Section A -Research paper

EVALUATION OF PULMONARY MANIFESTATIONS IN PATIENTS WITH RHEUMATIC DISEASES

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Abstract:
Lung ailments in rheumatic diseases present unique challenges for diagnosis and management and are a source of significant morbidity and mortality for patients. Unlike the idiopathic interstitial pneumonias, patients with rheumatic diseases experience lung disease in the context of a systemic disease that may make it more difficult to recognize and that may present greater risks with treatment. Despite recent advances in our awareness of these diseases, there is still a significant lack of understanding of natural history to elucidate which patients will have disease that is progressive and thus warrants treatment. What we do know is that a subset of patients with rheumatic disease experience parenchymal lung disease that can prognostically resemble idiopathic pulmonary fibrosis, such as in rheumatoid arthritis, and that others can have aggressive inflammatory lung disease in the context of autoimmune myositis, systemic sclerosis, or an undifferentiated autoimmune process. As we enter into a paradigm shift where we view lung health as a cornerstone of our care of patients with rheumatic diseases, we hopefully will improve our ability to identify those patients at highest risk for pulmonary disease and progression, and offer emerging treatments which will result in better outcomes and a better quality of life.

Keywords: Pulmonary, Rheumatic Diseases, Connective Tissue Diseases.

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Introduction:

The connective tissue diseases (CTDs) refer to the spectrum of systemic rheumatologic illnesses characterized by immune dysregulation with autoimmune phenomena (e.g., circulating auto antibodies) and immune-mediated organ dysfunction. In general, they include rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis (SSc),polymyositis/dermatomyositis (including anti-synthetase syndrome), primary Sjögren's syndrome, mixed CTD (MCTD), and undifferentiated CTD. While these disorders are often considered as a group, there is significant clinical heterogeneity among them. Each can potentially impact all organ systems, with the lungs as a common target; and all patients with CTD are at risk for developing associated clinically significant lung disease **(1).**

There are a wide variety of pulmonary manifestations associated with the CTDs, with essentially every anatomic compartment of the respiratory tract at risk of injury. Certain characterized diseases are more commonly associated with specific patterns of lung involvement **(Table 1).** As examples, in patients with SSc, pulmonary involvement is the leading cause of mortality and is typically manifested by interstitial lung disease (ILD) or pulmonary hypertension (PH). In contrast, in SLE, ILD and PH occur much less frequently—while pleural disease occurs quite commonly **(2).**

Patients with rheumatoid arthritis (RA) and Sjögren's syndrome often develop airways disease (bronchiolitis and bronchiectasis) and ILD,whereas patients with poly-/dermatomyositis frequently develop ILD and yet rarely develop airway complications **(3).**

Depending upon the clinical context, CTD associated lung disease varies by time of onset, pattern of lung involvement, and disease severity. Indeed, ILD may be the initial manifestation of a CTD (with extrathoracic features of the CTD developing months or even years later) **(4)** or may be identified in well-established, longstanding CTD **(2).**

Furthermore, abnormalities found on chest imaging or pulmonary physiology may be subclinical, asymptomatic and stable, or chronically progressive or may present in a fulminant, life-threatening manner.

Table (1): Most common CTD-associated pulmonary manifestations

	SSc	**RA**	**Primary Sjogren's**	**MCTD**	**PM/DM**	**SLE**
Airways	-	++	++	+	-	+
ILD	+++	++	++	++	+++	+
Pleural	-	++	+	+	-	+++
Vascular	+++	-	+	++	+	+
DAH	-	-	-	-	-	++

The number of + signs indicates relative prevalence of each manifestation **SSc** systemic sclerosis, **RA** rheumatoid arthritis, **CTD** connective tissue disease, **MCTD** mixed connective tissue disease, **PM/DM** polymyositis/dermatomyositis, **SLE** systemic lupus erythematosus, **ILD** interstitial lung disease, **DAH** diffuse alveolar hemorrhage**(5)**

ILD in Established CTD:

Chest imaging evidence of ILD is commonly identified in patients with an established, preexisting CTD. In fact, recent studies have shown radiographic prevalence rates of subclinical ILD of33–57 % in various CTD cohorts **(5).** ILD is particularly common in patients with SSc, PM/DM, RA, primary Sjögren's syndrome, and MCTD. However, just because a patient with CTD is identified to have parenchymal lung disease does not mean the two are necessarily related. For example, the presence of preexisting SSc may

be associated with the development of lung injury due to other causes (e.g.,aspiration-associated pneumonitis).

Furthermore, because CTD patients are often on immunosuppressive medications, the finding of new pulmonary infiltrates in these patients should raise suspicion of respiratory infection with either typical or atypical pathogens and medication-induced lung toxicity. As with any patient that presents with interstitial infiltrates, a comprehensive evaluation is needed to explore all potential etiologies (e.g., infection, medication toxicity, environmental and occupational exposures, familial disease, smoking- related lung disease, malignancy, etc.). The determination that the ILD is truly *associated* with the preexisting CTD requires a thorough process of elimination, and this evaluation is enhanced by a multidisciplinary approach **(6).**

Clinical Features:

Demographic features can help distinguish the patient with an underlying CTD. In comparison to IPF, patients with CTD-ILD are more likely to be younger and female. A detailed review of systems and thorough physical examination is useful. Certain specific clinical features lend more support for underlying CTD than others. Of the CTD symptoms encountered in patients with IIP, perhaps none is as important as Raynaud's phenomenon.

The presence of Raynaud's phenomenon is associated with a pattern of NSIP and when identified in a patient with ILD should raise strong suspicions for underlying CTD in general and SSc (with or without overt skin thickening) in particular. Indeed, Raynaud's phenomenon is encountered in nearly all patients with SSc and is a common finding in patients with PM/DM, anti- synthetase syndrome, primary Sjögren'ssyndrome, MCTD, SLE, and UCTD. Performing nailfold capillary microscopy is useful when assessing a patient with Raynaud's phenomenon.

In particular, the presence of dilated or tortuous capillary loops or significant areas lacking capillary loops (i.e., capillary drop out) may be suggestive of SSc or PM/DM **(Fig.1).**

The reporting of symmetric joint swelling or stiffness, or identifying synovitis on physical examination, is very useful. Because inflammatory arthritis is encountered in all of the CTDs, autoantibody profiles may be needed to clarify which specific CTD is present. In contrast, symptoms such as gastro esophageal reflux, pain, fatigue, dry eyes, dry mouth, alopecia, and weight loss are not nearly as helpful because they are ubiquitous and not nearly as specific for CTD.

The cutaneous manifestations of SSc and anti synthetase syndrome are worthy of special mention because these two disorders are so commonly associated with ILD and their extra thoracic features are very specific and yet often quite subtle. It is important to recognize that the "mechanic's hands" sign of anti-synthetase syndrome can be as subtle as only mild distal digital fissuring **(Fig. 2.)**and that palmar telangiectasia may be limited to the finding of only few scattered dilated capillaries. Nonetheless, when such findings are present in a patient with an IIP, they are highly suggestive of underlying CTD.

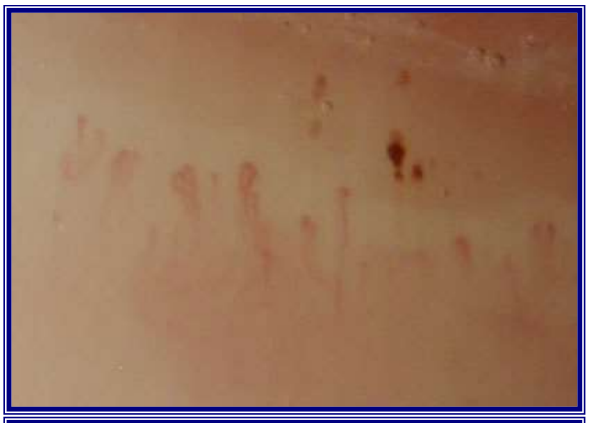

Fig. (1): A nailfold capillary microscopic image from a patient with systemic sclerosis. Note the presence of marked capillary loop tortuosity, dilation, and areas of vascular dropout. **(5)**

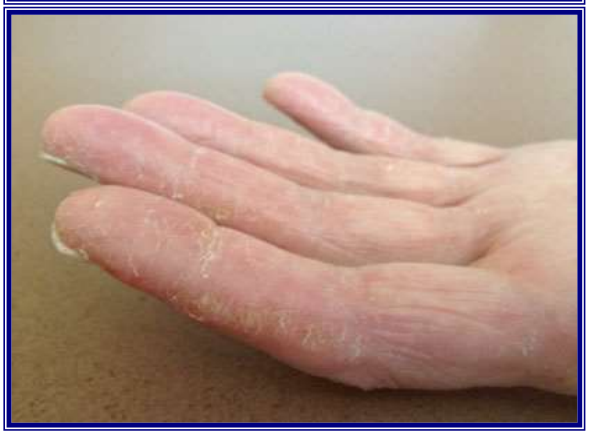

Fig. (2): A photograph of the distal digital fissuring characteristic of "mechanic's hands" in a patient with the anti- synthetase syndrome **(5)**

Circulating Autoantibodies:

Autoantibody assessment is an important part of the evaluation of patients with IIP. For patients with ILD in whom there is clinical suspicion of an underlying CTD, we recommend a broad panel of auto antibodies as a screening test **(Table 2).** It is also important to take note of the pattern of immune fluorescence when the ANA is positive, as the nucleolar-staining ANA pattern in patients with ILD may suggest SSc spectrum of disease **(7).** Importantly, we highlight that the ANA and RF are relatively poor screening tests: they have low specificityparticularly when present at low titerand can be seen in healthy individuals. In addition, given that a negative ANA and RF may dissuade some clinicians from pursuing further evaluation, cases of occult CTD that may be ANA and RF negative (e.g., anti-synthetase syndrome) are missed.

Table (2): Useful antibodies for CTD-ILD assessment

Autoantibody	**Commomnly associated CTD**
High-titer ANA (>1:320 titer)	Many
High-titer RF(>60 IU/mL)	RA, Sjogren's syndrome, SLE
Anti-CCP	RA
Anti-centromere	Systemic sclerosis
Anti-nuclear-ANA	Systemic sclerosis
Anti-Ro (SS-A)	Many

Anti-La (SS-B)	SLE, Sjogren's syndrome
Anti-Smith	SLE
Anti-ribonucleoprotien	SLE, MCTD
Anti-dsDNA	SLE
Anti-topoisomerase(Scl-70)	Systemic sclerosis
Anti-tRNA synthase antibodies	Poly-/dermatomyositis (anti-synthase syndrome)
Anti-PM-Scl	Systemic sclerosis/myositis overlap
Anti-Th/To	Systemic sclerosis
Anti-U3 ribonucleoprotien	Systemic sclerosis
Anti-MDA-5 (CADM)	Clinical amyopathic dermatomyositis

(5)

Chest Imaging Features:

Thoracic HRCT imaging plays a central role in the evaluation of ILD by providing detailed information on the pattern, distribution and extent of the ILD, and the presence of extra parenchymal abnormalities including pleural disease and pericardial and esophageal features. In contrast to IIP, patients with CTD-ILD are more likely to have pleural effusions, pericardial effusions, pericardial thickening, and esophageal dilatation **(8).**

Patients with CTD are also more likely to have an HRCT pattern suggestive of NSIP when compared to patients without CTD. HRCT has varying degrees of correlation with histopathologic pattern. Among CTD-ILD patients with a typical HRCT pattern for UIP, the histopathology almost always correlates **(8).**

Interestingly, the converse does not hold true; CTD patients with histopathologic patterns of UIP may have HRCT patterns suggestive of NSIP **(9).** As discussed previously, noting atypical patterns of lung injury may impact decisions to perform surgical lung biopsy.

Pulmonary Function Testing:

Serial assessment of the forced vital capacity (FVC) and diffusing capacity for carbon monoxide (DLCO) allows for objective quantification of ventilatory capacity and gas exchange, respectively.

These parameters are useful in assessing the degree of respiratory impairment due to ILD and may provide clues about the presence of coexistent PH as well. They are especially helpful when trying to assess for disease progression and response to therapy. Changes in FVC, and to a lesser degree of confidence in DLCO, over time predict survival in IPF and, therefore, are commonly used as surrogate markers for response to therapy in ILD in general **(10).**

Patients who decline ≥10 % of predicted FVC or ≥15 % of DLCO are considered to have clear and clinically significant evidence of progressive disease. In patients with CTD-ILD, pulmonary physiology appears to be a stronger predictor of survival than underlying histopathologic pattern seen at the time of diagnosis **(11).**

Thoracic High-Resolution Computed:

- ***Tomography:***

HRCT imaging yields valuable information about ILD including the pattern and extent of disease, an assessment of disease progression, and the evaluation of extraparenchymal abnormalities. In many cases of CTD-ILD, a specific radiologic pattern (e.g., UIP or NSIP) can be determined with a high degree of confidence. This pattern recognition within specific clinical scenarios may obviate the need for surgical lung biopsy and provide prognostic information.

The presence of a fibrotic radiographic pattern as evidenced by reticular opacities, traction bronchiectasis, and honeycombing is predictive of poor outcomes in both IIP and RA-ILD **(12).** A recent

study of 215 subjects with SSc-ILD demonstrated that the HRCT extent of fibrosis and degree of FVC reduction provide discriminatory prognostic information **(13).**

The authors proposed a sub classification of SSc-ILD as "limited" or "extensive" based upon the estimation of extent of fibrosis on HRCT and impairment in FVC. This simple staging system provided a more accurate prognostic separation than has been achieved with any single index in isolation **(13).**

References:

1. Desai, O., Winkler, J., Minasyan, M., & Herzog, E. L. (2018). The role of immune and inflammatory cells in idiopathic pulmonary fibrosis. Frontiers in Medicine, 5, 43.
2. Opinc, A. H., Makowski, M. A., Łukasik, Z. M., & Makowska, J. S. (2021). Cardiovascular complications in patients with idiopathic inflammatory myopathies: does heart matter in idiopathic inflammatory myopathies? Heart Failure Reviews, 26(1), 111–125.
3. Doyle, T. J., Hunninghake, G. M., & Rosas, I. O. (2012). Subclinical interstitial lung disease: why you should care. American Journal of Respiratory and Critical Care Medicine, 185(11), 1147–1153.
4. Singh, J. A., Guyatt, G., Ogdie, A., Gladman, D. D., Deal, C., Deodhar, A., Dubreuil, M., Dunham, J., Husni, M. E., & Kenny, S. (2019a). 2018 American College of Rheumatology/National Psoriasis Foundation guideline for the treatment of psoriatic arthritis. Journal of Psoriasis and Psoriatic Arthritis, 4(1), 31–58.
5. Baughman, R. P., Costabel, U., & Lower, E. E. (2012a). Drug therapy for interstitial lung disease. Diffuse Lung Disease: A Practical Approach, 101–120.
6. Rushworth, G. F., & Megson, I. L. (2014). Existing and potential therapeutic uses for N-acetylcysteine: the need for conversion to intracellular glutathione for antioxidant benefits. Pharmacology & Therapeutics, 141(2), 150–159.
7. Broen, J. C. A., & van Laar, J. M. (2020). Mycophenolate mofetil, azathioprine and tacrolimus: mechanisms in rheumatology. Nature Reviews Rheumatology, 16(3), 167–178.
8. Gutsche, M., Rosen, G. D., &Swigris, J. J. (2012). Connective tissue disease-associated interstitial lung disease: a review. Current Respiratory Care Reports, 1, 224–232.
9. Lee, C. G., Herzog, E. L., Ahangari, F., Zhou, Y., Gulati, M., Lee, C.-M., Peng, X., Feghali-Bostwick, C., Jimenez, S. A., & Varga, J. (2012). Chitinase 1 is a biomarker for and therapeutic target in scleroderma-associated interstitial lung disease that augments TGF-β1 signaling. The Journal of Immunology, 189(5), 2635–2644.
10. Cottin, V., Hirani, N. A., Hotchkin, D. L., Nambiar, A. M., Ogura, T., Otaola, M., Skowasch, D., Park, J. S., Poonyagariyagorn, H. K., & Wuyts, W. (2018b). Presentation, diagnosis and clinical course of the spectrum of progressive-fibrosing interstitial lung diseases. European Respiratory Review, 27(150).
11. Lin, Y.-J., Anzaghe, M., &Schülke, S. (2020a). Update on the pathomechanism, diagnosis, and treatment options for rheumatoid arthritis. Cells, 9(4), 880.
12. Shams, S., Martinez, J. M., Dawson, J. R. D., Flores, J., Gabriel, M., Garcia, G., Guevara, A., Murray, K., Pacifici, N., & Vargas, M. V. (2021). The therapeutic landscape of rheumatoid arthritis: current state and future directions. Frontiers in Pharmacology, 12, 680043.
13. Lange, S. M., & Parekh, M. (2020).Collagen-Vascular Disease Associated With Interstitial Lung.