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Clinical and Serological Evaluation and Management of Rheumatic Disease-Associated Interstitial Lung Disease

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Introduction

In 2011, the American Thoracic Society (ATS) recommended that antibody testing be included in the evaluation of patients with interstitial lung disease (ILD) to assess for an underlying connective tissue disease, particularly in cases of lingering diagnostic uncertainty, such as differentiating ILD from idiopathic pulmonary fibrosis.¹ Specifically, the ATS endorsed routine testing for antinuclear antibodies (ANA), rheumatoid factor (RF), and anti-cyclic citrullinated peptide (anti CCP) antibodies.

However, autoantibody testing in isolation is rarely diagnostic and results must be interpreted within a clinical context. Accordingly, the interpretation of autoantibody testing and its implications for the diagnosis and management of rheumatic disease-associated ILD remain central to optimizing care in this patient population.

Serology testing is best utilized as an adjunct rather than a standalone diagnostic tool. Over reliance on antibody results without

clinical correlation can result in misdiagnosis and inappropriate treatment. It is therefore important to integrate serologic data into the broader diagnostic workup of systemic autoimmune rheumatic disease-associated ILD.

Rheumatoid Factor and Anti Cyclic Citrullinated Peptide in Rheumatoid Arthritis

RF is an autoantibody, usually of the IgM isotype, directed against the Fc portion of IgG. RF demonstrates a sensitivity of approximately 70–80% and a specificity of 80–90% for rheumatoid arthritis (RA); however, 10–15% of RA patients remain seronegative. Seronegativity is particularly common early in the disease course of RA, with up to 40% of patients testing negative for these antibodies during the first year.² In addition, RF can be detected in 5–10% of healthy individuals and in many other clinical contexts, such as

infections and malignancies, thereby limiting its specificity.

CCP antibodies target citrullinated peptides formed by post translational modification of arginine residues and are measured using enzyme-linked immunosorbent assays (ELISA). While anti CCP antibodies have a sensitivity comparable to RF (67% vs 69%), they demonstrate a higher specificity for RA (90–95%), yet their presence alone is not diagnostic.²

According to the American College of Rheumatology (ACR) classification criteria for RA,³ the diagnosis requires that patients have findings of synovitis with additional factors such as joint symptom duration and elevations in inflammatory markers to suggest a possible diagnosis of RA.

Antinuclear Antibody and Connective Tissue Disease Serology

ANA testing is highly sensitive (95–100%) for systemic lupus erythematosus (SLE) but lacks specificity.⁴ ANA positivity can also be observed in other autoimmune conditions, infections, malignancies, medication-related side effects, and a substantial portion of the healthy population. This highlights the importance of interpretation within a clinical context. While a strongly positive ANA result (e.g., immunofluorescence titer of >1:640) may increase suspicion for an autoimmune disease, there is no specific diagnostic cut off. Moreover, ANA titers do not reliably correlate with disease activity or guide longitudinal disease monitoring.

Classic ANA staining patterns on immunofluorescence are not sufficiently specific to distinguish connective tissue disease subtypes and cannot replace disease specific testing. Additional serologic studies, including anti-double-stranded DNA (dsDNA) antibodies, extractable nuclear antigen (ENA) panels, and complement levels, can further assist in elucidating the underlying diagnosis once SLE is suspected based on clinical assessment and a positive ANA result.

Anti-dsDNA antibodies show high specificity for SLE (approximately 95%) but only moderate sensitivity (70%) and their levels may display either concordance or discordance with disease activity.⁴ ENA testing covers a range of antibodies, which may vary by laboratory but commonly include anti-Ro and anti-La (associated with Sjogren's syndrome), anti-Jo1 (associated with anti-synthetase syndrome), anti histone antibodies (associated with drug induced lupus), and anti Scl-

70 (associated with diffuse systemic sclerosis). These antibodies can assist in establishing the diagnosis and identifying disease phenotypes, although none are diagnostic in themselves.

Serum complement levels, specifically C3 and C4, may be elevated in acute and chronic inflammation but are particularly informative when decreased, as this could indicate SLE disease activity. Complement levels tend to fluctuate with disease activity in SLE and are therefore useful both in supporting the diagnosis and monitoring disease activity.

Myositis Antibodies

Myositis-specific antibodies were not included in the 2011 ATS recommendations but are increasingly utilized to assist in the diagnosis of Idiopathic Inflammatory Myopathies (IIM). These antibodies are commonly tested as part of a panel that includes a variety of antibodies associated with distinct IIM phenotypes.⁵ Amongst the many myositis antibodies, anti MDA5 and anti synthetase antibodies typically carry the strongest association with ILD as a clinical manifestation. In contrast, ILD is rare in association with other myositis antibodies, such as TIF1-gamma.⁵

Several anti MDA5 clinical phenotypes have been described with varying degrees of muscle involvement, ranging from significant myositis to no muscle involvement (i.e., amyopathic).⁶ Distinctive cutaneous manifestations can occur in the form of tender palmar violaceous lesions that can provide an early clinical clue to the diagnosis. Digital ulcerations, reflecting a significant underlying vasculopathy, are also a common dermatological manifestation. A particularly concerning manifestation is rapidly progressive ILD, which is associated with high rates of morbidity and mortality, particularly among Asian and Mediterranean populations.

Anti synthetase antibodies constitute a group of antibodies targeting aminoacyl tRNA synthetase enzymes. They can be categorized into anti-Jo1 and non-Jo1 antibodies. Non-Jo1 antibodies, including anti-PL-7, PL-12, OJ, and EJ, are typically associated with a higher risk of more severe lung disease.⁷ The clinical phenotype of anti-synthetase syndrome is diverse and may include varying degrees of involvement of the skin, Raynaud's phenomenon, muscle, joints, and lungs.⁷ While some patients present with multiple features, others may manifest with isolated lung involvement. The severity of organ

involvement, including lungs, also varies widely, from asymptomatic interstitial lung abnormalities detected on imaging to rapidly progressive ILD.⁷

Diagnosis of Rheumatic Conditions Affecting the Lung

Serologic evaluation is recommended in patients with ILD to identify the possibility of an underlying rheumatic disease. However, serological findings must be interpreted within a holistic clinical context of rheumatic disease extra pulmonary manifestations.

Rheumatoid Arthritis-associated Interstitial Lung Disease

Rheumatoid arthritis-associated ILD is common, with a global pooled prevalence of approximately 21.4%.⁸ A usual interstitial pneumonia pattern occurs more frequently than a nonspecific interstitial pneumonia (NSIP).⁸ The 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria for RA incorporates joint distribution, serological markers (RF and anti CCP), symptom duration, and acute phase reactants, with a score of 6 or more supporting classification as RA. This classification framework can be a useful reference for the Respiriologist when RA ILD is under consideration.³

RF and anti CCP antibodies are often present in RA and may correlate with the risk of ILD; however, their primary validated roles are in diagnosis and prediction of erosive joint disease. Of note, a subset of RA patients test positive for these antibodies, and the diagnosis of RA can be made in the absence of these antibodies based primarily on joint manifestations. Therefore, assessment of joint symptoms and related physical examination findings in a patient with new ILD could facilitate early diagnosis of RA-ILD. Early diagnosis then allows timely initiation of treatment strategies tailored to both joint and pulmonary involvement that may reduce disease progression and damage.

Systemic Lupus Erythematosus and Systemic Sclerosis-associated Interstitial Lung Disease

SLE EULAR/ACR classification criteria for SLE includes pleural effusion as the principal lung manifestation.⁹ However, ILD is another possible

manifestation estimated to occur in approximately 5–10% of SLE patients, typically with an NSIP pattern on imaging.¹⁰ Given the multisystem nature of SLE, no one single test or physical examination finding is sufficient to immediately establish the diagnosis in isolation.

Systemic sclerosis carries a substantially higher burden of ILD, with prevalence estimates of 30–50%, usually with an NSIP pattern.¹¹ ILD is a leading cause of mortality in this patient population, emphasizing the importance of early identification of ILD in systemic sclerosis. Current classification criteria for systemic sclerosis incorporates clinical features such as skin tightening, digital ischemia, and gastrointestinal manifestations along with serologic markers such as anti-topoisomerase I-70 (Scl 70) and anti centromere antibodies.¹² These features, along with skin findings, help to distinguish diffuse from limited scleroderma phenotypes. Screening ILD patients for skin and gastrointestinal manifestations may assist in diagnosis. Of note, while skin involvement is typical, scleroderma sine sclerosis can occur in approximately 5–10 % of patients who have no skin involvement.¹³

Idiopathic Inflammatory Myopathies–Associated Interstitial Lung Disease

IIM are acquired autoimmune conditions with diverse clinical, serological, and pathological phenotypes.¹⁴ Proximal muscle weakness is the typical pattern of muscle involvement, while severe muscle involvement can also result in dysphagia and respiratory muscle weakness. Typical skin rashes may include malar rash, Gottron's papules, and Shawl- and V neck signs.

Screening ILD patients for clinical manifestations of IIM including skin rashes and muscle weakness may facilitate diagnosis. Measurement of creatine kinase (CK) with blood testing can also aid the diagnostic process; however, diagnosis often requires additional muscle specific testing such as electromyography, magnetic resonance imaging, and muscle biopsy.

Amyopathic disease can occur in which IIM manifests with extra-muscular manifestation such as ILD in the absence of muscle involvement. Similarly, a normal CK level does not exclude the possibility of inflammatory myopathy.

Given the broad phenotypic diversity of IIM, it has become clear that the dichotomous paradigm of dermatomyositis and polymyositis is obsolete, highlighting the broad spectrum of potential IIM

manifestations.¹⁴ This marked heterogeneity has resulted in difficulty developing encompassing classification criteria, including the 2017 ACR/EULAR criteria for inflammatory myopathies,¹⁵ requiring caution in applying these criteria in clinical practice.

Approach to Treatment of Rheumatic Disease-associated Interstitial Lung Disease

General Treatment Principles

Inflammation in rheumatic disease is reversible, whereas chronic sequela, such as joint damage, muscle atrophy with fibrosis, and fatty replacement, may lead to irreversible functional limitation and disability. Early initiation of effective therapy, both non-pharmacological and pharmacological, aimed at achieving disease control and ultimately remission, is paramount. Non-pharmacologic measures, such as physiotherapy, occupational therapy, speech-language pathology, respiratory therapy, and structured rehabilitation are vital and should be an integral part of the treatment plan, tailored to the individual patient's needs.

A common challenge with rheumatic disease treatment is the multisystem involvement that results in multiple therapeutic targets. While systemic glucocorticoids typically provide benefit across multiple systems, disease-modifying, steroid-sparing agents (DMARDs) typically demonstrate variable affinity to different organs and related manifestations. Furthermore, the severity of involvement may differ across organs, requiring careful balancing of the risks and benefits of immunosuppressive therapies.

A “treat-to-target” approach, in which medications are tailored to the individual patient based on specific disease manifestations and their severity, can provide a useful therapeutic framework. This approach involves identifying which disease manifestations are present and their severity, considering medication contraindications, and, if feasible, selecting medications that target multiple involved systems to limit polypharmacy. This approach is particularly relevant for complex presentations, such as anti-synthetase syndrome, in which lung, joint, skin, and muscle involvement may occur and evolve asynchronously.

Pharmacologic Treatment Modalities

Glucocorticoids are typically the cornerstone of initial management, with dosing determined by organ involvement and severity. While lower doses of prednisone could be sufficient to achieve a response in RA joint involvement, significant proximal muscle weakness in IIM may require initial dosing of up to 1 mg/kg/day followed by a slow taper over several months. High-dose glucocorticoids are especially critical in high-risk settings, such as rapidly progressive ILD, where early aggressive therapy may alter prognosis in a potentially life-threatening condition. Long-term monotherapy with glucocorticoids, however, is generally avoided owing to multiple potential side effects and the availability of steroid-sparing medications.

The selection of steroid-sparing medication depends on the diagnosis and the specific organ systems involved. Multiple treatment guidelines for rheumatic conditions have been published, typically focusing on isolated disease manifestations such as joint, kidney, or lung involvement. However, the approach for managing the patient with multisystem concurrent involvement remains challenging, given the paucity of data to guide clinicians in selecting optimal medications.¹⁶

Organ-targeted Disease-modifying, Steroid-sparing Agent Strategies

Pragmatic “target organ efficacy” profiles can help match disease-modifying agents with organ involvement. Methotrexate (MTX), for example, has established efficacy for joints, muscle, and skin in rheumatic disease,^{16,17} but is frequently avoided in the presence of lung involvement due to potential side effects. It is absolutely contraindicated during pregnancy and in patients with renal impairment.

In contrast, mycophenolate mofetil (MMF), azathioprine, and calcineurin inhibitors such as tacrolimus have demonstrated efficacy for lung and muscle involvement,^{16,18} but may not benefit inflammatory joint disease. In conditions such as anti-synthetase syndrome, where both joint and lung manifestations are present, these medications may provide benefit for the lung disease, while joint disease persists, necessitating the addition of a joint targeting medication.

Alternatively, a medication such as rituximab, which targets both lung and joint disease, could be considered. Rituximab has demonstrated efficacy in lung, joint, and muscle involvement, though its

effectiveness for skin involvement in IIM appears more limited, with higher rates of skin relapse reported.¹⁹ Therefore, in a patient with lung, joint, muscle, and skin disease, a combination DMARD approach might be needed.

Cyclophosphamide is typically reserved for severe or refractory lung and muscle manifestations of rheumatic disease and is commonly an important part of induction therapy for patients with rp-ILD.²⁰

Intravenous immunoglobulin (IVIg) has established efficacy as adjuvant therapy in patients with severe inflammatory myopathy involving muscle and skin. However, its benefit for lung involvement has not been clearly established.²¹

Emerging therapies such as Janus kinase/signal transducer and activator of transcription (JAK-STAT) inhibitors and interferon-targeting therapies are the focus of growing attention as their indications expand across a range of rheumatic conditions and may show benefit for lung involvement. However, clinical practice patterns, approved indications, and accessibility can vary widely across the world. For example, JAK-STAT inhibitors are commonly used for patients with MDA 5 with lung involvement in Asia,²² whereas IIMs are not currently recognized as an approved indication for these medications in Canada.

Antifibrotic Lung-directed Therapies

In addition to immunosuppressive therapy, lung-targeted antifibrotic therapies play an increasing role in managing rheumatic disease-associated lung involvement, particularly when lung fibrosis is a dominant feature. Nintedanib, a tyrosine kinase inhibitor, has demonstrated benefit in slowing forced vital capacity decline in progressive fibrosing ILD, including systemic sclerosis-associated ILD.²³ Nerandomilast, a phosphodiesterase-4B (PDE-4B) inhibitor, has also demonstrated benefit in preserving forced vital capacity in this context.²⁴ Antifibrotic options are generally used as adjuncts to immunomodulatory therapy, particularly when fibrosis is established and disease progression persists despite adequate control of systemic inflammation.

Conclusion

Serologic testing can support diagnosis, phenotyping, and risk stratification in rheumatic disease-associated ILD; however, results must

always be interpreted within a well-defined clinical context. Therefore, detailed history and physical examination focused on stigmata of rheumatic disease are paramount in establishing the clinical context for interpreting antibody findings.

Evolving classification paradigms, particularly in IIM, recognize a broad spectrum of clinical, serological, and pathological phenotypes. The wide variability in disease severity and organ involvement poses potential diagnostic pitfalls such as IIM-ILD in the absence of typical muscle or skin findings.

A “treat-to-target” framework that focuses on disease manifestations can assist in tailoring treatment to the individual patient. This framework is particularly relevant in multisystem organ involvement, where a single standard medication regimen is likely not feasible and high-quality evidence to guide management is frequently lacking. These complexities in diagnosis and management highlight the need for collaborative, multidisciplinary care to improve patient outcomes.

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