similar findings with mycophenolate. There are no robust clinical trials supporting specific treatments for RA-ILD or IIM-ILD, but rituximab in RA-ILD, and cyclophosphamide, mycophenolate and calcineurin inhibitors in IIM-ILD show promise.

Summary—Though ILD contributes substantially to morbidity and mortality in patients with CTD, there is minimal data to guide its management except in SSc-ILD.

Keywords

Connective tissue disease; Interstitial lung disease; Treatment

Introduction

Interstitial lung disease (ILD) is one of the most serious complications associated with connective tissue disease (CTD), resulting in significant morbidity and mortality. Rheumatologic diseases frequently complicated by ILD include systemic sclerosis (SSc), idiopathic inflammatory myopathy (IIM), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Sjögren's syndrome, mixed connective tissue disease (MCTD), and undifferentiated connective tissue disease (UCTD). ILD may also be the first manifestation

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of CTD; up to 15% of patients initially diagnosed with idiopathic NSIP have underlying CTD on further investigation(1). Prevalence, histologic/radiographic classification, and clinical manifestations vary between these conditions (Table 1)(2).

There are many subtypes of ILD, originally defined histologically. Common types include usual interstitial pneumonia (UIP), nonspecific interstitial pneumonia (NSIP), lymphocytic interstitial pneumonia (LIP), and organizing pneumonia (OP) (Figure 1). The most prevalent CTD-associated ILD is NSIP, followed by UIP. The UIP pattern is most commonly seen in RA, and typically portends a poorer prognosis, though still perhaps better than that of patients with idiopathic interstitial pneumonia (IIP) (3–5). The severity of ILD is graded based on clinical assessment, degree of restriction and impaired gas exchange seen on pulmonary function testing (PFT), and histologic and radiographic criteria(6). The pattern and distribution of radiographic abnormalities observed on high-resolution CT (HRCT) can accurately predict pathologic findings(7), and scoring systems for HRCT have been shown to amplify prognostic yield in some conditions, especially SSc(8, 9). Many CTDs are also associated with non-interstitial pulmonary manifestations, which are outside the scope of this review.

Survival in patients with CTD-ILD is higher than in patients with IIP(10, 11), attributed primarily to the higher prevalence of the favorable NSIP pattern(12, 13). Most disease-specific prognostic data available is from SSc-ILD, in which median survival has been reported as 5–8 years(14). In these patients, the presence of UIP, severity of restriction on PFT, and extent of fibrosis on HRCT seem to be the most important prognostic variables(8, 9). Few studies exist in others CTD, though there is evidence suggesting that patients with RA-ILD have worse survival than those with SSc-ILD, potentially due to the association of RA-ILD with UIP and the lack of routine screening for ILD in this population.

Management of CTD-ILD is challenging given the lack of robust data regarding the therapies used, the heterogeneity of diseases within this broad group, and the scarcity of well-defined outcome measures. Treatment decisions are often made clinically, based on functional impairment, physiologic or radiographic progression, and exacerbating or mitigating factors such as age and comorbidity burden. We here review how to approach the patient with CTD-ILD, with a focus on long-term treatment strategies.

Initial approach to the patient with CTD-ILD

The rheumatologist must maintain a high level of suspicion for ILD in patients with known CTD, as subclinical disease is common and even clinically apparent symptoms are often nonspecific, insidious, and easy to overlook or attribute to alternative causes. For instance, fatigue and dyspnea on exertion might easily be attributed to deconditioning, anemia, or non-rheumatologic cardiac or pulmonary comorbidities. Dyspnea may be masked by inactivity due to disease-associated pain or weakness. Cough could be attributed to medication side effects, smoking, or recurrent infections in an immunosuppressed patient. More overt manifestations, such as digital clubbing, hypoxemia, and pulmonary hypertension/right heart failure occur late in the disease course if at all, and are not useful for early disease screening. We believe any patient with known or suspected CTD and

complaints of dyspnea, cough with or without sputum, and rales on chest exam lasting more than a month, should undergo workup including HRCT and PFTs. In patients with known or suspected CTD and similar complaints lasting less than a month, chest x-ray should be considered, acknowledging that it is neither sensitive nor specific for diagnosing early ILD. There is not sufficient data to support HRCT/PFT in these patients.

Pulmonary function testing

ILD is characterized by PFT showing restrictive lung physiology and impaired diffusion capacity for carbon monoxide (DLCO), the latter frequently predating other testing abnormalities(6). Restrictive physiology is defined as decreased total lung capacity (TLC) compared to matched controls, typically with a flow volume loop which is normal in shape but decreased in magnitude on both X and Y axes relative to controls (Figure 2). TLC is difficult to measure as it requires body plethysmography, and forced vital capacity (FVC), obtained through routine spirometry, is often used as a surrogate measure. Reduction in FVC also determines the severity of restrictive physiology; FVC <80% of control is abnormal, and FVC <50% of control severely abnormal. A patient with purely restrictive physiology will also demonstrate a normal ratio of forced expiratory volume in 1 second (FEV1) to forced vital capacity (FVC), representing the maximum proportion of vital capacity a patient can exhale in the first second of expiration. PFT should not be used in isolation to diagnose ILD as they lack specificity(15).

Other clinical conditions coexisting with restrictive physiology can complicate PFT interpretation. For example, superimposed obstructive lung physiology, defined as FEV1/FVC ratio <0.7, causes pseudo normalization of lung volumes but severe reduction of DLCO. A disproportionate decrease in DLCO is also seen in patients with pulmonary hypertension.

HRCT

HRCT has become standard of care for initial evaluation of patients with suspected ILD, both to determine disease subtype (Table 2) and to assess disease severity. A confident radiologic diagnosis of UIP has a 90% correlation with surgical lung biopsy in the IIP population(16), though the correlation between NSIP pattern and biopsy findings is less robust. HRCT scoring systems used to assess the severity of ILD in specific CTD will be discussed below.

Other testing

Surgical lung biopsy is the gold standard for confirming ILD subtype. It is performed less frequently in CTD-ILD than in IIP patients, given their favorable prognosis and the frequent presence of other CTD manifestations justifying immunosuppression.

6-minute hallwalk is useful for determining functional capacity and degree of oxygen desaturation. However, it is confounded by non-pulmonary factors such as joint pain, weakness, and anemia. It is a useful adjuvant to tracking overall functional status and hypoxemia over time, but cannot replace HRCT or PFT for ILD diagnosis or determination of severity.

Treatment of CTD-ILD

Corticosteroids have commonly been used as an initial treatment option for CTD-ILD. While high-dose corticosteroid therapy can play a role in the treatment of some forms of CTD-ILD such as OP, there is little evidence to justify their use in more typical forms of CTD-ILD. The exception to this is acute, fulminant IIM-associated ILD, in which high-dose corticosteroid treatment has shown benefit. Steroids are not frequently used in SSc-ILD due to lack of proven efficacy and association with renal crisis in patients with early disease, and when used are generally limited to doses of 10mg daily or less(17). We will focus on data for steroid-sparing treatments.

SSc-ILD

SSc-ILD is among the best-researched subtypes of CTD-ILD, and currently one of the leading causes of death in SSc patients (18, 19). It is common in all SSc subtypes, though the presence of anti-topoisomerase I (SCL-70) antibodies and nucleolar pattern on ANA (representing anti-SCL-70, anti-PM-SCL, anti-Th/To and anti-U3NRP antibodies) predict lung involvement(19, 20). Early disease, though often asymptomatic, may be rapidly progressive, with plateau in severity not reached until 3–5 years after disease onset. Furthermore, pulmonary symptoms and functional status may not correlate well with pulmonary physiology(21) due to confounding conditions such as pulmonary hypertension, arthritis, deconditioning, anemia, superimposed infections, etc. Thus, we believe all patients with SSc should undergo antibody testing, HRCT and complete PFT at diagnosis, as well as baseline echocardiogram with Doppler to evaluate for pulmonary hypertension. Patients with a normal baseline evaluation should undergo spirometry with DLCO every 6–12 months for 3–5 years after disease onset, and yearly thereafter. Patients with ILD should have PFT every 3–4 months with treatment considered if these show meaningful progression of ILD, which has been defined as relative decline in FVC or TLC 10%, or relative decline in DLCO 15%, over 3–12 months(21). It is important to realize that an isolated or disproportionate decrease in DLCO can signal pulmonary hypertension in this population.

No data clearly suggest that routine HRCT monitoring is useful in this population, and HRCT should be performed only in situations where FVC or DLCO decline within measurement errors (as defined above) with concomitantly increasing pulmonary symptoms or other confounding factors.

The majority of SSc patients will have ILD manifestations, but not everyone needs treatment. Goh et al established that “extensive” ILD involving >20% of total lung volume on HRCT, with concomitant FVC of <70% used as a cutoff when HRCT is indeterminate, correlated with future mortality in SSc-ILD patients(8). A systematic review including >1,000 SSc-ILD patients also identified disease extent on HRCT as the only variable independently predicting both disease progression and mortality(9). The Scleroderma Lung Study I produced similar findings, and importantly suggested that patients with moderately severe disease on HRCT responded better to cyclophosphamide than did less affected patients(22, 23). DLCO is also a sensitive indicator of disease severity, correlating well with HRCT findings and often decreasing earlier than and out of proportion to FVC and TLC(19). A single-center study of 398 patients identified lower DLCO as an independent

risk factor for both mortality and ILD in SSc patients(19) and data from Scleroderma Lung Study I and II confirmed DLCO as an independent predictor of HRCT-defined severity of ILD(24). Serum IL-6 level >7.67 pg/mL was predictive of both physiologic deterioration and death in a cohort of 212 patients with either IIP or SSc-ILD. The effect was maintained in patients with FVC > 70% but not those with lower FVC(25). IL-6 level thus may help identify patients with early SSc-ILD in whom treatment is appropriate despite preserved physiology.

We recommend treatment in SSc patients with respiratory symptoms and recent disease onset (as the majority of ILD progression occurs 2–5 years after non-Raynaud's symptom onset), with low FVC% and/or DLCO or >20% lung involvement on HRCT(8), progressive lung volume restriction on serial PFT evaluations as discussed above, and/or the presence of other disease manifestations warranting immunosuppressive treatment(26). Based on current data, including data from the Scleroderma Lung Study II recently presented as an abstract(27), we recommend mycophenolate 3g/day as first-line treatment for most SSc-ILD, as it was found to be as efficacious as oral cyclophosphamide but better tolerated. Oral or IV cyclophosphamide for 6–12 months followed by either mycophenolate or azathioprine should be used as first-line treatment for severe or progressive disease, or disease unresponsive to mycophenolate(17, 22, 28). For refractory ILD, rituximab, a combination of cyclophosphamide and rituximab or autologous hematopoietic stem cell transplant could be considered(28–32). While on treatment, we recommend spirometry and DLCO evaluation every 3–6 months, with HRCT for changes in symptoms or lung function without a clear clinical etiology, or with a suspected etiology other than ILD progression.

The current treatment options for SSc-ILD, and the data supporting them, are ummarized in Supplemental Table 1.

RA-ILD

While articular RA has been extensively studied, there is little data on treatment of extra-articular manifestations of RA, especially RA-ILD. It is currently thought that RA-ILD is much more prevalent than previously believed, but mild and slowly progressive in the majority of cases(33). For this reason, and because information about guidelines for RA-ILD screening and predictors of progression is lacking, diagnosis and treatment are often delayed until late in disease course. This delay, combined with the higher frequency of UIP in the RA-ILD population(5, 33) and the lack of clinical trials demonstrating improved outcomes in patients with known disease, mean that RA-ILD is traditionally viewed as unresponsive to immunosuppressive treatment. In addition, existing studies do not differentiate RA-ILD patients with UIP from those with non-UIP (NSIP, OP, etc). This creates difficulty in determining whether those with non-UIP disease would respond more favorably to treatment.

Data on the effect of early aggressive articular RA treatment on the incidence and progression of RA-ILD are conflicting. Early treatment with DMARDs and prompt escalation to biologics as needed is thought to reduce the overall incidence of extra-articular RA manifestations. However, concern that commonly used RA treatments, both conventional DMARDs and newer biologics, may induce or exacerbate ILD, and that

immunosuppression-related pulmonary infections may hasten pulmonary decline, may make clinicians hesitate to escalate treatment in patients with known RA-ILD. There is no data at present to recommend antifibrotic agents such as pirfenidone and nintedanib for the treatment of RA-ILD (or other CTD-ILD), though upcoming studies will address this.

There are no universally accepted guidelines regarding RA-ILD screening or treatment initiation. A thorough history and physical examination combined with chest X-ray at RA diagnosis is a reasonable screen in patients with no pulmonary symptoms, although it may not detect early ILD due to its lack of sensitivity and the typically later onset of RA-ILD(33). Newly diagnosed RA patients with preexisting pulmonary conditions or symptoms should undergo workup, which may include HRCT and PFT, prior to initiating DMARD or biologic therapy. Current multinational recommendations advocate a chest x-ray within 1 year of methotrexate initiation as well(34). Patients with significant restriction or HRCT abnormalities should be managed concomitantly with pulmonology. RA patients developing new pulmonary symptoms while on RA treatment should undergo PFT and chest imaging, while simultaneously excluding infection. If ILD or other abnormalities are present, pulmonology referral is reasonable, and the potential offending immunosuppressive agent(s) should be held while workup is ongoing.

The current treatment options for RA-ILD, and the data supporting them, are summarized in Supplemental Table 2. A large number of drugs used to treat RA have been found to have direct interstitial pulmonary toxicity, or to possibly exacerbate preexisting ILD. A summary of these complications can also be found in Supplemental Table 2. Non-interstitial pulmonary complications of these medications are not addressed here.

There is not sufficient data at present to recommend specific RA-ILD treatment, or to advise against any commonly used joint-targeted treatment, in any RA-ILD patient. For RA-UIP, referral to lung transplant center should be initiated(35). If ILD is rapidly progressive, or worsens with traditional joint-targeted treatment, rituximab(36, 37) and cyclophosphamide are reasonable initial considerations, with mycophenolate a reasonable second-line or maintenance agent(38). While data suggesting significant clinical benefit in RA-ILD is lacking, these agents have limited or no reports of lung toxicity, and small cohort studies and case series suggest they may stabilize lung volumes.

Extrapolating from the SSc-ILD literature, spirometry and DLCO evaluation every 3–6 months during treatment, with HRCT for unexplained clinical or spirometric worsening, is reasonable.

Idiopathic Inflammatory Myositis-ILD

IIM-ILD is common and associated with substantially poorer prognosis than IIM overall(39). It occurs most frequently in patients with the antisynthetase syndrome, also characterized by arthritis, mechanic's hands, Raynaud's phenomenon, fever, and the presence of anti-aminoacyl-tRNA synthetase antibodies such as the common anti-Jo-1 (anti-histidyl-tRNA synthetase) and the rarer anti-PL-7 (anti-threonyl-), anti-PL-12 (anti-alanyl-), anti-KS (anti-asparaginyll-) and anti-OJ (anti-isoleucyl-) antibodies. ILD prevalence in these patients ranges from 67–100%, and can precede muscle symptoms or occur without clinical

myositis in 10–20% of patients(40). Other myositis-associated antibodies, such as anti-MDA-5, anti-PM-SCL, and anti-Ro-52 are also associated with a higher risk of ILD as well as typical clinical phenotypes. The association between clinically amyopathic dermatomyositis (CADM), anti-MDA-5 positivity, and acute and/or rapidly progressive ILD, which all portend high mortality and poor response to immunosuppression(41, 42) is one of the most prognostically significant, especially in patients of East Asian descent.

IIM-ILD ranges in severity from mild subclinical disease which does not progress, to a rapidly progressive acute interstitial pneumonitis with high short-term mortality. It is often present at diagnosis, but clinical course is variable(40, 41) and cannot be predicted from baseline evaluation. The most common patterns on HRCT are NSIP and COP, followed by UIP; diffuse alveolar damage is often present histologically in patients with acute, rapidly progressive disease(41). Most IIM-ILD responds well to immunosuppression, though acute fulminant pneumonitis is characteristically unresponsive regardless of HRCT pattern(39, 43). As in other CTD, IIM-UIP is less responsive than other forms of IIM-ILD, though still more responsive than is RA-UIP or IIP(44). There are no conclusive correlations between specific disease phenotypes/antibodies and HRCT pattern, disease severity or treatment responsiveness. Anti-synthetase antibodies have been associated with greater treatment responsiveness and risk of ILD recurrence(45), with PL-7 and PL-12 often denoting more severe ILD(42, 46). The association among CADM, anti-MDA-5 positivity, and acute, severe ILD is described above.

There are no generally accepted guidelines for ILD screening in IIM patients. It is important to remember that other disease-related factors (respiratory muscle weakness, aspiration and related infections, cardiac disease, iatrogenic lung injury, spontaneous pneumomediastinum, lung cancer, etc.) can cause abnormal lung physiology and HRCT findings, and might mimic ILD. Paraneoplastic lung disease must also remain a consideration given the association between IIM and occult malignancy. Studies to evaluate for these conditions may thus be helpful in distinguishing them from ILD. At baseline, all IIM patients with anti-synthetase syndrome or MDA-5 antibody positivity should have screening PFT and HRCT. For others, careful history is appropriate, with evaluation both for ILD and other causes of pulmonary disease (as above) if new pulmonary symptoms develop during treatment. Patients with known IIM-ILD should start treatment once the diagnosis is confirmed, as earlier disease is generally more responsive to therapy(47, 48) Follow-up PFT every 3–4 months if disease progresses, then every 6 months once stable, is reasonable

Current treatment options for IIM-ILD, and the data supporting them, are summarized in Supplemental Table 3. Treatment of IIM-ILD is generally recommended, as above. However, asymptomatic IIM-ILD patients on evidence-based background immunosuppression for IIM, such as methotrexate, azathioprine, the combination of the two, IVIG or rituxan, can reasonably be monitored without specific ILD-targeted treatment, as these are frequently effective in controlling disease progression. Corticosteroid therapy is standard of care in IIM patients, and all treatment regimens below should be considered adjuncts to rather than replacements for it. There are no controlled trials to support any steroid-sparing IIM-ILD treatment. Case series and small cohort studies support the use of azathioprine(49), mycophenolate(38, 49), or a calcineurin inhibitor(42, 50, 51) in patients

with mild to moderate ILD. Cyclophosphamide has been used with success in rapidly progressive or refractory disease(48), with transition to mycophenolate or a calcineurin inhibitor after 6–12 months. If disease progresses despite the above, or if non-ILD manifestations of IIM warrant their use, rituximab, IVIG, and “triple therapy” with corticosteroids, cyclophosphamide and a calcineurin inhibitor(37, 52, 53) have also shown success in small series.

Other CTD-ILD

There is limited data regarding treatment of ILD associated with SLE, Sjögren’s syndrome, MCTD and UCTD. Typically, pulmonary manifestations in SLE, MCTD, and UCTD occur in the context of other manifestations with more evidence-based treatment, and are treated concomitantly with these. However, case reports and case series suggest mycophenolate(38) and rituximab(37, 54–56) may be useful for SLE-associated ILD specifically. Similar reports show promise of azathioprine(57, 58), mycophenolate(38) rituximab(59, 60) and cyclophosphamide (58) in primary Sjögren’s-associated ILD.

Conclusion

ILD contributes significantly to morbidity and mortality in patients with CTD. Its presentation and prognosis are variable, though typical patterns exist for SSc-ILD, RA-ILD, and IIM-ILD. ILD can be reliably diagnosed and its severity and radiographic subtype determined. However, guidelines for treatment and monitoring are generally lacking, especially in non-SSc connective tissue disease, due to disease heterogeneity and the small number of affected patients. Clinical trials in SSc-ILD, and preliminary data in RA-ILD and IIM-ILD patients, have shown promise for several therapeutic agents which warrant further study.

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Key Points

- CTD-ILD contributes significantly to morbidity and mortality in patients with autoimmune disease.
- Outside of the systemic sclerosis literature, there is little data and few guidelines to assist the clinician in treating and monitoring CTD-ILD.
- Current treatment strategies are based on extrapolation from the scleroderma literature, preliminary data in RA-ILD and IIM-ILD, and accepted treatments for non-pulmonary CTD manifestations.

Figure 1. Characteristic HRCT appearance of a) UIP, b) NSIP, c) LIP, and d) OP

A: Usual interstitial pneumonia in a 58 year old woman with SSc. Note the characteristic lower lung predominant interlobular septal thickening with honeycombing (arrow) and traction bronchiectasis (horizontal arrowhead) in a heterogeneous distribution as well as the incidentally noted patulous esophagus (vertical arrowhead).

B: Nonspecific interstitial pneumonitis in a 62 year old woman with SSc, characterized by lower lung predominant homogeneously distributed ground glass abnormality, interlobular/intralobular septal thickening and traction bronchiectasis. Note the absence of honeycombing; all cystic spaces are bronchiectatic airways.

C: Lymphocytic interstitial pneumonitis in a 37 year old woman with Sjögren's syndrome, demonstrating diffuse ground glass abnormality, mild interlobular septal thickening and lower lung predominant thin walled cysts (arrow).

D: Organizing pneumonia in a 67 year old woman with amyopathic dermatomyositis, showing multifocal areas of subpleural and peribronchial foci of airspace consolidation (arrows).

Figure 2. Flow volume loops demonstrating a) normal physiology and b) restrictive physiology. Dots represent flow loop for a person with normal physiology.

Table 1

Prevalence and characteristics of ILD in various connective tissue disorders.

CTD type	ILD Prevalence	Characteristics
Systemic Sclerosis	<ul style="list-style-type: none"> 70–90%: consistent HRCT changes Up to 45%: moderate-to-severe ILD* 	<ul style="list-style-type: none"> NSIP ≫ UIP Usually develops in first 5 years of disease course, majority of cases diagnosed 2 years from non-pulmonary symptom onset Association with nucleolar pattern on ANA, anti-SCL70, anti-Th/T_o, anti-U3RNP, and anti-PM-SCL antibodies Consider PFT and HRCT in all patients at diagnosis
Idiopathic Interstitial Myopathy	<ul style="list-style-type: none"> 15–70% 	<ul style="list-style-type: none"> NSIP ≫ UIP Dermatomyositis > polymyositis More common with anti-synthetase antibodies Can occur in clinically amyopathic disease Poor prognosis in patients with acute disease and/or anti-MDA5 or Ro-52 antibodies. Prevalence estimates unclear due to lack of screening
Rheumatoid Arthritis	<ul style="list-style-type: none"> 4–68% 	<ul style="list-style-type: none"> UIP > NSIP > OP Usually seropositive with severe, longstanding joint disease Possible associations with smoking, male gender Prevalence estimates unclear due to lack of screening
Mixed Connective Tissue Disease	<ul style="list-style-type: none"> 20–85% 	<ul style="list-style-type: none"> NSIP ≫ UIP Usually associated with SSc-type clinical findings and antibodies Prevalence estimates unclear due to lack of screening
Sjogren's Syndrome	<ul style="list-style-type: none"> 10–30% 	<ul style="list-style-type: none"> NSIP most common; lymphocytic interstitial pneumonia, organizing pneumonia, UIP can occur Must also consider pulmonary lymphoma Prevalence estimates unclear due to lack of screening
Undifferentiated Connective Tissue Disease	<ul style="list-style-type: none"> Limited data 	<ul style="list-style-type: none"> NSIP ≫ UIP Often have other RA or SSc features Lung-dominant CTD: idiopathic ILD + autoantibody positivity with insufficient extrathoracic features to diagnose a specific CTD Prevalence estimates unclear due to lack of screening
Systemic Lupus Erythematosus	<ul style="list-style-type: none"> 2–10% with diffuse disease Up to 30% with focal occult interstitial abnormalities on HRCT 	<ul style="list-style-type: none"> Typically in patients with multiple end-organ manifestations NSIP ≫ LIP and OP ≫ UIP very uncommon Must be distinguished from alveolar hemorrhage (rare) and lupus pneumonitis (1–10%) Prevalence estimates unclear due to lack of screening

* defined by moderate-to-severe restriction on PFT or moderate-to-severe lung involvement on HRCT

ILD = interstitial lung disease, UIP = usual interstitial pneumonia; NSIP = nonspecific interstitial pneumonia, OP = organizing pneumonia, SSc = systemic sclerosis, RA = rheumatoid arthritis, CTD = connective tissue disease, HRCT = high resolution CT, LIP = lymphocytic interstitial pneumonia

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Table 2

Radiographic features of ILD subtypes common in CTD-ILD

	HRCT findings
NSIP	Bilateral, symmetric, basilar, peripheral ground-glass opacities Traction bronchiectasis Intra- and interlobular septal thickening and consolidation can be seen Subpleural sparing characteristic if seen
UIP	Bilateral, basilar, subpleural fibrosis with volume loss and architectural distortion Subpleural cysts ("honeycombing") Traction bronchiectasis/bronchiolectasis common
LIP	Perivascular thin-walled cysts Can have surrounding ground glass or centrilobular nodules Associated septal/bronchovascular thickening common
OP	Airspace consolidation, often bilateral, usually patchy but can be lobar. Alternatively, can be nodular Subpleural and/or peribronchovascular distribution Surrounding ground glass opacities Area of involvement can change over time