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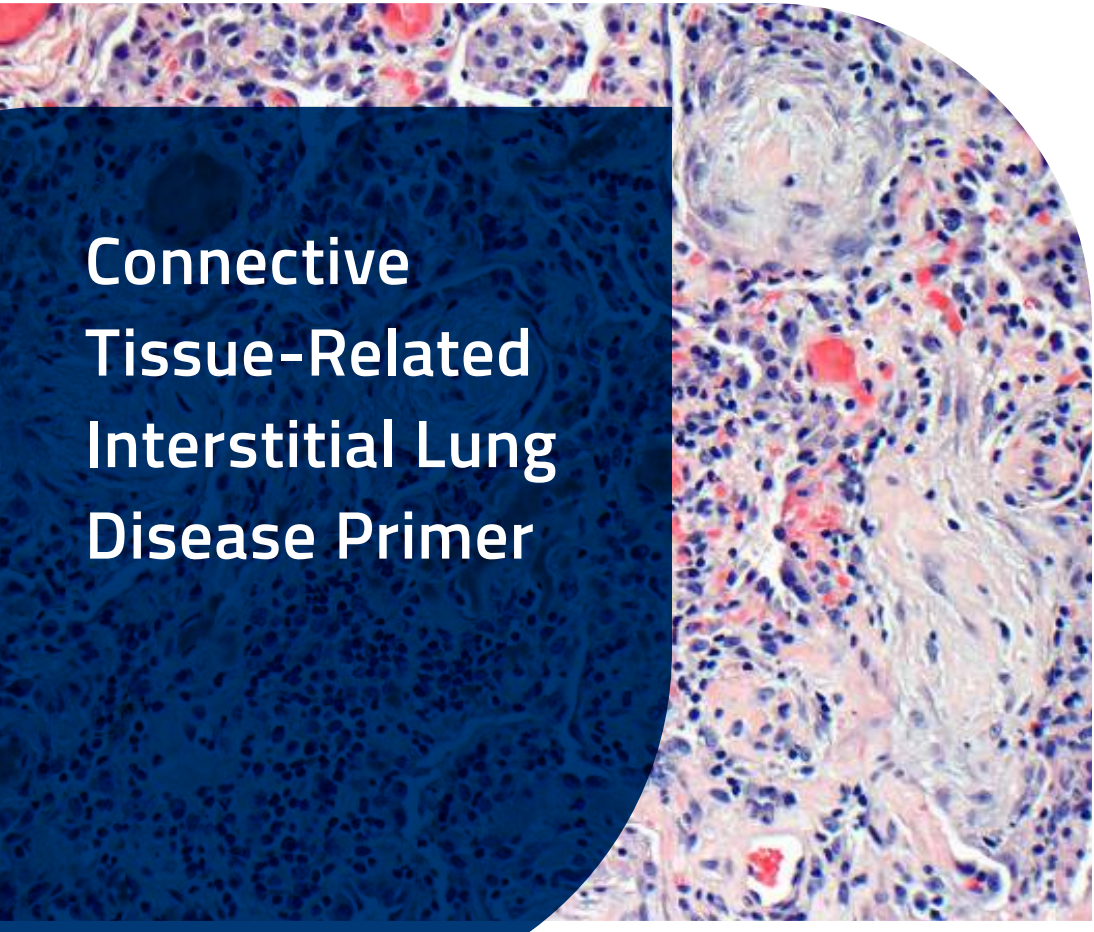

Connective Tissue-Related Interstitial Lung Disease Primer

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List of abbreviations and acronyms

ADM: Amyopathic dermatomyositis
AB: Antibody
ANA: Antinuclear antibody
ASS: Antisynthetase syndrome
CPK: Creatine phosphokinase
CT: Computed tomography
CTD: Connective tissue disease
CTD-ILD: Connective tissue disease-associated interstitial lung disease
CYC: Cyclophosphamide
DAD: Diffuse alveolar damage
dcSSc: Diffuse cutaneous systemic sclerosis
DLCO: Diffusion capacity of lung for carbon monoxide
DM: Dermatomyositis
FEV1: Forced expiratory volume in 1 second
FGF-R: Fibroblast growth factor receptor
FVC: Forced vital capacity
GERD: Gastroesophageal reflux
HRCT: High resolution computed tomography
IIMs: Idiopathic inflammatory myopathies
IV: Intravenous
ILD: Interstitial lung disease
IPAF: Interstitial pneumonia with autoimmune features
IPF: Idiopathic pulmonary fibrosis
lcSSc: Limited cutaneous systemic sclerosis
JDM: Juvenile dermatomyositis
MCTD: Mixed connective tissue disease
MDA5: Melanocyte differentiation-associated gene 5
MIP/MEP: Maximal inspiratory and expiratory pressures
MMF: Mycophenolate mofetil
MUC5B: Mucin 5B
NSIP: Non-specific interstitial pneumonia
OP: Organizing pneumonia
PDGF-R: Platelet-derived growth factor receptor
PFT: Pulmonary function test
PH: Pulmonary hypertension
PM: Polymyositis
RA: Rheumatoid arthritis
RF: Rheumatoid factor
RNA: Ribonucleic acid
RNP: Ribonuclear protein
RTX: Rituximab
RVSP: Right ventricular systolic pressure
SLE: Systemic lupus erythematosus
SS: Sjögren's syndrome
SSc: Systemic sclerosis
TGF-β: Transforming growth factor - beta
TNF: Tumor necrosis factor
UIP: Usual interstitial pneumonia
US: United States
VEGF-R: Vascular endothelial growth factor receptor

ILD in Established CTD

Introduction

- Interstitial lung disease (ILD) is a common manifestation of connective tissue diseases (CTDs).
- ILD can be seen in all CTDs but most commonly in rheumatoid arthritis (RA), systemic sclerosis (SSc), and idiopathic inflammatory myopathy (IIM).
- This primer will focus on the general features of CTD-ILDs along with distinct features noted in RA, SSc, and IIM-associated ILD.

Definition

- CTD-ILD is defined as evidence of ILD demonstrated by CT (i.e., some combination of reticulation, ground-glass opacities, traction bronchiectasis, honeycombing, and/or cysts) in the setting of an established CTD.
- Other causes of parenchymal lung disease in CTD need to be ruled out:
  - Infection
  - Drug-induced lung disease
  - Malignancy
  - Idiopathic and other interstitial lung diseases

Background

- Though all CTDs have the risk of ILD, it is more common in RA, SSc and IIM. (Table 1)

Table 1: Features of the most common connective tissue disease-associated interstitial lung diseases

	RA-ILD	SSc-ILD	IIM-ILD
Common HRCT and pathologic pattern	UIP	NSIP	NSIP with OP
Pathologic findings	UIP pattern with lymphoid aggregates and germinal centers	Bland pauci-cellular fibrosis uniformly throughout interstitium, with preservation of alveolar architecture	Typical NSIP
Risk factors	Smoking High-titer CCP Male sex	Anti-topoisomerase ab Black race Higher skin score	Anti-Jo1 Anti-PL-7 Anti-PL-12 Black race
Prevalence	19-67%	Up to 90%	Up to 75%
Outcome	5-year survival 36% in UIP and 94% in NSIP	5-year survival 85%	5-year survival 60 to 80%

Rheumatoid arthritis

- RA is a systemic inflammatory disease with small joint inflammation predominantly involving the wrists, hands, and feet.
- All organ systems can be involved.
- Some risk factors for RA include genetics, family history, middle age, female sex, lower socioeconomic status and smoking.
- It is the most common CTD, seen in 0.5-1% of the United States (US) population, with a global prevalence of 0.24% (or 18 million people).
- RA is among the top 50 contributors to global disability and leads to an estimated $19.3 billion in annual healthcare expense in the US with a mean total 5-year cost of $173,000 per patient.
- ILD is one of the many extra-articular manifestations in RA and a leading cause of death and disability.
- ILD in RA has risk factors in common with RA (i.e. smoking) and distinct risk factors (e.g. male sex).

Systemic sclerosis

- SSc is a heterogeneous autoimmune disease characterized by immune dysregulation, vasculopathy, and progressive fibrosis with multi-organ involvement. The most common organ systems involved include the skin, lungs, gastrointestinal tract, and musculoskeletal system.
- Patients with SSc are classified as having limited cutaneous SSc (lcSSc) or diffuse cutaneous SSc (dcSSc) based on the extent of skin involvement.
- Patients with lcSSc develop skin involvement of the face and skin distal to the elbows and knees, and dcSSc patients have more extensive skin involvement including the trunk and extremities.
- ILD is the leading cause of death in SSc. Patients with SSc-ILD have a varied progression with some patients having a slow indolent course and others developing a rapid progression of symptoms.

Idiopathic inflammatory myopathies

- The IIMs encompass a group of autoimmune disorders characterized by a combination of muscle weakness, rash, and autoantibodies (designated myositis-specific antibodies, Table 2). ILD is often a common finding and can occur prior to or after diagnosis.
- Inflammation is central to the three main forms of myositis that are associated with ILD.
  - > Dermatomyositis (DM) has a characteristic rash and muscle weakness, with pathogenesis felt to be humorally mediated. An entity called amyopathic dermatomyositis (ADM) is found in a subset of DM patients and characterized by cutaneous manifestations of classic DM with no clinical evidence of muscle weakness or muscle enzyme abnormalities. (1)
  - > Polymyositis (PM) is characterized by muscle weakness without the rash that is noted in DM, and pathogenesis is thought to be cell-mediated.
  - > Antisynthetase syndrome (ASS) is characterized by antibodies directed against aminoacyl-tRNA synthetase along with clinical features that include ILD, myositis, Raynaud's phenomenon, fevers, mechanic's hands, and arthritis.

Other CTDs

- ILD also occurs in patients with other CTDs including Sjögren's syndrome, systemic lupus erythematosus, and mixed connective tissue disease.
  - > Sjögren's syndrome is characterized by the development of sicca symptoms including xerostomia and keratoconjunctivitis sicca, circulating antibodies to Ro (SS-A) and La (SS-B), lymphocytic infiltration, and damage to exocrine glands. There is a panel of antibodies being developed (against the parotid secretory protein, carbonic anhydrase 6, and salivary protein-1) to diagnose early SS when there is a high degree of suspicion and negative conventional markers. Subclinical pulmonary involvement is seen in up to 75% of patients and includes both airway disease and ILD.

- SLE is a chronic autoimmune disease that can affect virtually any organ. Patients can present with mild clinical features ranging from arthralgias and skin involvement to more severe renal, cardiac, hematologic, or central nervous system involvement. Pulmonary manifestations include pleuritis, ILD, pulmonary hypertension, and alveolar hemorrhage. ILD is less common in SLE than other CTDs.
- MCTD is an overlap syndrome associated with anti-U1 RNP antibodies that incorporates various clinical features of SLE, SSc and IIM. ILD occurs in about 50 to 66 % of patients with MCTD. Risk factors for the development of ILD in MCTD include Raynaud's phenomena and symptoms of dysphagia, and arthritis.

Table 2: Myositis specific autoantibodies and clinical features of disease

Autoantibody	Target antigen	Clinical features
Jo-1, PL-7, PL-12, EJ, OJ, KS, YRS (HA), Zo	Aminoacyl-tRNA synthetase	Anti-synthetase syndrome with high incidence of ILD
SRP	Signal recognition particle	Neuromuscular weakness, cardiac involvement, refractory to treatment
Mi-2	Helicase protein	Mild disease, typical skin lesions and mild myositis, responsive to treatment
TIF1-γ (anti p155/140)	TIF gamma/alpha	Cancer associated myositis (CAM)
SAE	Small ubiquitin like modifier 1 activating enzyme	Dermatomyositis features
MDA5 (CADM -140)	Melanoma differentiation-associated gene 5	Rapidly progressive ILD with severe skin manifestations in Japanese population, less severe disease in Caucasian population
NXP-2	Transcriptional regulation and activation of p53	Predominantly Juvenile dermatomyositis, severe muscle disease, calcinosis, and skin disease
HMGCR	3-hyroxy-3-methylglutaryl-coenzyme A reductase	Associated with statin use in adults, necrotizing myopathy

Incidence/prevalence of ILD in CTD

- **RA: Lung involvement (i.e. parenchymal, pleural, and airway) is seen in 60 to 80% of patients, though a significant number of these cases are either subclinical (no associated symptoms) or not clinically significant (not contributing to death or disability) (2).**
  - ILD prevalence in unselected subjects ranges from 19 to 67% depending on the modality of diagnosis. The 3-year cumulative incidence is 6.8% and the lifetime risk is 7.7%.
  - Lung involvement may pre-date the joint disease in up to 20% of subjects.
  - Though the incidence appears stable, the prevalence and death from ILD among decedents with RA are on the rise.
- **SSc: The overall incidence globally ranges from 8 to 56 new cases per million persons per year, and the prevalence rates are between 38 and 341 cases per million persons.**
  - ILD is generally thought to be more prevalent in patients with diffuse SSc than with limited SSc though both subsets can develop ILD.
- **IIMs: The incidence is 1-19 cases per million persons per year, and prevalence is approximately 1 per 100,000. The prevalence of ILD in this population varies based on criteria (HRCT vs. physiologic screening) and ranges from 9-78%. In 10-30% of patients, ILD can be the first manifestation and precede the diagnosis of autoimmune disease by several years (3).**

Risk factors for CTD-ILD

- **Potential risk factors differ depending on the underlying CTD.**
  - RA
    - Though there are several reported risk factors for RA-ILD, there is strong support for advanced age, smoking, male sex, and RA disease score (2).
    - There is weaker support for anti-cyclic citrullinated protein levels, methotrexate use, anti-tumor necrosis factor (TNF) agents, and genetics.
    - The strongest genetic risk factor for idiopathic pulmonary fibrosis (IPF), a gain-of-function variant in the promotor region of a gene encoding mucin 5b (MUC5B), was found in up to 32% of patients with RA-ILD (4).
  - SSc
    - Both patients with limited or diffuse SSc can develop ILD.
    - The auto-antibody profile is important in predicting SSc-ILD.
    - Scl-70 is a marker associated with increased risk for ILD compared to centromere antibody pattern (5).
    - Patients with a nucleolar pattern antinuclear antibody (ANA) are also at higher risk for ILD.
    - The nucleolar pattern ANAs are often anti-Th/To and U3-ribonuclear protein (RNP) antibodies and these have been associated with severe ILD (6).
    - Other risk factors include a higher modified Rodnan skin score, Black race, elevated creatine phosphokinase (CPK) levels, and cardiac involvement.
  - IIMs
    - There is growing evidence of genetic associations in the development of ILD in patients with IIMs. For example, there is a strong association with HLA-DRB1*03:01 and HLA-B*08:01.
    - IIMs are at least twice as common in females than males.
    - The risk of ILD is noted to be higher in patients of Black race.
    - Patients of East Asian race are noted to have a higher risk of rapidly progressive ILD unresponsive to treatment and are often found to have the MDA-5 autoantibody (3).

Clinical presentation of CTDs

- **All of the CTDs have defined diagnostic criteria proposed and updated by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR).**
- **Clinical findings in RA**
  - The typical presentation of RA is a gradual onset of polyarticular synovitis manifested by pain, stiffness (usually in the morning), and swelling.
  - Rarely patients can have an acute onset with monoarticular symptoms, intermittent symptoms, or migratory symptoms.
  - Systemic symptoms (fevers, weight loss, myalgias, fatigue) are seen in less than half of patients.
- **Clinical findings in SSc**
  - SSc is traditionally classified based on the extent of skin involvement into limited and diffuse forms of the disease.
  - Skin involvement is for the most part a universal feature of the disease. Early symptoms including edema, puffy hands, or pruritis.
    - Only a small percentage of patients with SSc have no skin involvement, termed SSc sine scleroderma.
  - Raynaud's phenomenon is present in a majority of patients with SSc and typically precedes the disease onset by years. Nailfold capillaroscopy can help evaluate patients for SSc (capillary changes include dilated and giant capillaries, hemorrhages, disorganized vascular arrays, ramified/bushy capillaries, and capillary dropout).
  - Patients often have significant fatigue and also discomfort from skin involvement, Raynaud's, and digital ulcers.

- **Clinical findings in IIM**
  - Loss of strength is often noted in the upper or lower proximal limbs, shoulder girdle, and anterior neck muscles. Sometimes, posterior pharyngeal muscles are involved. Symptoms include difficulty running, getting up from a seated position, climbing stairs, chewing, swallowing, and dysphonia.
  - Skin findings can include a violaceous rash over the eyes, face, chest, shoulders, and thighs. Extensor surface papules most often noted over the metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints are termed Gottron's papules and are unique to the myositis family. Mechanic's hands, which appear as dry cracking or fissuring skin along the sides of the fingers are considered pathognomonic for IIMs.
  - ADM can present with a rash typical for DM with no objective weakness.
- **ILD should be on the differential diagnosis list for any suspected or confirmed CTD patient with any of the following signs and symptoms:**
  - Unexplained breathlessness
  - Dry persistent cough
  - Crackles on exam
  - Hypoxemia at rest or with activity
  - Unexplained reduction in exercise capacity
  - Restriction on screening pulmonary function tests (PFTs) and/or unexplained decrease in diffusing capacity for carbon monoxide (DLCO)

Evaluation of CTD

- **Lab studies**
  - Autoantibodies include ANA, as well as disease specific antibodies.
    - RA: rheumatoid factor (RF) and anti-cyclic citrullinated peptides (anti-CCP antibodies)
    - SSc: Scl-70, centromere and RNA polymerase antibodies
    - IIM: myositis-specific (Table 2) and myositis-associated antibodies. Certain antibodies such as Jo-1, PL-7, and PL-12 are strongly associated with the development of ILD (8). Anti MDA-5 antibody may be found in amyopathic dermatomyositis patients and strongly correlates with the development of rapidly progressive ILD (9).
    - Sjogren's syndrome: SS-A and SS-B antibodies. Antibodies to parotid secretory protein, carbonic anhydrase 6, and salivary protein-1 in early disease.
    - MCTD: RNP
- **Echocardiogram**
  - Elevated right ventricular systolic pressure (RVSP) indicative of pulmonary hypertension (PH) may be noted, but right heart catheterization is required for a definitive diagnosis.
  - Cardiomyopathy or relaxation abnormalities may be noted.
  - Screening ECHO should be considered in all patients with CTD-ILD.
- **Esophagram**
  - An esophagram may reveal abnormal peristalsis, dysmotility, and gastroesophageal reflux (GERD).
- **Skin & muscle biopsy**
  - Is useful in the diagnosis of IIMs if clinical and serologic findings are lacking.

Diagnosis and workup of ILD

- **A multidisciplinary team discussion is important in reconciling clinical, lab, and imaging data, as well as providing a means to coordinate the views of pulmonologists and rheumatologists in formulating diagnostic and treatment strategies (7).**

- **Pulmonary function tests (PFTs)**
  - PFTs may be normal in early disease.
  - A restrictive pattern with reduced forced vital capacity (FVC) and normal or high forced expiratory volume in 1 second (FEV1)/FVC is often seen.
  - DLCO may be reduced due to pulmonary vascular disease.
  - Airflow obstruction suggested by a FEV1/FVC of < 0.70 can be seen with airway involvement, most common in RA and Sjögren's syndrome.
  - Decreased maximal inspiratory and expiratory pressures (MIP/MEPs) may be noted in patients with IIM and respiratory muscle involvement.
- **High-resolution computed tomography (HRCT)**
  - The most common HRCT patterns in patients with CTD-ILD are non-specific interstitial pneumonia (NSIP) (Figure 1) and usual interstitial pneumonia (UIP) (Figure 2), with the isolated organizing pneumonia (OP) pattern seen less frequently.
    - In RA only, the most common radiographic pattern seen is UIP, with NSIP seen less commonly and OP pattern is seen rarely.
    - The most common pattern seen in SSc is NSIP. UIP is seen in up to 40% of cases of SSc.
    - ILD associated with IIMs is often characterized by an overlapping pattern of NSIP and OP (Figure 3).
  - Three radiographic findings have been identified that suggest an ILD secondary to CTD (10):
    - Anterior upper lobe sign, which is the concentration of fibrosis in the anterior upper lobes with relative sparing of the rest of the upper lobe. The positive likelihood ratio of CTD-ILD in patients with this finding is 1.99.
    - Exuberant honeycombing, which is extensive honeycombing comprising greater than 70% of the fibrotic areas of the lungs. The positive likelihood ratio of CTD-ILD with this finding is 3.69.
    - Straight edge sign, which is the isolation of fibrosis to the lung bases without extension along the lateral margins of the lung. The positive likelihood ratio of CTD-ILD is 4.22.

Figure 1: NSIP in RA

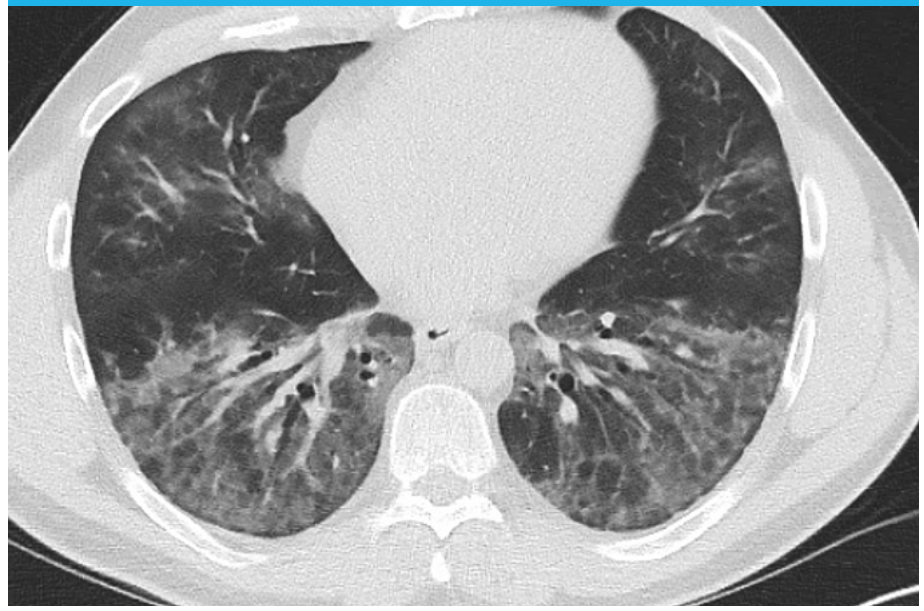


Figure 2: UIP in RA

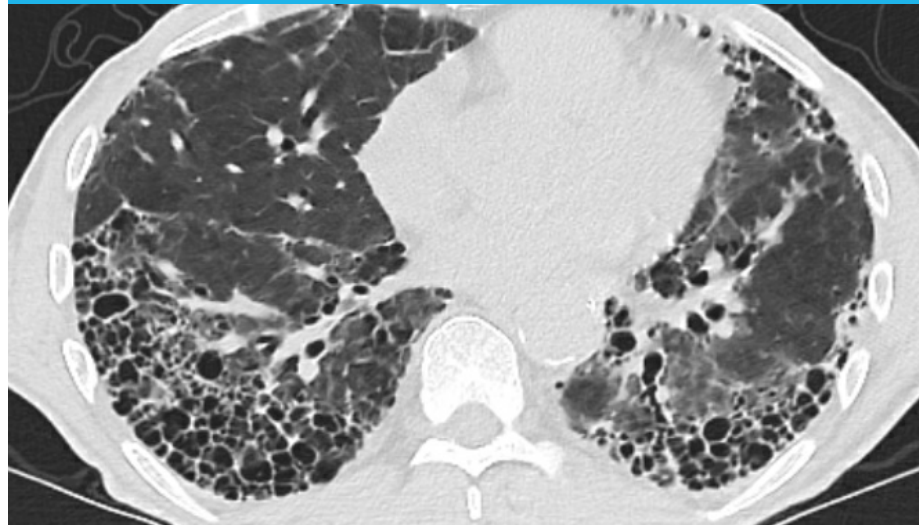


Figure 3: OP with a background of NSIP

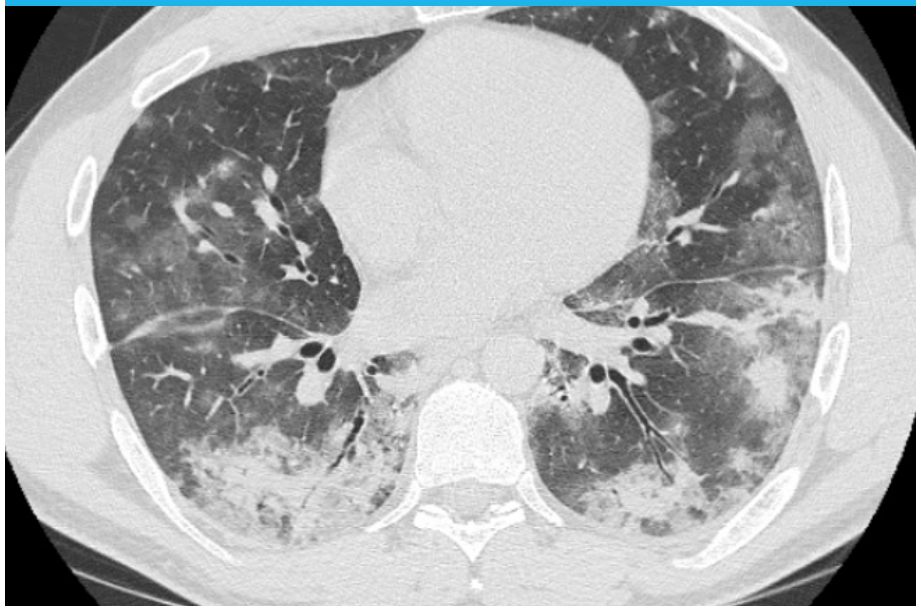
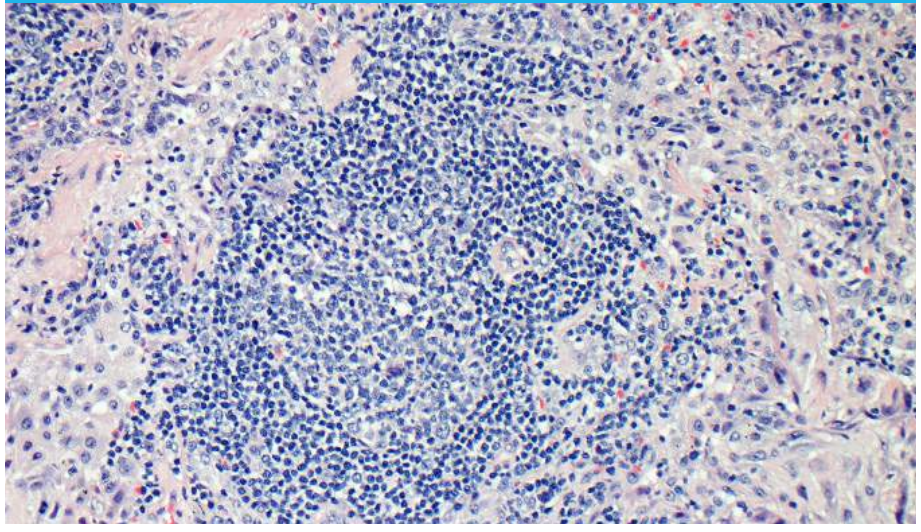
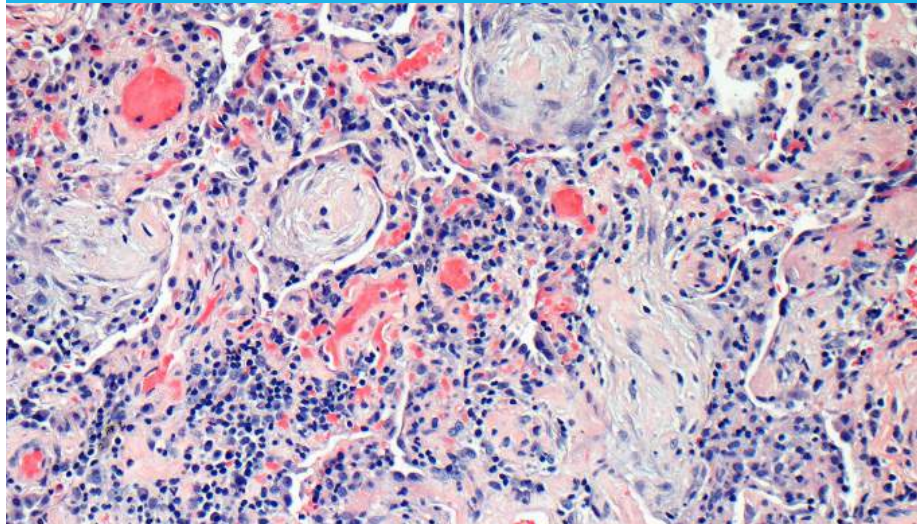


Figure 4: Lymphoid follicle on surgical lung biopsy from a patient with CTD-ILD



- **Lung pathology**
  - NSIP - This is characterized by temporally and geographically homogeneous infiltration of the interstitium by inflammatory cells with varying degrees of fibrosis. Patients may have more inflammation ("cellular NSIP"), more fibrosis ("fibrotic NSIP"), or a combination of both ("mixed NSIP").
  - UIP - In comparison to the UIP pattern seen in IPF, UIP in CTD has more lymphoid aggregates and germinal centers with fewer fibroblast foci (Figure 4) (11).
  - OP – This is defined by the presence of inflammatory cells, fibroblasts, and connective tissue in the alveoli and distal airspaces. It is often found in conjunction with NSIP in patients with ILD associated with IIMs (Figure 5).
  - Diffuse alveolar damage (DAD) – This is the predominant finding in acute exacerbations of ILD and is associated with a poor prognosis. It is characterized by an acute phase with edema and hyaline membrane formation, and an organizing phase with alveolar septal fibrosis and type II pneumocyte hyperplasia.

Figure 5: OP with background of NSIP on surgical lung biopsy from a patient with DM



- **All patients with lung disease should have indices of oxygenation checked at rest, with activity, and overnight.**
- **As CTDs are systemic diseases, other systems can be involved that can affect respiratory symptoms or PFTs and should be investigated.**
  - PH, most commonly seen in the lcSSc variant of SSc, can cause dyspnea, hypoxemia, decreased exercise tolerance, and a reduction in DLCO out of proportion to reduction in lung volume.
  - Muscle weakness, most commonly associated with the myositis-spectrum of disease, can lead to dyspnea, reduced exercise tolerance, and a reduction in lung volumes out or proportion to the degree of ILD. Muscle weakness can be evaluated with MIP/MEP and looking at the maximal voluntary ventilation.
  - Cardiac involvement, in the form of obstructive coronary disease or direct pericardial or myocardial involvement, can be seen in many of the CTDs and can lead to dyspnea out of proportion to the degree of lung disease.

Monitoring for disease progression

- **During the initial evaluation of patients with CTD-ILD, short term PFTs (within 3 months) and HRCT (within 6 months) should be considered to clarify the rate of progression.**
- **For the first 1 to 2 years of mild CTD-ILD disease, PFT's should be done every 6 months in these patients.**
- **More frequent PFTs, every 3-6 months should be done for more moderate-severe ILD at baseline or progressive disease.**
- **Non-contrast HRCT is often performed yearly during the first 3 years of diagnosis to identify patients who may have progressive disease.**
- **An echocardiogram is often used every 1-2 years to assess RVSP and assess cardiac function.**

Treatment

- **All treatment decisions should be made in close collaboration with a rheumatologist.**
- **As there are medications that can treat both ILD and CTD, an effort should be made to find one medication that is effective for both diseases.**
- **In general, medication therapy involves either immunosuppressive and/or anti-fibrotic therapy and depends on the subtype of ILD (i.e. the more inflammatory NSIP and OP or the more fibrotic UIP).**
- **An important concept to remember is that control of the CTD does not correlate to control of the lung disease and the ILD needs to be followed regardless of the activity level of the CTD.**
- **Outside of SSc-ILD, treatment of CTD-ILD is severely hindered by a lack of randomized controlled trials.**
- **Nintedanib, a tyrosine kinase inhibitor shown effective in IPF, has been approved, based on the results of the INBUILD Trial, for all patients with progressive fibrosing ILD, defined as a fibrosing ILD (including CTD-ILD) with one of the following criteria in the prior 24 months (12):**
  - A relative decline in the FVC of 10% of the predicted value or
  - A relative decline in FVC of 5 to <10% and either worsening in respiratory symptoms or increase in the extent of fibrosis on HRCT or
  - Worsening in respiratory symptoms and increase in the extent of fibrosis on HRCT
- **RA-ILD**
  - Treatment regimens are limited to case reports and case series without a dedicated phase 3 trial.
  - The only Food and Drug Administration-approved therapy is nintedanib which is approved for progressive fibrotic ILD regardless of etiology.
  - There are limited reports of successful treatment with methotrexate, azathioprine, cyclosporine, mycophenolate, TNF-alpha inhibitors, and rituximab.

- **SSc-ILD**
  - Traditional immunosuppressive therapy, mycophenolate mofetil (MMF) or cyclophosphamide (CYC) have been used as initial treatment for SSc-ILD. (Table 3)
  - MMF has become the treatment of choice given its superior side effect profile over CYC. Mycophenolic acid is considered equal to MMF in clinical practice.
  - Azathioprine is an option, but has fallen out of favor for the treatment of SSc-ILD given mixed results.
  - The use of systemic steroids in the treatment of SSc-ILD is debated.
    - Data on the use of high dose steroids in SSc-ILD is limited.
    - Steroids need to be weighed with the risk of renal crisis as this is typically associated with doses of prednisone > 15mg daily.
  - Nintedanib, an oral tyrosine kinase inhibitor was recently approved for the treatment of SSc-ILD based on the results of the SENSCIS Trial (13).
    - Annual rate of decline in FVC was lower in nintedanib treated patients by 44% compared to placebo.
    - The secondary endpoint of change in modified Rodnan skin score was not met.
    - The most common adverse event was diarrhea.
  - Tocilizumab is an anti-IL-6 inhibitor that has been recently approved for the treatment of SSc-ILD.

- **IIM-ILDs**
  - There are no large randomized controlled trials of treatment in myositis-associated ILD, but a multitude of immunosuppressants in conjunction with steroids have been successfully used (Table 3)

Table 3: Proposed therapies for CTD-ILD

Medication	Dose	Mechanism of action	Disease	References
Steroids	Acute disease: Solu Medrol 500-1000 mg/day IV X 3 days Subacute disease: prednisone 1mg/kg/day up to 60mg	Inhibits circulating leukocytes and synthesis of pro-inflammatory cytokines	RA, IIMs, SS *not advisable in pts with SSc given risk of renal crisis, consider ACE/ARB inhibitors and use Pred < 15/daily	
Mycophenolate mofetil	2000-3000mg/daily given in divided doses twice daily	Reduces T and B cell proliferation by inactivation of inosine monophosphate dehydrogenase	RA, SSc, IIMs, SS	(18) Case series
Mycophenolic acid	720 to 1080mg bd			
Azathioprine	2-3 mg/kg/daily	Purine analog that reduces T and B cell proliferation	RA, SSc, IIMs	Case series
Tacrolimus	1-3 mg/daily	Calcineurin inhibitor, inhibitor of T cell proliferation and activation	IIMs	Case series
Cyclophosphamide	IV monthly: 750mg/m2 body mass index X 6 months OR oral: 1.5 – 2.5 mg/kg/day	Alkylating agent that targets T cells	RA, SSc, IIMs	(18), (19) Case series
Rituximab	1000mg IV 0, 2 weeks then q6 months	Monoclonal antibody against CD20	RA, SSc, IIMs	Case series
Nintedanib	150 mg PO twice daily	Tyrosine kinase inhibitor of FGF-R, PDGF-R and VEGF-R	RA, SSc, IIMs	SENSCIS (13) INBUILD (12)

Adjunctive therapies

- **Oxygen therapy**
  - Oxygen should be prescribed based on resting, exercise, and nocturnal saturations to ensure that the patient maintains oxygen saturations >88%.
- **GERD treatment**
  - Esophageal dysfunction leading to reflux and aspiration may exacerbate SSc-ILD.
  - Typically, all patients with SSc-ILD are treated with high doses of proton pump inhibitors.
- **Pulmonary rehabilitation**
  - Pulmonary rehabilitation can improve exercise performance, symptoms, and quality of life.
- **Vaccines**
  - Influenza and pneumococcal vaccines should be provided to reduce the risk of infections.
  - Consider inactivated herpes zoster vaccine in patients initiating prolonged immunosuppression.
- **Supportive/palliative care**
  - Consider as part of patient care throughout the course of the disease, not only as the patient nears the end of their life.
- **Lung transplant**
  - Transplant should be considered in all patients with disease that progresses despite of therapy.
  - In general, outcomes with transplant in CTD-ILD are similar to outcomes with other ILDs.
  - Certain features of the CTD can affect a patient's likelihood of qualifying for a transplant.
  - Historically, lung transplantation in SSc has been difficult given esophageal dysmotility and risk for recurrent aspiration. However, studies evaluating outcomes after lung transplant in SSc-ILD show a similar 1- and 5-year survival rates compared to other ILDs.

Prognosis

- **In general, the prognosis of CTD-ILD is more favorable than that of IPF, the most common of the ILDs (14).**
- **Prognosis is influenced by factors such as ILD subtype, age, and type of CTD.**
- **RA**
  - The presence of ILD increases mortality by 2 to 10-fold and patients with RA-ILD have a median survival of 6.6 to 7.8 years and a 35% to 40% 5-year mortality.
  - Older studies found that RA with UIP had survival rates similar to that of IPF (median survival of 3.2 to 5.5 years) though more recent studies have found a better survival in this subtype (7.9 to 10.4 years).
  - Predictors of mortality include subtype of ILD on HRCT (with UIP portending a worse outcome), older age, male sex, lower DLCO, and the presence of fibrosis on pathology.
  - Changes over time in physiology predict outcome, with a 10% decline in FVC at any point in follow-up leading to a more than doubling in a patient's mortality (15).
  - Progression is common - 50% with early asymptomatic ILD and 60% with UIP progress over 1.5 years.
  - Acute exacerbations are more common in RA-ILD compared to the other CTD-ILDs (3 to 11% yearly) and are a significant contributor to death in RA-ILD.

- **SSc**
  - The presence of ILD in a patient with SSc predicts increased mortality.
  - Older age, lower FVC, and extent of ILD on HRCT are associated with increased mortality.
  - An algorithm to assess the extent of fibrosis on HRCT to characterize patients as extensive or limited lung involvement has been proposed (16).
    - Patients with >20% involvement on HRCT or lesser degrees of fibrosis with a decline in FVC<70% are characterized as extensive disease and have worse survival.
- **IIMs**
  - Prognostic factors in myositis-associated ILD include the type of autoantibody (Table 2), radiographic pattern of ILD, and in some cases, race. There is also a 5 to 7-fold increase in the risk of malignancy associated with a diagnosis of DM, and less so with PM. Age and sex appropriate cancer screening is recommended, and more comprehensive testing can be pursued if suspicion of malignancy remains high.
  - Patients with NSIP and/or OP generally have a good response to treatment.
  - Those with Jo-1 and Ro-52 positivity tend to have more severe ILD compared to those with Jo-1 positivity alone.
  - Patients with rapidly progressive disease or those with a 10% decline in FVC or DLCO during a 6 month follow up despite treatment should be referred to a lung transplant center for evaluation.

Interstitial pneumonia with autoimmune features (IPAF)

- **A sizable portion of ILD patients present with clinical, serologic and radiographic features suggesting CTD-ILD but do not meet established diagnostic criteria for CTD-ILD.**
- **IPAF is an American Thoracic Society / European Respiratory Society proposed research term for patients that fall into this category.**
- **The term allows for standardization of diagnosis so that these patients can be further studied.**
- **NSIP and UIP are the most common radiographic patterns.**
- **Treatment decisions are based on clinical evaluation as there are no randomized clinical trials of treatment in this population (17).**

Summary & conclusions

- **ILD is a significant cause of morbidity and mortality in patients with CTDs.**
- **The management of patients with CTD-ILDs should be individualized and involve close collaboration between rheumatologists and pulmonologists.**
- **Immunosuppression is the mainstay of therapy for CTD-ILDs with a prominent inflammatory component, while the anti-fibrotics play a role in progressive fibrotic ILD.**

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