

RHEUMATOID ARTHRITIS ASSOCIATED INTERSTITIAL LUNG DISEASE: A REVIEW

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Abstract Rheumatoid arthritis is a common inflammatory disease affecting about 1% of the population. Interstitial lung disease is a serious and frequent complication of rheumatoid arthritis. Rheumatoid arthritis associated interstitial lung disease (RA-ILD) is characterized by several histopathologic subtypes. This article reviews the proposed pathogenesis and risk factors for RA-ILD. We also outline the important steps involved in the work-up of RA-ILD and review the evidence for treatment and prognosis.

Key words: rheumatoid arthritis, interstitial lung disease, pathogenesis, risk factors

Resumen *La artritis reumatoide asociada a la enfermedad intersticial pulmonar: una revisión.* La artritis reumatoide es una enfermedad inflamatoria común, que afecta cerca del 1% de la población. La enfermedad pulmonar intersticial es una complicación frecuente y seria de la artritis reumatoide y esta asociación está caracterizada por diferentes subtipos histológicos. Este artículo analiza la patogénesis y los factores de riesgo de esta asociación. Además señala los esfuerzos realizados y las evidencias para el diagnóstico y tratamiento.

Palabras clave: artritis reumatoide, enfermedad intersticial pulmonar, patogénesis, factores de riesgo

Rheumatoid arthritis (RA) is a common systemic inflammatory disorder of unknown etiology. It is characterized by symmetric arthritis and synovial inflammation leading to progressive joint erosion and eventually, deformity¹. The world-wide prevalence of RA ranges from 0.5% to 1%, while the incidence is estimated to be 30 cases per 100,000 people per year, and varies based on gender, population and ethnicity^{2,3}. In the United States, there is some evidence that the incidence and the prevalence of RA has been increasing over the past 20 years⁴.

Women are more commonly affected than men. This gender imbalance has been observed across different ethnic populations, as well as in familial studies⁵. There are important clinical differences between men and women with RA. Men have later RA disease onset. They are more likely to have positive anti-cyclic citrullinated peptide (CCP) antibodies, and higher titers. Men are more likely to have a history of smoking and a higher prevalence of extra-articular manifestations⁶. One explanation for this difference between men and women is genetic variability causing increased susceptibility to autoimmunity⁶. In ad-

dition, there may be hormonal factors contributing to this increased susceptibility. Early menarche and irregular menses are associated with increased risk of RA, while breast feeding seems to be protective against the development of RA⁷. Men with RA have been shown to have lower levels of bio-available testosterone, with low levels of luteinizing hormone. This suggests that low testosterone levels may play a role in the pathogenesis of RA⁸.

The etiology of RA is unknown. Known genetic susceptibility are thought to predispose to RA, which can be triggered by environmental exposures such as smoking and air pollutants⁹. Different genetic loci have been found to be significantly associated with presence of RA in genome wide association studies and replications cohorts^{10,11}. Presence of HLA-DR alleles within the major histo-compatibility complex are strongly associated with RA and can account for about one third of the genetic susceptibility to the disease¹².

The disease burden of RA is significant. Patients with RA have lower wages, more missed workdays, lower employment rates and higher limitations at work and home compared to healthy adults. Even after adjusting for age, sex, gender, income and education, people with RA were 53% less likely to be employed compared to those without RA¹³.

The disease burden is even greater in patients who develop extra-articular manifestations of RA, which affects

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approximately 40% of patients¹⁴. Pulmonary involvement is a common extra-articular feature of RA. The chest manifestations are varied and include pleuritis and pleural effusions, airways disease such as bronchiolitis obliterans, rheumatoid nodules and interstitial lung diseases (ILD)¹⁵.

Interstitial lung diseases are a group of diseases characterized by fibrosis and inflammation of the pulmonary interstitium. Interstitial lung disease can be secondary to RA, but can also be caused by the medications used to treat RA. Several anti-inflammatory and biologic drugs have been associated with the development of ILD¹⁶. The focus of this review will be RA associated ILD (RA-ILD), including the epidemiology and pathogenesis, work-up and treatment, and prognosis of RA-ILD.

Rheumatoid arthritis associated interstitial lung disease

Epidemiology

The prevalence of RA-ILD has been reported to be between 4 and 50%¹⁷⁻²¹. The variability in the reported prevalence can be attributed to the method of detection used in each study. Studies in which a higher proportion of subjects are found to have ILD are those in which the lung involvement is identified on computed tomography (CT) scan. Computed tomography scanning has been shown to be highly sensitive for detecting ILD and can identify patients with asymptomatic and subclinical disease. One study identified 33% of subjects with early RA to have abnormal CT scans, but only 6% had an abnormal chest radiograph²². A significant number of those subjects have mild abnormalities that are subclinical. While some of these patients have progression of RA-ILD, others have disease that never becomes clinically significant^{22, 23}.

The 30-year cumulative incidence of developing clinically significant RA-ILD in cohorts of RA subjects is between 6 and 8%^{14, 24}. One study looking at the prevalence of ILD in U.S. decedents with RA found a prevalence of RA-ILD of 6.6% at the time of death²⁵. Results of this study also suggested that the age-adjusted mortality rates from RA-ILD have been increasing over the past 25 years in women, despite decreasing mortality rates from RA alone. Patients with RA-ILD have a median survival after ILD diagnosis of 2.6 years, which translates to a threefold higher risk for death than for RA patients without ILD²⁴.

Etiology and pathogenesis

The etiology of RA-ILD is unknown. It is likely that most patients have some underlying genetic predisposition to fibrosis that is triggered by some form of injury to the lung. Some of the genetic polymorphisms that have been studied in RA have been studied in patients with RA-ILD. Spe-

cifically, certain polymorphisms of the human leukocyte antigen (HLA)-DRB shared epitope have been associated with increased risk of ILD (e.g. HLA-DRB1*1502), while others appear to be protective against the development of ILD (e.g. HLA-DRB1*04, DQB1*04 and DRB1*16)²⁶. One study investigated the association between the MUC5B polymorphism, a polymorphism associated with idiopathic pulmonary fibrosis (IPF), and the presence of RA-ILD, but found no significant association²⁷.

A new mouse model for RA has been developed with a single abnormality in the *skg* gene. These SKG mice develop a spontaneous autoimmune CD4+T cell mediated illness that resembles RA joint disease and its extra-articular manifestations²⁸. They develop cellular and fibrotic interstitial pneumonia when subjected to cigarette smoke and bleomycin, while normal mice do not²⁹. This suggests that both genetic predisposition and lung injury with inflammation are required for the development of ILD in RA.

Risk factors

Risk factors have been identified in the development of RA-ILD. Some risk factors are patient-specific while others are related to the RA itself. ILD has been shown to be more common in males compared to females in some studies^{21, 30}, but not in others^{31, 32}. Older age is also associated with increased risk of ILD in RA. One study found that for each 10-year increase in age, the likelihood of having ILD increased by 64%³². In another study, age above 65 years increased the risk of ILD more than four-fold³¹.

Smoking is a risk factor for the development of RA³³. Risk of developing RA increases with increasing numbers of pack-years smoked⁹. It is also an important modifiable risk factor for the development of ILD in this population. Cigarette smoking was found to be associated with presence of radiographic interstitial abnormalities as well as with reduced pulmonary function, both diffusion capacity for carbon monoxide (DLCO) and forced vital capacity (FVC)³⁴.

There is also data to suggest that the severity of RA may be related to the development of ILD. Presence of erosive joint disease, high levels of erythrocyte sedimentation rate (ESR) and presence of rheumatoid nodules are risks factors for the development of ILD^{24, 32}. In one study, high titers of rheumatoid factor (>100 IU/mL) significantly increased the risk of RA-ILD, while there was a trend towards high levels of anti-CCP antibodies and RA-ILD³¹. A recent preliminary study showed that higher levels of a variety of specific anti-citrullinated peptide antibodies and an expanded repertoire of these antibodies were present in patients with RA-ILD with lung function abnormalities³⁵. This suggested a link between autoimmunity against citrullinated proteins and RA-ILD.

Diagnosis

Usually, RA-ILD is diagnosed in patients with RA presenting with symptoms suggestive of lung disease, such as dyspnea (on exertion or at rest) or cough. They are often found to have pulmonary function impairment or abnormal chest imaging. Rarely, RA-ILD will be diagnosed on surgical lung biopsy.

Other causes of lung disease in RA should be excluded. The differential diagnosis for lung disease includes drug toxicity and infection. Drugs that have been associated with ILD in RA include disease-modifying agents such as methotrexate, leflunomide, gold, and cyclophosphamide, as well as biologics, including anti-TNF-alpha agents.[36, 37] Infection, especially atypical infections (e.g., *Mycobacterium* species, *Pneumocystis jirovecii*), should also be ruled out³⁸.

Subtypes of RA-ILD

Several histopathologic subtypes of ILD can be observed in patients with RA. The most common subtypes are the usual interstitial pneumonia pattern (UIP) and the non-specific interstitial pneumonia pattern (NSIP)^{39,40}. Other patterns of ILD seen in RA include organizing pneumonia (OP), lymphocytic interstitial pneumonia (LIP), desquamative interstitial pneumonia (DIP), and diffuse alveolar damage (DAD).

There is increasing data to suggest that RA-ILD patients with a UIP pattern may have a distinct clinical phenotype and natural history compared to the other histopathologic phenotypes observed in RA-ILD, primarily those with NSIP (**Table 1**). RA-ILD patients with the UIP pattern tend to be older, more likely to be male, and have a more significant smoking history^{21,30,39-42}. In contrast,

those without the UIP pattern tend to be younger, more likely to be women, and have a less significant smoking history. What is most compelling is the observed survival difference between RA-ILD patients with and without a UIP pattern. Patients with RA-ILD and a UIP pattern appear to have a worse survival compared to those without a UIP pattern^{41,43}. In addition, the RA-ILD patients with UIP pattern have a similar clinical phenotype and natural history seen in patients with IPF, a disease characterized by idiopathic UIP pattern.

Work-up of RA-ILD

The steps involved in the work-up of patients with RA-ILD are summarized in **Table 2**.

Clinical symptoms and signs: Clinical symptoms suggesting RA-ILD are non-specific. Dyspnea, usually on exertion, is the most frequently reported symptom. Because of physical limitations from articular disease, exertional dyspnea may not be apparent in the early stages of the disease. Cough, sputum production, wheezing and chest pain can also be reported^{44, 45}. A subset of patients can have subclinical disease, which is apparent on CT scan, but patients are clinically asymptomatic⁴⁶. Patients who have abnormal pulmonary function tests are more likely to report respiratory symptoms⁴⁵.

Pulmonary function tests: About one third of all RA patients will have pulmonary function abnormalities⁴⁵. Pulmonary function tests (PFTs) in RA can be used as screening tools for early RA-ILD and a method to assess for disease progression. Patients most commonly have a restrictive pattern on their PFTs, like in other ILDs. A mean FVC between 60 and 70% of predicted has been reported in cohort studies of RA-ILD, with a reduced DLCO of 40 to 60% of predicted values^{40, 41}.

TABLE 1.— Differences between UIP and non-UIP in RA-ILD

	UIP	non-UIP	Comments and references
Age	Older	Younger	Trend towards older age in RA-UIP ^{39, 41}
Gender	M>F	F>M	21, 30, 41
Smoking	More smoking	Less smoking	40, 42
RA Disease duration	Unrelated	Unrelated	23, 42
RA severity	Unknown	Unknown	
Anti-CCP antibodies	Lower	Higher	Trend towards lower CCP in one study ⁶⁶
Baseline PFT	Restrictive	Restrictive	No difference in severity of restriction and diffusion abnormalities ^{41, 43}
Response to treatment	Poor	Better	Anecdotal evidence and subgroup analysis data ⁵⁶
Acute exacerbations	Reported	Not reported	Case reports and observational study ^{62, 63, 67}
Survival	Worse	Better	Better in some studies ^{41, 43, 63} but not in others ⁴⁰

Abbreviations: UIP, usual interstitial pneumonia; CCP, cyclic citrullinated peptide; PFT, pulmonary function tests.

TABLE 2.– Work-up for rheumatoid-arthritis related interstitial lung disease

	Description of findings in RA-ILD	Recommended in work-up of RA-ILD	References
Clinical symptoms and signs	Symptoms: Dyspnea on exertion Cough Chest tightness Wheezing Sputum (rare) Signs: Crackles Wheezing (in presence of airways disease) Clubbing (rare)	Yes - important as part of initial assessment and for follow-up to evaluate for disease progression	23, 44, 45
Pulmonary function tests	Restrictive pattern with reduced FVC and DLCO Mixed obstructive pattern in presence of concomitant airways disease	Yes – important as part of initial assessment and for follow-up to evaluate for disease progression	24, 40, 41, 45, 46
HRCT	UIP: Reticulations, traction bronchiectasis and honeycombing Non-UIP: Reticulations, ground-glass opacities, consolidation, nodules can all occur	Yes – important for diagnosis and for establishing pattern of disease. HRCT is more sensitive than chest radiograph	21, 44, 47, 48
Bronchoalveolar lavage	There may be an increased cellularity and neutrophils on BAL. Results are inconsistent across studies and not diagnostic of RA-ILD.	No – unless it's to rule out infection	42, 51
Lung biopsy	Histopathologic pattern of disease --Usual interstitial pneumonia --Non-specific interstitial pneumonia --Organizing pneumonia --Lymphocytic interstitial pneumonia --Diffuse alveolar damage	No – unless the diagnosis of RA is unknown/unclear	39, 40
Biomarkers	Some citrullinated peptides in serum have been shown to be specific for presence of RA-ILD, but further research is required to determine the clinical utility of individual serum citrullinated proteins in RA-ILD.	No – not validated, anti-CCP antibodies may be obtained to aid with the diagnosis of RA	54, 55

Abbreviations: RA-ILD, rheumatoid arthritis associated interstitial lung disease; FVC, forced vital capacity; DLCO, diffusion capacity for carbon monoxide; HRCT, high resolution computed tomography of the chest; UIP, usual interstitial pneumonia; CCP, cyclic citrullinated peptides.

Computed tomography imaging: High resolution CT scan is essential in evaluating RA-ILD. Figure 1 illustrates different radiographic abnormalities observed. Most studies assessing CT abnormalities in RA-ILD did not differentiate between the different subtypes of ILD. The main abnormalities observed are reticulations and ground glass opacities^{21, 44, 47}. When severe and extensive, interstitial fibrosis leads to parenchymal architectural distortion, traction bronchiectasis, and honeycombing⁴⁸. Nodules that are centrilobular or perilymphatic can also be seen in RA-ILD, either alone, or with reticulations⁴⁷.

The UIP pattern in RA-ILD shares the same definition as in the idiopathic interstitial pneumonias (IIPs). It is characterized by presence of subpleural, basilar predominant reticulations, traction bronchiectasis, and honeycombing with absence of nodules, ground glass opacities or consolidation⁴⁹. Similar to the IIP literature, the radiologic pattern of a definite UIP pattern on CT scan has been shown to be highly specific and moderately sensitive for the UIP pattern on histopathology in patients with RA-ILD⁵⁰ (Fig. 1).

Bronchoscopy and bronchoalveolar lavage: There is little role for bronchoscopy and bronchoalveolar lavage

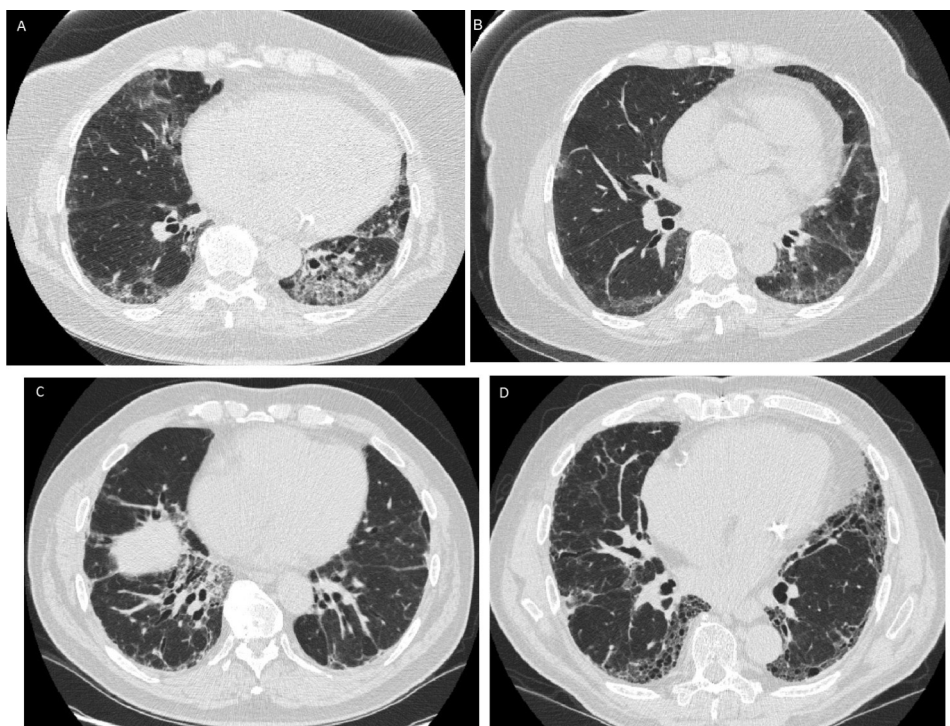


Fig. 1.— CT abnormalities in patients with RA-ILD. Figure illustrates different patterns and abnormalities that can be seen on chest computed tomography: a. Bilateral, basilar predominant ground glass opacities and consolidation; b. Ground glass opacities with reticulations; c. Bilateral reticulations and traction bronchiectasis; d. Honeycombing with reticulations, consistent with the usual interstitial pneumonia pattern

(BAL) in the diagnostic algorithm of RA-ILD. One study found increased cellularity in BAL compared to normal controls, but not when compared with RA patients without ILD⁵¹. In another study, BAL showed an increase in neutrophil percentage, but this correlated poorly with extent of disease on CT scan⁴². BAL can be useful in patients who develop acute or subacute respiratory worsening in the context of RA-ILD in order to rule out opportunistic infection.

Surgical lung biopsy: Surgical lung biopsy as a diagnostic tool is generally not performed in the context of connective tissue diseases (CTD), unless the diagnosis of CTD is unclear or not established. In contrast to the IIPs, where histopathologic subtype is critical to the management of the ILD, ascertaining histopathologic subtype in CTD-ILD, including RA-ILD, is not done. This is primarily because management and treatment of RA-ILD is irrespective of histopathologic phenotype at this time.

Biomarkers: At this time, no biomarker has been shown to be sensitive or specific to RA-ILD disease activity or disease progression. KL-6 (Krebs von den Lungen-6) is a glycoprotein expressed by type-II pneumocytes and epithelial cells. It is a serum indicator for pulmonary fibrosis that has been evaluated in RA-ILD. It was shown to be correlated with reticular opacities and honeycombing on CT scan⁵². However, KL-6 has poor sensitivity in RA-ILD⁵³.

Protein citrullination is thought to be associated with extra-articular manifestations of RA, including RA-ILD⁵⁴. Serum citrullinated proteins Hsp90 isoforms α and β were found to be highly specific for RA-ILD in a cohort of RA patients, but poorly sensitive⁵⁵. This suggests that they may be biomarkers for RA-ILD, although correlation with disease activity and severity has not yet been established.

Treatment

The management of RA-ILD in patients with subclinical disease remains unclear. It is not known whether treatment will alter the course of the disease in these patients. The mainstay of treatment in RA-ILD is immunosuppression. First line therapy is prednisone at high doses, for prolonged duration. Observational studies suggest that there may be benefit in using other forms of immunosuppression, such as steroid sparing agents, in the treatment of RA-ILD. In a cohort of 40 patients with RA-ILD, the addition of disease-modifying anti-rheumatic drugs (DMARDs) to tapering doses of prednisone was associated with improving doses of prednisone in baseline FVC. The DMARDs used by treating physicians in this study included methotrexate, leflunomide and azathioprine⁵⁶. There was no difference in pulmonary function improvement between the different agents used. In a subgroup analysis, patients with a lower

fibrosis score on CT were the ones who had a response to treatment. In this study, patients with RA-UIP had a higher mean fibrosis score. In another cohort of patients, the presence of ILD was associated with an increased odds of developing leflunomide induced pneumonitis and ILD (OR 8.2)⁵⁷.

Anti-TNF alpha agents have been used in RA for several years to treat articular disease. There were reports of increased risk of developing ILD in RA patients using these biologic agents⁵⁸. However, several studies have since demonstrated that these agents do not cause increased risk of developing RA-ILD^{36, 59}.

No study thus far has looked at response to treatment according to histopathologic subtype of RA-ILD. Lung transplant in end stage RA-ILD is being performed in some centers, but no long-term data has been published.

Prognosis

Patients with RA-ILD have an increased mortality compared to patients with RA but no evidence of ILD⁶⁰. Median survival ranges between 3 and 8 years from time of diagnosis of RA-ILD^{40, 41, 43}. Older age, male sex and greater impairment in pulmonary function at diagnosis have been associated with worse prognosis^{32, 37, 41}. In one study, greater RA disease severity was associated with an increased hazard of death in RA-ILD³⁷. Presence of rheumatoid factor and high LDH have also been shown to confer a poorer prognosis⁶¹.

Patients with RA-ILD may experience bouts of acute exacerbations (AE) similar to those reported in other patients with ILD, especially those with RA-ILD and a UIP pattern (RA-UIP)^{62, 63}. The etiology of AE in RA-ILD is unknown. These events are associated with older age at ILD diagnosis, a UIP pattern on HRCT and methotrexate usage. Acute exacerbations are also associated with worse prognosis in RA-ILD⁶³.

As previously mentioned, the underlying histopathologic and/or radiologic phenotype may inform prognosis in RA-ILD. In general, the extent of honeycombing and severity of traction bronchiectasis appear to be independently associated with increasing mortality in fibrotic ILD associated with CTD, especially in patients with RA-ILD⁶⁴. Furthermore, studies have demonstrated that RA-ILD patients with a UIP pattern have a worse prognosis compared to those without UIP^{41, 43, 63}. In one of those studies, the survival in patients with RA-UIP was similar to patients with IPF⁴¹. However, another study demonstrated that when IPF and RA-UIP patients are matched for age, sex, smoking and baseline lung function, RA-UIP patients have a longer survival time compared to IPF patients (median survival, 53 vs. 41 months in RA-UIP vs IPF, respectively, $p = 0.015$)⁶². Another study showed no difference in survival between the UIP and NSIP forms of RA-ILD, but this may be due to limited sample size. Regardless, survival in patients

with fibrotic ILD was reduced compared to non-fibrotic RA-ILD in this study⁴⁰.

ILD is a frequent complication of RA and is associated with increased morbidity and mortality. There are distinct histopathologic subtypes of RA-ILD, which appear to have different clinical phenotypes and natural histories. At this time, it remains unclear if there is benefit to classifying patients by their histopathologic subtype. However, if the pathobiology of UIP in RA-ILD is more similar to that of IPF than in non-UIP forms of RA-ILD, it may be that we are harming a subset of RA-ILD patients with our generalized approach to treatment of RA-ILD⁶⁵. Further research investigating the differences between those with and without UIP pattern in RA-ILD are needed as it may shift our current paradigm of RA-ILD management and treatment to be more in line with what has been established in the idiopathic interstitial pneumonias.

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I believe that everyone participating in a discovery, regardless of the stage at which he or she contributed, should be pleased by its outcome. Unfortunately, as scientific knowledge increases, the temporal impact of important early discoveries is frequently forgotten because they become incorporated into a foundation of facts that serves as the basis for ongoing research.

Creo que cada uno de los involucrados en un descubrimiento, independientemente de la etapa en que él o ella contribuyó, debería alegrarse del resultado. Desgraciadamente, a medida que el conocimiento científico aumenta, el impacto temporal de los muy importantes descubrimientos iniciales es frecuentemente olvidado porque se ven rápidamente incorporados en una colección de datos que sirven de base para la etapa siguiente de la investigación.

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Advancing our knowledge in biochemical genetics and microbiology through studies on tryptophan metabolism. *Ann Rev Biochem* 2001; 70: 37