Autoimmune Disease-Associated Interstitial Lung Disease (ILD)

SC-US-69223

Boehringer Ingelheim

Objectives

- Review the spectrum of autoimmune connective tissue disorders (CTDs) that can be associated with interstitial lung disease (ILD), as well as epidemiology and risk factors for autoimmune disease-associated ILD
- Describe the underlying pathogenesis in autoimmune disease-associated ILD, which is driven by inflammation or fibrosis
- Discuss best practices for diagnosing autoimmune disease-associated ILD, including the evaluation of radiological and histopathological features

Autoimmune Disease-Associated ILD Is a Combination of 2 Disease Subsets

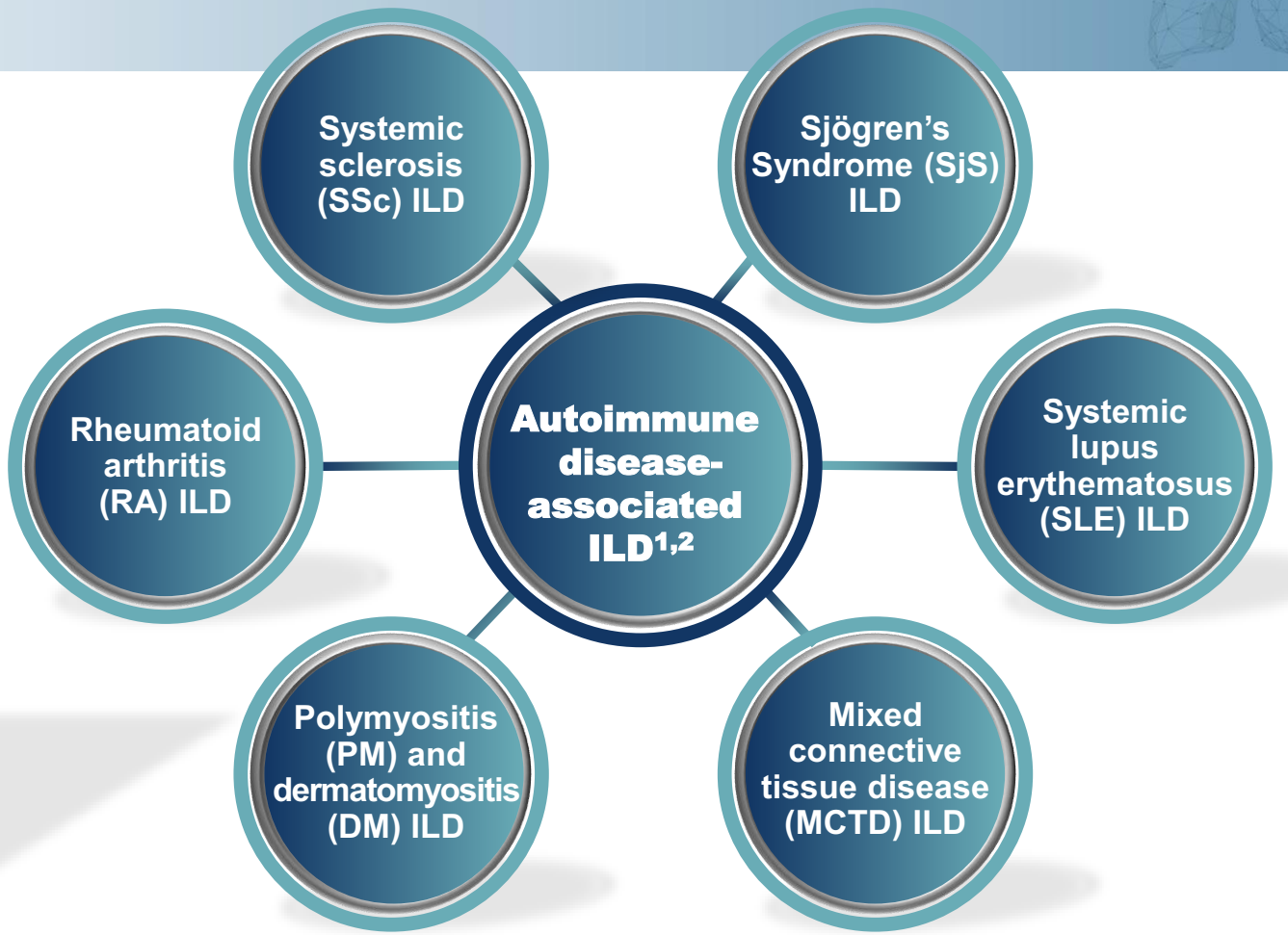
CTD's

Spectrum of systemic autoimmune disorders, characterized by immune-mediated organ dysfunction that can affect the lungs, resulting in inflammation and fibrosis.[1]

ILDs

Group of diffuse parenchymal lung diseases[1]

- Common manifestation in CTD
- ILD may develop at any point in the natural history of CTD and it is among the leading causes of morbidity and mortality in these patients



All patients with CTD are at risk of developing an associated ILD.[1]

1. Fischer A et al. *Arthritis Rheumatol.* 2019;71(2):182-195. 2. Oliveira RP et al. *Pulmonology;* 2020:S2531-0437(20)30004-0.

ILD Is Prevalent in a Significant Number of Patients With CTDs

ILD is present in ~40% of patients with CTDs, contributing to increased morbidity and mortality.[1]

Autoimmune disease-associated ILDs are the second most common diagnosis in tertiary ILD referral centers.[2]

The prevalence of autoimmune disease-associated ILD greatly varies across different CTD subgroups.[3]

CTD subgroup[3]	Estimated prevalence of ILD[3]
PM, DM, antisynthetase syndrome	**40%**
SjS	**40%**
SSc	**30%-40%** clinical, **80%** subclinical
RA	**10%** clinical, **30%** subclinical
SLE	**8%-12%**

1. Mira-Avendano I et al. *Mayo Clin Proc*. 2019;94(2):309-325. 2. Cottin V et al. *Eur Respir Rev*. 2018;27(150):180076. 3. Fischer A et al. *Arthritis Rheumatol*. 2019;71(2):182-195.

Risk Factors for Autoimmune Disease-Associated ILD

The risk of autoimmune disease-associated ILD is **higher in women** and in patients who are <50 years of age.[1]

Women are **4 times** more likely to **develop SSc than men.[1]**

- However, **male sex is a key risk factor** for developing **fibrosis**, particularly in patients with SSc and/or RA.[2,3]

Risk factors for patients with **RA-associated ILD** include[3]:

- Older age
- Cigarette smoking
- Male sex
- Rheumatoid factor positivity
- ACPA positivity
- More severe articular disease

Lung disease may precede the development of joint disease **in up to 20% of patients with RA-ILD**.[4]

In patients with **SSc and PM/DM, select autoantibodies** are the most reliable predictor of ILD.[3]

SSc[5]

Anti–Scl-70 (also known as anti-topoisomerase I) is associated with development of ILD in >85% of patients.

Titers of this antibody correlate with disease severity and activity of ILD.

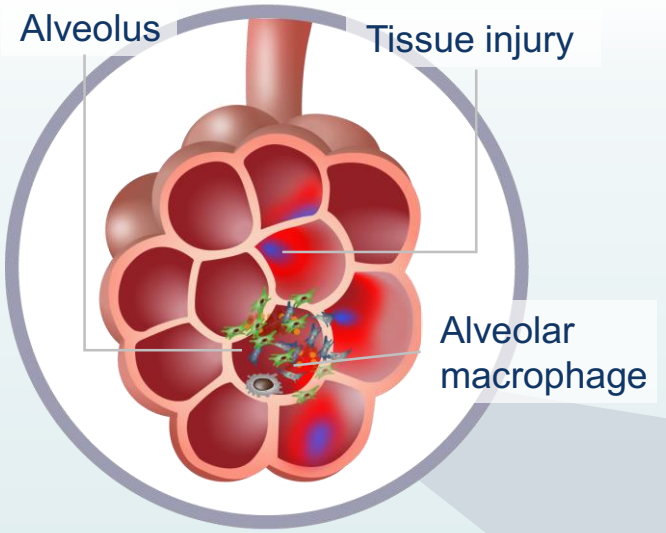
PM/DM[3]

Anti-PM-Scl, anti-MDA-5 antibody; antisynthetase antibodies (eg, Jo-1, PL-7, PL-12).

ACPA, anticitrullinated protein antibody; Anti-MDA-5, Anti-melanoma differentiation-associated protein 5.

1. Cottin V et al. *Eur Respir Rev*. 2018;27(150):180076. 2. Volkmann ER. *J Scleroderma Relat Disord.* 2020;5(2 suppl):31-40. 3. Fischer A et al. *Arthritis Rheumatol*. 2019;71(2):182-195.
4. Mira-Avendano I et al. *Mayo Clin Proc*. 2019;94(2):309-325. 5. Mathai SC, Danoff SK. *BMJ*. 2016;352:h6819.

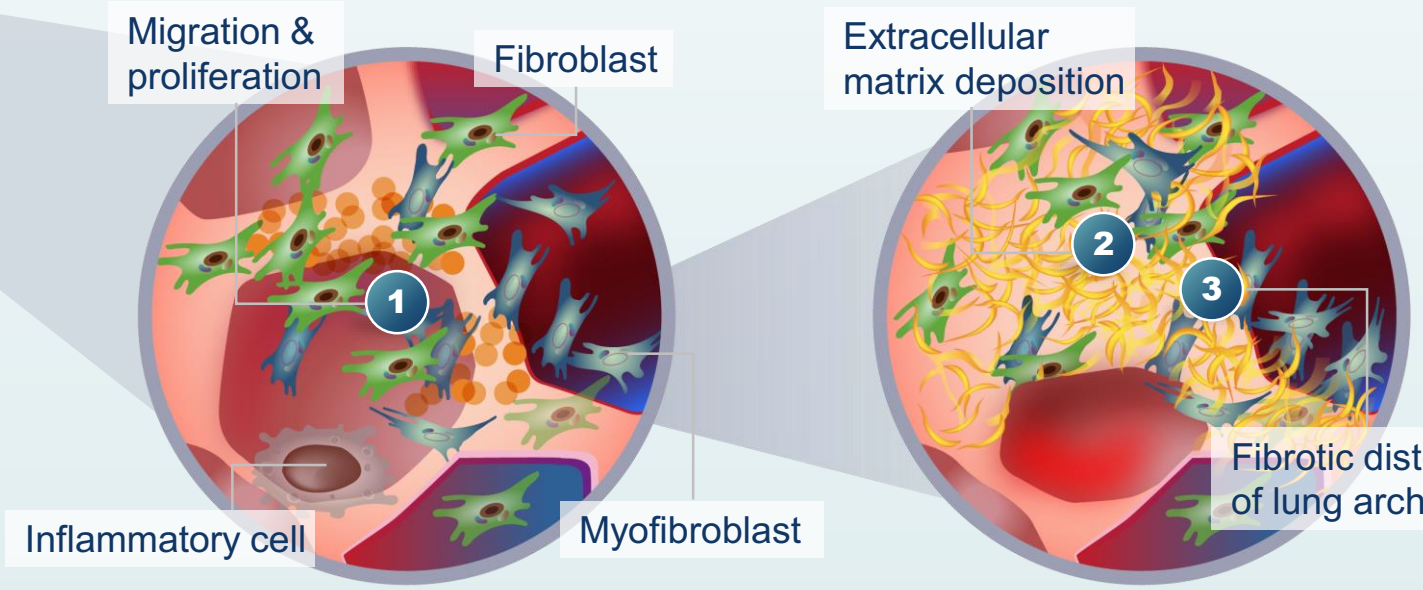
The Underlying Pathogenesis of Autoimmune Disease-Associated ILD Is Driven by Inflammation or Fibrosis, or a Combination of Both



1. Development of ILD-associated pulmonary fibrosis is thought to be mediated through the migration and proliferation of fibroblasts and their differentiation into myofibroblasts.[1]

2. As fibroblasts and myofibroblasts invade the pulmonary tissue, they continually synthesize and release collagen and extracellular matrix protein.[2]

3. Excessive extracellular matrix protein remodeling leads to irreversible distortion of lung architecture, compromising pulmonary capacity, function, and gas exchange.[2,3]



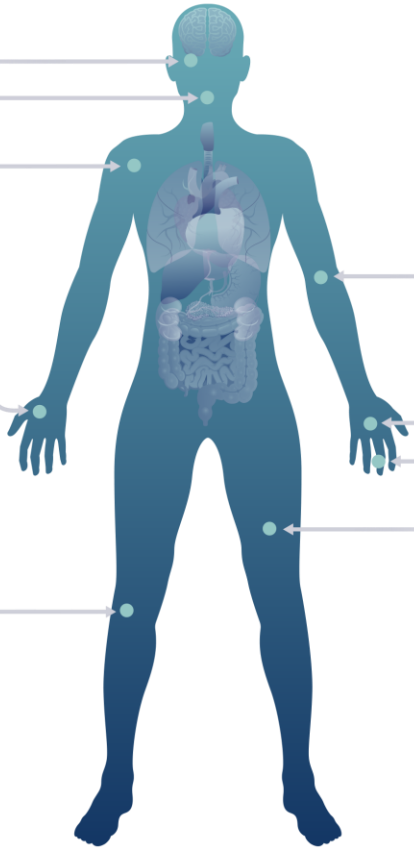
1. Bagnato G, Harari S. *Eur Respir Rev.* 2015;24(135):102-114. 2. Cottin V et al. *Eur Respir Rev.* 2018;27:180076 3. Selman M et al. *Ann Intern Med*. 2001;134(2):136-151.

Clinical Presentation of Autoimmune Disease-Associated ILD

Symptoms may present in varying degrees[1]:

- Some patients with CTD have **obvious symptoms** of lung disease at the time of ILD diagnosis
- Others have **"subclinical" disease** (ie, radiologic findings suggestive of ILD in the absence of symptoms)
- Some have **no evidence of lung disease** at the time of the CTD diagnosis, but are at risk of developing ILD

There are various clinical manifestations associated with CTDs, including ILD[2,a]



Mouth and eyes
- Dry mouth and dry eyes (sicca syndrome)

Skin
- Sclerodactyly
- Digital ulcerations or scars
- Telangiectasia
- Gottron's sign
- Heliotrope rash of the eyelids
- Rash of the neck and upper chest and shoulders (heliotrope rash, eg, photosensitivity)
- Mechanic's hand

Peripheral circulation
- Raynaud's phenomenon

Joints
- Joint pain or swelling (arthritis, arthralgia)
- Morning stiffness

Muscle
- Muscle pain and muscle weakness

[a]Although not an exhaustive list, focusing on these manifestations would be most efficient for pulmonologists.

1. Fischer A et al. *Arthritis Rheumatol*. 2019;71(2):182-195.. 2. Cottin V. *Eur Respir Rev*. 2013;22(129):273-280.

Disease Progression and Mortality in Autoimmune Disease-Associated ILD

The ability to predict progression of ILD in CTD is challenging[1,2]

- Some patients develop ILD that is **mild and nonprogressive**[1]
- Others have a **more progressive course** with a persistent decline in function, as seen in IPF[1]
- **RA-ILD and SSc-ILD** are among the autoimmune disease-associated ILDs associated with a **progressive, fibrosing** phenotype[2]

ILD is a leading cause of death in SSc and an important cause of death in RA[3]

- The risk of **death for individuals with RA-ILD** is approximately **3-fold higher** than that for patients with RA without ILD[4]
- **Median survival** after the diagnosis of RA-ILD is **~2.6 years**[4]
- **RA-ILD** accounts for **10% to 20%** of all **RA-related mortality**[4]
- Disease severity is most notable in predominantly **fibrotic ILD (eg, UIP),** with **mortality rates comparable to those of IPF**[1]

IPF, idiopathic pulmonary fibrosis; UIP, usual interstitial pneumonia.

1. Fischer A et al. *Arthritis Rheumatol*. 2019;71(2):182-195. 2. Cottin V et al. *Eur Respir Rev*. 2018;27(150):180076. 3. Oliveira RP et al. *Pulmonology*; 2020:S2531-0437(20)30004-0.
4. Mira-Avendano I et al. *Mayo Clin Proc*. 2019;94(2):309-325.

Best Practices for Diagnosing Autoimmune Disease-Associated ILD

Due to the similar radiologic, physiologic, and histopathologic characteristics that autoimmune disease-associated ILDs share with IIPs and other ILDs, **close collaboration between rheumatology, pulmonology, radiology, and pathology** is essential in arriving at the correct diagnosis and optimizing treatment.[1]

Clinicians must probe for extrapulmonary symptoms and for factors to point toward CTD, since symptoms can be nonspecific[1]

HRCT and PFTs are instrumental in the diagnosis of autoimmune disease-associated ILD[1]

- Respiratory examination will likely be unimpressionable
- ILD is associated with significant morbidity and mortality in patients with CTD

An underlying CTD is more likely in patients who present with an HRCT pattern of NSIP[2]

ILD may also be the first manifestation of CTD

- Underlying CTD can be found in up to 15% of patients initially diagnosed with idiopathic NSIP[3]

HRCT, high-resolution computed tomography; IIP, idiopathic interstitial pneumonia; NSIP, nonspecific interstitial pneumonia; PFTs, pulmonary function tests.

1. Mira-Avendano I et al. *Mayo Clin Proc.* 2019;94(2):309-325. 2. Cottin V. *Eur Respir Rev*. 2013;22:273-280. 3. Wallace B et al. *Curr Opin Rheumatol*. 2016;28(3):236-245.

Characteristic Histopathologic and Radiologic Findings Can Distinguish Between the Different CTDs

The underlying pathology in autoimmune disease-associated ILD is driven by inflammation, fibrosis, or a combination of both, and is characterized by distinct radiologic and histopathologic patterns.

CTD subgroup	Characteristic histopathologic pattern	Characteristic radiographic findings
RA	UIP	Reticular changes and honeycombing
	NSIP	Ground-glass opacities with basilar prominence
SSc	NSIP	Increased reticular markings, ground-glass opacification, basilar prominence
	UIP	Peripheral and bibasilar reticulonodular opacities with honeycombing
PM/DM	NSIP	As above
	UIP	As above
	COP	Patchy airspace consolidation, ground-glass opacities
	DAD	Diffuse ground-glass opacities
SjS	NSIP	As above
	LIP	Thin-walled cysts, ground-glass opacities, centrilobular nodules
SLE	AIP	Ground-glass opacities
MCTD	NSIP	Septal thickening and ground-glass opacities

AIP, acute interstitial pneumonia; COP, cryptogenic organizing pneumonia; DAD, diffuse alveolar damage; LIP, lymphocytic interstitial pneumonia.

Castelino FV, Varga J. *Arthritis Res Ther*. 2010;12(4):213.

Various Thoracic Imaging Abnormalities May Be Encountered in Patients With CTDs[1,2]

CTD	Relative Frequencies of Computed Tomography Imaging Patterns Among CTDs[1]								
	UIP	NSIP	OP	LIP	DAD	Hemorrhage	Airway[a]	Nodules[b]	Serositis[c]
RA	+++	++	++	+	+	–	+++	+++	+++
SSc	+	+++	+	–	+	–	–	–	–
PM/DM	+	+++	+++	–	++	–	–	–	–
SjS	+	++	–	++	+	–	+	+	–
SLE	+	++	+	++	++	+++	–	–	+++
MCTD	+	++	+	–	–	–	–	–	+

– = absence of finding + = lowest +++ = highest

- **Autoimmune disease-associated ILDs most commonly present as NSIP** on HRCT assessments[2]
- Autoimmune disease-associated ILD **may also present with a pattern of UIP**, which is why it is important to **differentiate it from IPF**[2]

[a]Bronchiectasis, bronchial wall thickening, small centrilobular nodules (that may reflect follicular bronchiolitis), and constrictive bronchiolitis. [b]Typically ≥1 cm (not centrilobular). [c]Pleural or pericardial fluid or thickening.

OP, organizing pneumonia.

1. Mira-Avendano I et al. *Mayo Clin Proc*. 2019;94(2):309-325. 2. Cottin V et al. *Eur Respir Rev*. 2018;27:180076.

Radiographic Patterns of ILD Common in Autoimmune Diseases

HRCT is essential in the initial evaluation of any suspected ILD to detect disease pattern and extent.[1,2]

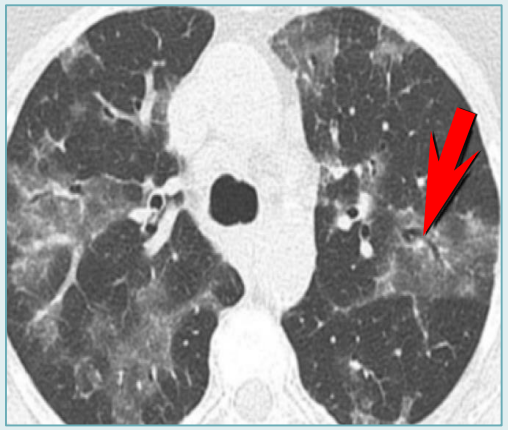
	HRCT Findings[2]
NSIP	• Bilateral, symmetric, basilar, peripheral ground-glass opacities • Traction bronchiectasis • Intra- and interlobular septal thickening and consolidation can be seen • Subpleural sparing characteristic if seen
UIP	• Bilateral, basilar, subpleural fibrosis, with volume loss and 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

1. Mira-Avendano I et al. *Mayo Clin Proc*. 2019;94(2):309-325. 2. Wallace B et al. *Curr Opin Rheumatol*. 2016;28(3):236-245.

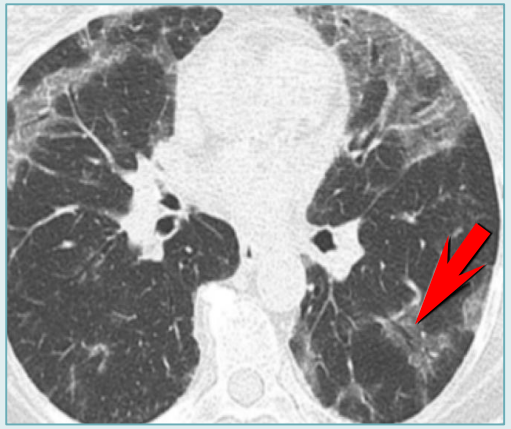
Certain Imaging Patterns Can Indicate a CTD-Associated Etiology

Mixed NSIP-OP pattern:

When a basal-predominant fibrotic abnormality shows a superimposed OP pattern, CTD should be suspected. [a]

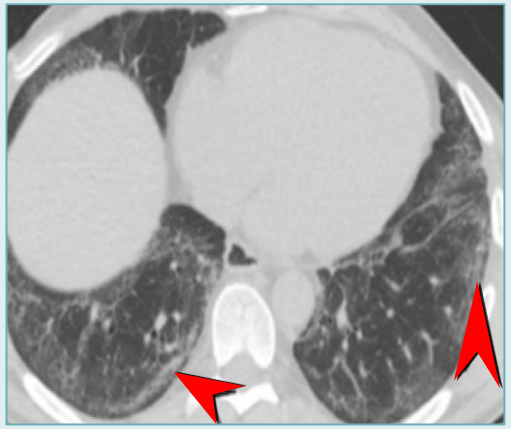


Upper Lung



Middle Lung

Axial image through the upper and middle lungs shows patchy areas of ground-glass opacity with a **peribronchiolar distribution** (**arrows**), suggesting the presence of **OP.**



Lower Lobes

Peripheral ground-glass opacity and reticulation, with **subpleural sparing (arrows),** more suggestive of **NSIP.**

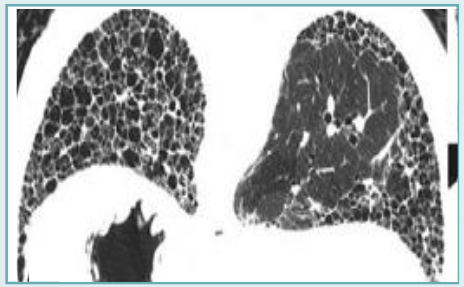
[a]The patient was subsequently diagnosed as having PM/DM.

Mira-Avendano I et al. *Mayo Clin Proc*. 2019;94(2):309-325.

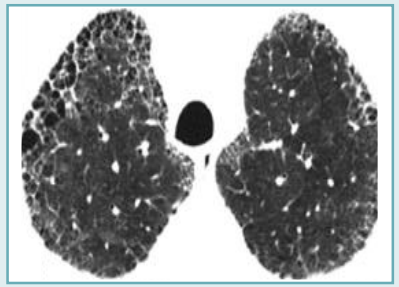
Certain Imaging Patterns Can Indicate a CTD-Associated Etiology (cont'd)

Factors favoring CTD-UIP over IPF-UIP

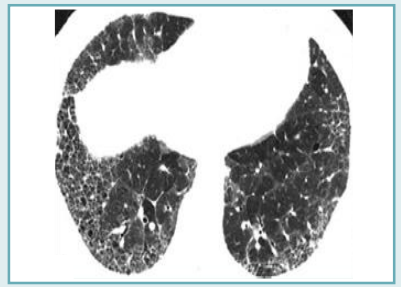
- **Exuberant honeycombing sign** (extensive honeycomb cyst formation; >70% of fibrotic-appearing lung)
- **Anterior upper lobe sign** (reticulation and honeycombing in the anterior upper lobes)
- **Straight-edge sign** (fairly straight interface between fibrotic and normal lung)



Prone image shows extensive basal fibrosis characterized by extensive honeycombing, consistent with the exuberant honeycombing sign.

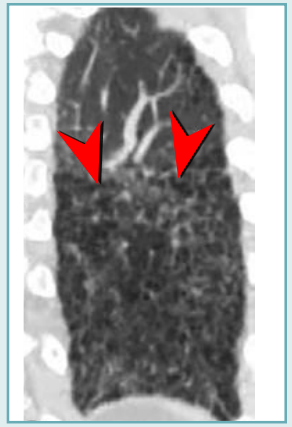


Upper Lobe



Lower Lobe

Substantial upper lobe subpleural reticulation and honeycombing, concentrated anteriorly, as pronounced as the basal fibrotic findings, consistent with the anterior upper lobe sign.



Coronal Image of the Left Lung

Basal-predominant honeycomb lung and fibrotic changes, with an abrupt transition from the extensively involved basal lung, forming a fairly straight interface between the region of extensive fibrosis inferiorly and the less involved lung superiorly **(arrowheads),** consistent with the straight-edge sign.

Mira-Avendano I et al. *Mayo Clin Proc*. 2019;94(2):309-325.

Histologic Features Associated With Underlying CTD

- ☑ Prominent lymphoid aggregates with germinal center formation
- ☑ Increased lymphocytic inflammation with plasma cell infiltrates
- ☑ Overlapping features of peripheral honeycombing with central fibrosis
- ☑ Involvement of multiple pulmonary compartments (interstitial disease with additional small airway, vascular, or pleural disease)
- ☑ NSIP pattern with additional OP

Microscopic examination of surgical lung biopsy specimens from patients with CTDs often yields **histologic clues** indicating that the **etiology is of an autoimmune nature,** as opposed to being idiopathic or associated with another disease.

Some of these **histologic features** (eg, fibrosis) have been shown to be **related to prognosis.**

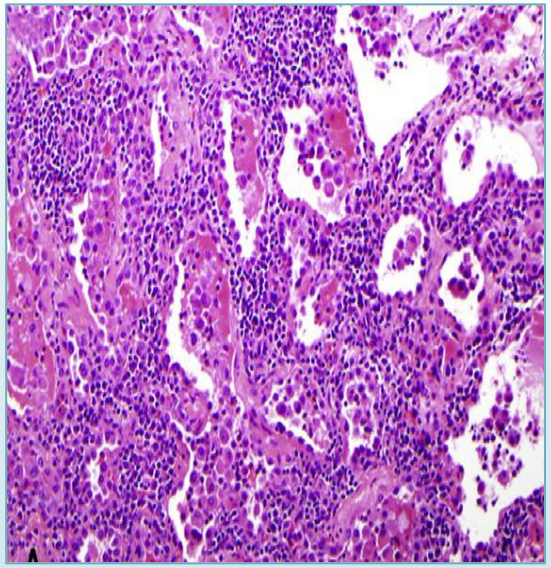
Fischer A et al. *Arthritis Rheumatol*. 2019;71(2):182-195.

Histopathologic Features Suggestive of Autoimmune Disease-Associated ILD

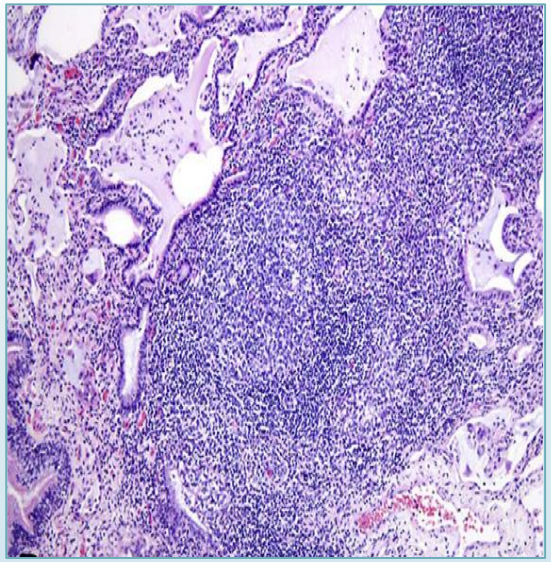
- **The histologic differences between CTD-UIP and IPF-UIP** have not been clearly defined, but select histologic criteria that help differentiate between these conditions include:

Fibroblastic foci	Lymphoid aggregates	The presence of an NSIP pattern

- **CTD-UIP** has been shown to have fewer and smaller fibroblast foci than IPF-UIP
  - Of patients with CTD-UIP, those with **RA-UIP** may have more and larger lymphoid aggregates than patients with IPF-UIP
- **Coexistence of UIP and NSIP** patterns can be key in distinguishing CTD-UIP from IPF-UIP



Heavy lymphoplasmacytic infiltrates in the alveolar interstitial septa, diagnostic for LIP



Lymphoid follicle with prominent germinal center is seen in a background of interstitial fibrosis in a patient with RA

Mira-Avendano I et al. *Mayo Clin Proc*. 2019;94(2):309-325.

PFTs Are Instrumental in Monitoring for Progression of ILD

ILDs are typically characterized by a **restrictive ventilatory defect,** which includes:

- Reduced total lung capacity
- Normal FEV_1/FVC ratio
- Reduced DL_{CO}

Spirometry may be normal in patients with mild disease or mixed obstructive restrictive disease, such as coexisting emphysema.

For serial monitoring, FVC and DLCO are most commonly used, along with oximetry.

Oximetry: Used to monitor oxygen saturation, assess the need for supplemental oxygen, and as an indicator of lung function impairment.

DL_{CO}, diffusing capacity of the lung for carbon monoxide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.

Mira-Avendano I et al. *Mayo Clin Proc*. 2019;94(2):309-325.

Future Directions and Unmet Needs of Autoimmune Disease-Associated ILD

The ACR helped support a **multidisciplinary panel of international specialists** in pulmonology, rheumatology, thoracic radiology, and lung pathology specialties (with interests and expertise in ILD) for a **summit on autoimmune disease-associated ILD.**

These experts identified **key areas of interest and unmet needs** yet to be addressed **in autoimmune disease-associated ILD.**

Deliver international guidelines that standardize clinical, radiologic, histopathologic, and biologic parameters for the diagnosis and classification of autoimmune disease-associated ILD

Define the natural history of autoimmune disease-associated ILDs

Develop and utilize early screening and detection strategies for ILD

Generate ILD imaging repositories across the spectrum of CTD-associated ILD that correlate with histopathologic specimens

Refine cryobiopsy techniques to enrich the availability of parenchymal lung tissue specimens

Create new, and optimize existing, quality-of-life measures in autoimmune disease-associated ILD

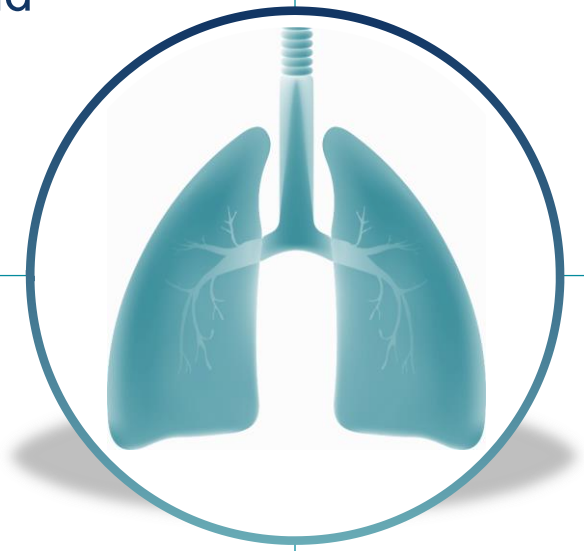
ACR, American College of Rheumatology.

Fischer A et al. *Arthritis Rheumatol*. 2019;71(2):182-195.

Summary

Autoimmune disease-associated ILD is a combination of systemic autoimmune disorder and an interstitial lung disease that can result in progressive fibrosis.

The underlying pathogenesis of autoimmune disease-associated ILD is driven by inflammation or fibrosis, or a combination of both.



HRCT is essential in the initial evaluation of any suspected ILD to identify radiologic pattern and disease extent.

- **NSIP** is the most common ILD pattern seen on HRCT

Unmet needs have been identified that will improve future diagnosis and risk assessment of autoimmune disease-associated ILD.