



Interstitial lung disease in the connective tissue diseases; a paradigm shift in diagnosis and treatment

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ABSTRACT

Interstitial lung disease (ILD) in the connective tissue diseases (CTD) is amongst the most challenging aspect of care of patients with rheumatic diseases and is the source of significant morbidity and mortality. While there has been progress in our understanding of the natural history of these complications, we still suffer from a limited reservoir of data to confidently determine which patients are at highest risk for disease and those who are at highest risk for disease progression. Treatment options until recently have been limited to anti-inflammatory therapies but with the emerging availability of anti-fibrotic therapies, a shift in strategy is emerging to target therapies based on the specific radiographic, histopathologic features and biomarker profiles that are unique to patients with rheumatic diseases and ILD.

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1. Prognosis in ILD in the CTD

Previously ILD in the CTD was considered to be a more benign process compared to idiopathic pulmonary fibrosis (IPF), but emerging data has shown that the presence of UIP (usual interstitial pneumonia) in association with any CTD portends a prognosis that rivals the mortality associated with IPF [1]. For example in RA, up to 10% of patients may have clinically significant ILD and up to 60% of those have the UIP pattern [2,3]. In scleroderma, the predominant pathologic pattern is nonspecific interstitial pneumonia (NSIP) and overall survival in this cohort is more favorable than in those with UIP associated with a connective tissue disease though fibrotic NSIP may have a worse prognosis compared to cellular NSIP [4]. As such, surveillance and identification of those at highest risk is important for surveillance and consideration for established and emerging therapeutic options.

2. Interstitial lung disease: radiologic and histopathologic patterns seen in the rheumatic diseases

The most common patterns of interstitial lung disease observed in the rheumatologic diseases include NSIP, UIP, organizing pneumonia (OP), lymphocytic interstitial pneumonia (LIP), acute interstitial pneumonia (AIP)/diffuse alveolar damage (DAD). The rheumatic diseases most commonly affected by ILD include (in order of descending

frequency) systemic sclerosis (SSc)/scleroderma, idiopathic inflammatory myopathies (IIM), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Sjogren's syndrome, and undifferentiated rheumatoid disorders. In some patients more than one histological pattern of disease may be present, for example, NSIP and OP may be seen together in IIM.

Nonspecific interstitial pneumonia: NSIP is commonly seen in most rheumatic diseases, especially in IIM and SSc. The prognosis associated with NSIP is more favorable compared to UIP, although fibrotic NSIP may parallel UIP. Diagnosing NSIP by high resolution computed tomography (HRCT) is difficult due to less agreed upon features seen on imaging, which may in some cases necessitate a biopsy. In general, patients with rheumatic disease and ground-glass changes without honeycombing or traction bronchiectasis and without infection most likely have a predominately inflammatory process such as cellular NSIP, which may be amenable to empiric anti-inflammatory therapy.

Usual interstitial pneumonia: The UIP pattern in rheumatic disease portends the worst prognosis with a 5-year mortality of >50% [1]. It can be seen in most rheumatic disease but is most frequently seen in RA (up to 60% of RA-ILD). Traditionally, disease-modifying antirheumatic drugs (DMARDs) such as mycophenolate mofetil (MMF) or azathioprine (AZA) have been utilized in patients with UIP. However, data from the PANTHER-IPF trial showing anti-inflammatory therapy to be deleterious in UIP related to IPF suggests

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that a similar approach in UIP associated with rheumatic disease may be detrimental [5]. In that context, prospective trials using antifibrotic agents in such patients are ongoing and anticipated. Given the poor prognosis seen in UIP in general, early consideration for transplant is important.

Organizing pneumonia: OP is characterized by intraluminal fibrosis in distal airways associated with interstitial inflammation. It can be seen in most rheumatic diseases and is especially notable in inflammatory myositis (IIM), and particularly the antisynthetase syndrome. OP related to rheumatic disease may have a worse prognosis compared to cryptogenic OP [6]. The presence of new onset OP requires a detailed investigation for a connective tissue disease, especially the antisynthetase syndrome.

Lymphocytic interstitial pneumonia: LIP is an interstitial process characterized by a lymphoplasmacytic infiltrate, nodules and lymphoid follicles. It is often seen in Sjogren's syndrome but can also be seen in RA. Nodular lesions may appear to be inflammatory in appearance but can represent lymphoma, especially the mucosa associated lymphoid tissue (MALT) type.

3. Challenges in assessment and determination of the presence of ILD

One of the great challenges associated with ILD in the CTD is the heterogeneity of clinical presentations and variability of natural history from patient to patient. Patients may have a mix of inflammatory and fibrotic disease. Given the dynamic nature of disease, patients may have multicompartamental disease including airway disease, ILD and pleural disease. In Scleroderma and in other CTDs, concomitant pulmonary vascular disease may confound the etiology of dyspnea and potential responses to therapy. As in IPF, esophageal disease is a common finding and may serve to initiate or propagate ILD [7]. Finally, the ability to predict decline in ILD in CTD is challenging as some patients develop ILD but then do not progress, while others will have a progressive course with intermittent exacerbations and further decline as seen in IPF.

4. Risk factors for the development and progression of ILD in the CTD

Risk factors have been identified based on demographic data, physiologic decline and radiographic features that will make it possible to begin to select specific populations that are at higher risk not only for the presence of ILD but those at higher risk for population.

In rheumatoid arthritis, highest risk for disease involve older age, male, smoker with elevated Rheumatoid factor and CCP antibody. Higher mortality is associated with a decline in FVC of >10% at anytime during their disease [8,9].

In scleroderma, those at greatest risk for developing progressive ILD in SSc include those who are SCL-70 antibody positive, African Americans, older age, and male sex with an early decline in forced vital capacity (FVC) and diffusion capacity of carbon monoxide (DLCO) and greater Extent of disease on HRCT [10,11]. Prognostically, patients with a combination of ILD and PAH fare poorly versus ILD alone [12].

In inflammatory myositis, a worse prognosis is noted in older age groups, acute and subacute presentations with low initial FVC, amyopathic cases, concomitant PAH and MDA5 antibody [13]. Specifically in ILD associated with the antisynthetase syndrome, a variety of potential environmental exposures and genetic associations are under active investigation.

5. Pathways and mechanisms of disease in fibrotic lung disease

Most of our knowledge regarding the development of fibrosis is derived from research in IPF. However, while molecular and genetic mechanisms that may drive fibrosis in IPF may apply to CTD, unique

immunologic features in CTD require a dedicated inquiry into this unique patient population.

In RA, efforts have focused on the role of inhalation of antigens that may either initiate or propagate the systemic features of RA. Airway changes have been noted early in RA and emerging evidence suggests that upper respiratory exposure to antigens such as citrulline and resultant autoimmunity may initiate or propagate RA. Smoking, common amongst RA patients, promotes citrullination in the lungs which may lead to ACPA (anti-citrullinated protein antibodies) which may result in lung inflammation and damage [14]. The presence of CCP antibodies in a group of patients without RA but active lung disease offers potential support of the importance of citrullination in the lungs as an important event in the development of fibrosis [15]. Auto antibodies that target citrullinated versions of heat shock proteins (hsp 90) subunits have been found to be highly specific for RA ILD and pathophysiologically may play a role in the development of ILD in RA patients [16].

In scleroderma, pathogenesis is thought to involve injury to alveolar parenchyma and vascular endothelium, leading to the production of endothelin, connective tissue growth factor (CTGF), TGF-beta, thrombin and growth factors signaled by the Wnt/catenin pathway. This results in the activation of fibroblasts which transform to myofibroblasts and lead to excessive accumulation of extracellular matrix and decline in oxygen transfer [17].

6. Biomarkers in ILD associated with connective tissue disease

Numerous biomarkers that have been identified as markers of ILD and disease severity in IPF are now also being investigated in CTD ILD specifically, MMP7, PARC, SP-D, KL-6, SP-A, IL-6, IL-8, ICAM -1 and VCAM-1 [18–20]. In scleroderma and RA, KL-6 has been shown to predict decline in FVC and IL-6 levels have been noted in early ILD associated with scleroderma, potentially representing insights towards a screening and therapeutic strategy [21–23]. In RA, a combination of serum biomarkers MMP7, PARC and SP-D have been utilized in combination with demographic and clinical risk factors to create a risk assessment model to ascertain the presence of ILD in RA and thus target surveillance and treatment and trial options for a select cohort [24].

In addition to serum markers, alveolar proteins derived from BAL including PDGF, TGF-B2 and INF gamma have been noted to be elevated in RA ILD and elevated levels of IL 8 and MCP -1 in alveolar fluid have been noted to be prognostically significant in patients with SSc ILD [25,26].

7. Genetic factors in ILD and CTD

Much of our knowledge of genetic factors in ILD and CTD derives from investigation in IPF and many of these factors may be applicable to CTD including MUC5B polymorphisms, surfactant gene mutations, and telomerase gene mutations [27–29]. A variety of emerging technologies using next generation sequencing and individual cell immune responses in serum and tissue may offer greater clarity regarding mechanisms of disease in CTD and ILD within individual patients and hopefully inform us towards unique and patient specific therapies.

8. Screening strategies in ILD CTD

Delineation of screening strategies for pulmonary disease is a work in progress. Early referral by the rheumatologist or primary care provider to pulmonary medicine is important in the face of pulmonary symptoms, examination findings or decrements on initial or subsequent pulmonary function testing (PFT) or parenchymal changes noted on CT scanning. Conversely, given that many patients with ILD may have an underlying rheumatic disease, a detailed assessment by a rheumatologist is an important component of the evaluation. In either case, close collaboration between pulmonologist, rheumatologists, radiologists, and pathologists is important in the diagnosis and treatment of these complex patients.

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