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Interstitial Lung Disease for the Rheumatologist: Pearls and Insights

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Introduction

Interstitial lung disease (ILD) is a potentially life-threatening complication of systemic autoimmune rheumatic diseases (SARDs). Its prevalence varies according to the underlying SARD, being highest in anti-synthetase and anti-melanoma-differentiation-associated protein 5 (MDA5) syndromes, but affecting the greatest number of individuals in rheumatoid arthritis due to its higher overall frequency. Because ILD onset may precede, coincide with, or follow SARD diagnosis, rheumatologists may uncover an undiagnosed SARD during ILD evaluation or, conversely, detect ILD through screening of patients with established SARD. The spectrum of SARD-ILD is broad: some patients have mild, stable disease, others experience slowly progressive disease, and some deteriorate rapidly despite treatment, leading to oxygen dependence, lung transplantation, or death. Drug therapies, including immunosuppressive and anti-fibrotic agents, can slow the progression of SARD-ILD.

This article addresses three key clinical questions pertinent to rheumatologists. First, we explore clinical, serological, and morphological features that can aid in diagnosing SARD in patients with ILD, offering practical pearls. Second, we examine screening—covering who to screen, when, how, and at what frequency. Finally, we outline our approach to SARD-ILD management.

1. Reason for Consultation: ILD - Rule Out SARD

Approximately one third of ILD patients have an underlying SARD, making prompt recognition important for guiding management and follow-up.[1] Even subtle extrapulmonary clinical features may provide important diagnostic clues. The challenge is greatest when ILD presents as the first—or even sole—manifestation of SARD. Screening with autoantibody panels is helpful to detect clinically occult SARDs, but careful interpretation of the results is key to avoid misdiagnosis.

Table 1 reviews the prevalence, diagnostic clues, and prognostic risk factors in autoimmune myositis, systemic sclerosis (SSc), mixed connective tissue disease (MCTD), Sjögren disease (SjD), rheumatoid arthritis (RA), anti neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV), and interstitial pneumonia with autoimmune features (IPAF).[2-10]

Pearl #1. *Extrapulmonary features of anti-synthetase syndrome (ASyS) are frequently observed in patients with anti-Jo-1-positive antibodies, but are often absent in those with anti-PL-12 and anti-PL-7 antibodies.*

In the absence of extrapulmonary clinical features, other clues should be sought to strengthen confidence in the diagnosis. These include: a fine speckled cytoplasmic pattern on anti-nuclear antibody (ANA) immunofluorescence (AC-19 or AC-20);[11] concomitant anti-Ro52 antibodies;[12] non-specific interstitial pneumonia (NSIP) and organizing pneumonia (OP) patterns on high resolution computed tomography (HRCT); and a scleroderma-like pattern on nailfold capillaroscopy (e.g., with giant, ramified, or bushy capillaries), which may be present even in patients without Raynaud's phenomenon.[13] In the absence of any of these supporting features, a false-negative anti-synthetase antibody result should be suspected, especially if antibody titers are low.[3]

SARD	ILD Prevalence	Clinical Clues	SerologiCAL CLUES	HRCT Clues	POOR Prognostic factors
Autoimmune myositis	70–100% of anti-synthetase and -MDA5 syndromes Up to 20–25% in other myositis subtypes	• Mechanic's hands • Arthritis/arthralgia • Raynaud's phenomenon • Myositis • Dermatomyositis rash • Nailfold capillaries showing scleroderma-like pattern • Palmar papules, skin ulcerations (MDA5)	• AntiJo1, PL7, PL12, EJ, OJ, KS, Ha, Zo • Anti-MDA5 • Cytoplasmic ANA (AC19/20) • Anti-Ku • Anti-Pm/Scl • Anti-Ro52 • *Other myositis antibodies have lower ILD risks	• NSIP/OP > DAD/AIP > UIP	**Predictors of anti-MDA-5 RP-ILD:** • High anti-MDA5 titre, serum ferritin, LDH, and C-reactive protein • Male sex • Age >50 years
Systemic sclerosis	50% of diffuse SSc 30% of limited SSc	• Raynaud's phenomenon • Skin thickening • Sclerodactyly/puffy fingers • Telangiectasia • Calcinosis • Digital ulcers or pitting scars • Salt and pepper pigmentation • Nailfold capillaries showing scleroderma pattern • Esophageal reflux/dysmotility • Myositis	• Antitopoisomerase I (-Scl70) • Nucleolar ANA • Anti-U1 RNP • If scleroderma panel available: anti-RNA polymerase III, -Th/To, -fibrillarin, -Pm/Scl, -Ku, -Ro52 • If immunoprecipitation available: Anti-U11/U12 RNP (or RNPC3), -RuvBL1/2 (cytoplasmic) • *Anticentromere antibodies have lower ILD risks (< 20%)	• NSIP > UIP • Lower esophageal dilatation • Pulmonary artery enlargement	**Predictors of severe disease:** • Male sex • African descent • Diffuse cutaneous subtype • Anti-topoisomerase I antibodies • Severe GERD • Myositis/myocarditis **Predictors of progressive disease:** • HRCT extent >20% • Lower baseline FVC • Elevated C-reactive protein • Elevated serum KL-6
Mixed connective tissue disease	Up to 40%	• SSc clinical features • Raynaud's phenomenon • Myositis • Arthritis/arthralgia • Dysphagia	• Anti-U1RNP • Speckled ANA	• NSIP	**Predictors of progressive disease:** • Male sex • Elevated anti-U1RNP titres • Presence of anti-Ro52 antibodies • Absence of arthritis • Presence of digital ulcers
Sjögren disease	Up to 20%	• Xerostomia (especially with high caries burden) • Parotid swelling • Older age • Lymphopenia • Raynaud's phenomenon	• AntiSSA/SSB • Rheumatoid factor • Speckled ANA • Anti-Ro52 • Polyclonal hypergammaglobulinemia • L	• NSIP > UIP > OP, LIP	**Predictors of progressive disease:** • Older age • Male sex • Non-sicca onset • Reticular pattern on HRCT • High baseline LDH • Lower baseline FVC

SARD	ILD Prevalence	Clinical Clues	SerologiCAL CLUES	HRCT Clues	POOR Prognostic factors
Rheumatoid arthritis	Up to 20%	• Symmetrical small joint polyarthritis • Risk factors for developing ILD: ◦ High disease activity ◦ Longer RA duration ◦ Male sex ◦ Older age ◦ Cigarette smoking ◦ Obesity	• Rheumatoid factor (high titres) • AntiCCP+ (high titres)	• UIP > NSIP > OP	**Predictors of progressive disease:** • Cigarette smoking • Older age • Male sex • High HRCT ILD extent • Rheumatoid factor >200 RU/ml • High titre anti-CCP (3x) • Reduced DLCO • UIP Pattern
Anca-associated vasculitis	20–45%	• Renal, skin, neurological, and ear/nose/throat manifestations	• Anti-MPO + (or p-ANCA) > Anti-PR3 (c-ANCA)	• UIP > NSIP	**Mortality risk factors:** • Older age • UIP pattern • Microscopic polyangiitis • Cigarette smoking
IPAF	100%	• Distal digital fissuring (i.e., "mechanic's hands") • Distal digital tip ulceration • Inflammatory arthritis or polyarticular morning joint stiffness ≥60 min • Palmar telangiectasia • Raynaud's phenomenon • Unexplained digital oedema • Unexplained fixed rash on the digital extensor surfaces (Gottron's sign)	• ANA ≥1:320 titre, diffuse, speckled, homogeneous patterns *or* ◦ ANA nucleolar pattern (any titre) or ◦ ANA centromere pattern (any titre) • Rheumatoid factor ≥2× upper limit of normal • Anti-CCP • Anti-dsDNA • Anti-SSA/SSB • Anti-ribonucleoprotein • Anti-Smith • Antitopoisomerase I (-Scl70) • Anti-PM-Scl • Anti-tRNA synthetase (e.g., Jo-1, PL-7, PL-12; others are: EJ, OJ, KS, Zo, tRS) • Anti-MDA5	• NSIP and/or OP, LIP • (may be UIP if meet criteria for clinical and serological domains) • Pleural or pericardial effusion/ thickening • Airways disease • Pulmonary vasculopathy	**Predictors of progressive ILD:** • Male • UIP pattern on HRCT

Table 1. Prevalence, diagnostic clues, and prognostic risk factors of SARD-ILDs; *courtesy of Laurence Poirier-Blanchette, MD, FRCPC, Océane Landon-Cardinal, MD, FRCPC, and Sabrina Hoa, MD, MSc, FRCPC*.

Abbreviations: AIP: acute interstitial pneumonia; **ANA:** anti-nuclear antibody; **Anti-CCP:** anti-cyclic citrullinated peptide; **DAD:** diffuse alveolar damage; **DLCO:** diffusing capacity of the lungs for carbon monoxide; **FVC:** forced vital capacity; **KL-6:** Krebs Von Den Lungen 6; **GERD:** gastroesophageal reflux disease; **HRCT:** high resolution computed tomography; **ILD:** interstitial lung disease; **IPAF:** interstitial pneumonia with autoimmune features; **LDH:** lactate dehydrogenase; **LIP:** lymphocytic interstitial pneumonia; **MDA5:** melanoma-differentiation-associated protein 5; **NSIP:** non-specific interstitial pneumonia; **OP:** organizing pneumonia; **RA:** rheumatoid arthritis; **RP-ILD:** rapidly progressive ILD; **SARD:** systemic autoimmune rheumatic disease; **SSc:** systemic sclerosis; **UIP:** usual interstitial pneumonia.

Pearl #2. *Anti-OJ antibodies have very low sensitivity on line immunoassay and should be suspected when typical ASyS clinical features or a cytoplasmic ANA pattern are present despite a negative myositis panel.*

Line immunoassays have been reported to have 0% sensitivity for detecting anti-OJ antibodies compared to protein immunoprecipitation. This discrepancy is likely explained by the fact that anti-OJ antibodies target conformational and quaternary epitopes within a multi-protein complex, whereas blotting assays rely on denatured antigens that lack these structures. Notably, other rare or newly described anti-synthetase antibodies are not included in commercially available myositis panels. Hence, if ASyS is clinically suspected, further testing with immunoprecipitation may be warranted to confirm the diagnosis and inform management.[14]

Pearl #3. *The presence of palmar papules, skin ulcerations, pneumomediastinum, and marked hyperferritinemia should heighten suspicion for anti-MDA5 syndrome even before serological confirmation.*

As anti-MDA5 syndrome is associated with rapidly progressive ILD, early recognition is key to ensure rapid treatment initiation. This syndrome typically presents with little or no muscle involvement, and can have overlapping features with ASyS, including rapidly progressive NSIP/OP, mechanic's hands, arthritis, Raynaud's phenomenon, fever, profound weight loss, cytoplasmic ANA, and a scleroderma-like pattern. Conversely, painful palmar papules, skin ulcerations, pneumomediastinum, and marked hyperferritinemia are more characteristic and specific to anti-MDA5 syndrome, and are thought to reflect underlying vasculopathy and massive alveolar macrophage activation.[15]

Pearl #4. *The presence of SSc-specific anti-Th/To antibodies should be suspected in patients with ILD and high-titer nucleolar ANA, even in the absence of cutaneous findings and a negative scleroderma panel.*

SSc-specific anti-Th/To antibodies are associated with an increased risk of ILD, but often present with no or very subtle skin thickening, which means that many patients do not meet classification criteria for SSc.[16] Commercially available scleroderma panels (line immunoassays) have limited sensitivity for detecting anti-Th/To antibodies, as they do not include the antigen's most frequently targeted subunit.[17] Despite these limitations, other diagnostic clues include a nucleolar ANA pattern (AC-8), a scleroderma pattern on nailfold capillaroscopy (e.g., giant capillaries, hemorrhages, avascular areas, and neoangiogenesis), and findings such as distal esophageal dilatation and pulmonary hypertension on HRCT. As a general rule of thumb, pulmonary hypertension should be suspected when the main pulmonary artery diameter exceeds that of the adjacent aorta.[18]

Pearl #5. *Lymphoid interstitial pneumonia (LIP) is a less common, but more specific, HRCT pattern observed in SjD-ILD.*

Although SjD-ILD is most commonly associated with NSIP and usual interstitial pneumonia (UIP), the presence of LIP, characterized by hallmark pulmonary cysts, should increase suspicion for an underlying SjD diagnosis. Referral to ophthalmology and oral medicine specialists can help identify objective signs of sicca, even in the absence of overt symptoms. In addition to classical anti-SSA and -SSB antibodies, the presence of positive ANA, rheumatoid factor, polyclonal hypergammaglobulinemia, or hypocomplementemia can also support the diagnosis. Challenges arise when ILD is the sole clinically apparent manifestation, or in seronegative SjD lacking classical autoantibodies. In these situations, biopsy of the minor salivary glands may help confirm the diagnosis and should be considered if it would alter management.[19]

Pearl #6. *RA-ILD can develop prior to the onset of joint symptoms in 10–20% of cases.*

Hence, in ILD patients with high titers of rheumatoid factor and/or anti-CCP antibodies, close monitoring for the subsequent development of arthritis is important.[20] Furthermore, in patients

with arthralgias, joint ultrasound and hand X-rays may be useful to detect subclinical synovitis or erosions, which can sometimes occur despite the absence of significant pain, as seen in *arthritis robustus*, typically observed in men.

Pearl #7. *ANCA-positive ILD may precede the development of AAV in up to 25% of cases.*

ILD affects up to 51% of patients with anti-MPO-positive AAV and 23% of those with anti-PR3-positive AAV, with UIP being the most commonly observed HRCT pattern. Two related entities are described: AAV-ILD (meeting AAV classification criteria) and isolated ANCA-ILD (without systemic features). ANCA-positive ILD may precede the development of AAV in up to 25% of cases, with a mean interval of approximately 2 years between ILD and AAV diagnoses. Hence, the *2020 International Consensus on ANCA Testing beyond Systemic Vasculitis* recommends systematic ANCA screening for all ILD patients, along with longitudinal surveillance for renal, skin, neurological, ear-nose-throat, and other systemic signs of AAV.[21-23]

Pearl #8. *Patients with ILD and autoimmune features who do not meet SARD classification criteria should be considered for IPAF classification.*

Defined by the 2015 ERS/ATS statement on IPAF, this research framework classifies ILD patients as having autoimmune features when they fulfill criteria from at least two out of three domains: clinical, serological, or morphological.[24] Some of these patients later develop a defined SARD, and many respond to immunosuppressive therapy similarly to those with established autoimmune disease, especially among patients with inflammatory ILD phenotypes.

2. Defining the Who, When, How, and Frequency of ILD screening in SARD

Because ILD may be asymptomatic in SARDs, screening is essential for early detection and management. Systematic HRCT and pulmonary function test (PFT) screening at diagnosis is recommended for patients with high-risk conditions such as ASyS and anti-MDA5 syndrome, SSc, and MCTD with SSc features. For RA and SjD, baseline screening should be performed in those with risk factors, while in AAV, it is advised for patients with respiratory symptoms, abnormal PFTs, or chest X-ray findings.[25–27]

If baseline screening is negative, continued surveillance is warranted given that ILD may develop later in the disease course.[2,28] Surveillance primarily relies on symptoms and physical examination, and PFTs can be repeated annually or more frequently according to the risk profile, although their sensitivity and specificity is limited.[25,26] Emerging tools such as serum KL-6 and lung ultrasonography are being investigated as sensitive, radiation-free alternatives to HRCT for screening purposes.[29]

For patients with confirmed SARD-ILD, disease is monitored using PFTs, ambulatory desaturation testing, and HRCT as indicated. PFTs are typically repeated every 3 to 12 months, with the frequency tailored according to disease duration, severity, and the presence of risk factors for progression (**Table 1**).[2,3,5-10,15]

3. Management of SARD-ILD

Recent guidelines for the treatment of SARD-ILDs have been published by several professional societies and can be consulted for detailed recommendations.[3,26,30,31] Drug interventions are generally recommended in the presence of symptomatic, moderate to severe, or progressive ILD. Glucocorticoids (GC) are often used as first-line induction agents, particularly in inflammatory (NSIP/OP) or rapidly progressive ILD phenotypes, except in SSc where GCs should be used with caution due to the risk of scleroderma renal crisis. Immunosuppressants should be started early to allow prompt GC tapering and minimize toxicity.

Table 2 outlines our approach to the management of SARD-ILD. Mycophenolate mofetil (MMF) is generally preferred as first-line therapy, supported by evidence from the Scleroderma Lung Study II, which demonstrated similar efficacy but superior safety compared to cyclophosphamide in SSc-ILD.[32] Azathioprine (for mild ILD) or calcineurin inhibitors (CNIs) are suitable alternatives during pregnancy or breastfeeding. CNIs are also often considered in myositis-ILD, as this drug class is also effective for muscle and skin involvement. In anti-synthetase syndrome and anti-MDA5

Disease	First-line Treatment	Second-line Treatment if Progression	Non-pharmaceutical
Anti-synthetase Syndrome	**GC + one of:** MMF or AZA or CNI or RTX **If rapidly progressive: IV GC + 1 or 2 of:** MMF, CNI, JAKi, RTX, or CYC ± IVIg	**Add/switch:** MMF, CNI, JAKi, RTX, CYC and/or IVIg	• Multidisciplinary assessment • Smoking cessation • Pulmonary rehabilitation • Avoid long-term GC • Immunization • GERD Control • Referral for lung transplant when indicated • Referral to tertiary care ILD center when indicated
Anti-MDA5 Syndrome	**GC + one of:** MMF or CNI or JAKi **If rapidly progressive:** IV GC + 1 or 2 of: MMF, CNI, JAKi, RTX, or CYC ± IVIg	**Add/switch:** MMF, CNI, JAKi, RTX, CYC and/or IVIg Consider rescue therapies: basiliximab, plasma exchange, ECMO, or polymyxin-B hemoperfusion	
Systemic Sclerosis	MMF **If contraindication:** AZA	**Add/switch:** RTX, TCZ, NIN, PIR, CYC and/or IVIg Consider AHSCT referral Consider short-term GC at the lowest effective dose if severe disease (use with caution; monitor for renal crisis)	
Mixed Connective Tissue Disease	GC + MMF **If contraindication:** AZA or CNI Consider GC if NSIP/OP with symptomatic or moderate-severe disease	**Add/switch:** RTX, TCZ, NIN, CYC and/or IVIg	
Sjögren Disease	MMF **If contraindication:** AZA or CNI Consider GC if NSIP/OP with symptomatic or moderate-severe disease	**Add/switch:** RTX, NIN, CYC and/or IVIg	
Rheumatoid Arthritis	**If active joint disease despite csDMARD:** TCZ or RTX **If no active joint disease:** MMF or AZA Consider GC if NSIP/OP with symptomatic or moderate-severe disease	**If active joint disease, add/switch:** TCZ, RTX, JAKi, *or* ABA **If no active joint disease, add/switch:** MMF, NIN, PIR, RTX, or CYC	
Anca-associated Vasculitis	RTX or AZA or MMF Consider GC if NSIP/OP with symptomatic or moderate-severe disease	**Add/switch:** RTX, MMF, CYC and/or NIN	
IPAF	MMF **If contraindication:** AZA Consider GC if NSIP/OP with symptomatic or moderate-severe disease	**Add/switch:** CNI, RTX, CYC, NIN and/or IVIg	

Table 2. Our approach to the management of interstitial lung disease in systemic autoimmune rheumatic diseases; *courtesy of Laurence Poirier-Blanchette, MD, FRCPC, Océane Landon-Cardinal, MD, FRCPC, and Sabrina Hoa, MD, MSc, FRCPC.*

Abbreviations: ABA: abatacept; **AHSCT:** autologous hematopoietic stem cell transplant; **AZA:** azathioprine; **CNI:** calcineurin inhibitors; **csDMARD:** conventional systemic disease-modifying anti-rheumatic drugs; **CYC:** cyclophosphamide; **ECMO:** extracorporeal membrane oxygenation; **GC:** glucocorticoids; **GERD:** gastroesophageal reflux disease; **IPAF:** interstitial pneumonia with autoimmune features; **IV:** intravenous; **IVIg:** intravenous immunoglobulins; **JAKi:** Janus kinase inhibitor; **MMF:** mycophenolate; **NIN:** nintedanib; **NSIP:** non-specific interstitial pneumonia; OP: organizing pneumonia; PIR: pirfenidone; **RTX:** rituximab; **TCZ:** tocilizumab.

syndrome with rapidly progressive ILD, early combination therapy is recommended and may include MMF, CNIs, Janus kinase inhibitors (JAKis), rituximab, cyclophosphamide, and/or intravenous immunoglobulin.[33,34]

As second-line treatment in cases of ILD progression, adding or switching to other immunosuppressive drugs is preferred when inflammatory phenotypes (NSIP/OP) ILD are present, or if there are active extrapulmonary SARD manifestations such as myositis, arthritis, inflammatory skin disease, or vasculitis. Among these immunosuppressant agents, rituximab (anti-CD20 monoclonal antibody) was shown to be as effective but safer than cyclophosphamide in the RECITAL trial, which included patients with SSc-, MCTD-, and myositis-ILD.[35] The EVER-ILD trial also showed that combining rituximab with MMF was more beneficial than MMF alone for NSIP.[36] Tocilizumab (anti-IL-6-receptor) was effective in preserving lung function as a secondary outcome in two SSc-ILD trials.[37,38] Cyclophosphamide is generally reserved for severe or refractory disease due to its toxicity.[32,35]

For patients with evidence of progression despite immunosuppressive therapy, particularly those with a fibrotic (UIP) phenotype, antifibrotic agents such as nintedanib or pirfenidone can be added. The SENSCIS and INBUILD trials demonstrated that nintedanib slows forced vital capacity decline in SSc-ILD and progressive pulmonary fibrosis (including SARD-ILDs), respectively.[39,40] Notably, combining nintedanib with MMF produced additive effects on lung function decline, suggesting that targeting both the immune and fibrotic pathways is central to ILD management.[39]

In RA-ILD, methotrexate is considered safe to continue, as large observational studies and meta-analyses have not demonstrated an increased risk of ILD development or progression.[41] However, as rare hypersensitivity pneumonitis may occur, we generally avoid initiating methotrexate in patients with advanced ILD, in whom a drug-induced reaction could have major consequences on lung function.

Finally, some experts advocate for treating subclinical SSc-ILD, particularly when risk factors for progression are present. However, this approach remains heterogeneous and not yet widely adopted; it is currently being evaluated in an ongoing randomized trial in Canada (NCT05785065).[42]

Conclusion

Overall, rheumatologists play a central role in the diagnosis and management of SARD-ILD. Early identification of SARD, appropriate screening for ILD alongside assessment of other target organ involvement, and tailored treatment are key to preserving lung function and quality of life. Future studies should focus on refining screening algorithms, integrating novel biomarkers and imaging modalities into clinical practice, and establishing evidence-based therapeutic approaches through randomized controlled trials, all with the ultimate goal of improving patients' outcomes.

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