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Review Article

Interstitial Lung Disease in Rheumatoid Arthritis: Clinical Diagnostic Challenges

Fanny Fachrucha[1], Farhana Syuaib[1], Arini Purwono[1], Fariz Nurwidya[1]

[1]Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Indonesia

Abstract

Interstitial lung disease (ILD) represents a major extra-articular manifestation of rheumatoid arthritis (RA) and is associated with substantial morbidity and mortality. Pulmonary involvement in RA is heterogeneous, affecting the lung parenchyma, airways, pleura, and pulmonary vasculature, with RA-associated ILD (RA-ILD) being the most clinically significant manifestation. RA-ILD may develop after the onset of joint disease or, in some cases, precede articular symptoms, posing diagnostic challenges for clinicians. Multiple factors contribute to RA-ILD development, including genetic susceptibility, environmental exposures, particularly cigarette smoking, and immune-mediated mechanisms involving protein citrullination and autoantibody production. High-resolution computed tomography (HRCT) remains the cornerstone of diagnosis, allowing identification of characteristic interstitial pneumonia patterns such as usual interstitial pneumonia (UIP) and nonspecific interstitial pneumonia (NSIP). However, many RA patients exhibit radiological abnormalities in the absence of respiratory symptoms, and not all detected abnormalities progress to clinically significant disease. Pulmonary function tests, bronchoalveolar lavage, and histopathology provide supportive information but have limitations in screening and diagnosis. A subset of patients develops progressive pulmonary fibrosis, which is associated with worsening respiratory function and increased mortality. The absence of validated screening strategies and the overlap of RA-ILD with other pulmonary conditions further complicate timely diagnosis. This review highlights current diagnostic approaches and emphasizes the challenges in identifying RA-ILD and its progressive forms, underscoring the need for multidisciplinary evaluation and improved risk stratification.

Keywords: Rheumatoid Arthritis, Interstitial Lung Diseases, High Resolution Computed Tomography, Progressive Pulmonary Fibrosis, Diagnostic Challenges

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***Corresponding author**: fanny.fachrucha@gmail.com

Introduction

Interstitial lung disease (ILD) is a serious complication in patients with rheumatoid arthritis (RA). RA is a systemic inflammatory disease that primarily affects the joints but may also involve other organs. Pulmonary involvement is the most common extra-articular manifestation of RA and may occur in 60–80% of patients during the course of the disease. Clinically, RA may affect all components of the lung, including the parenchyma (manifesting as ILD or rheumatoid nodules), the pleura (pleural inflammation and/or effusion), small and large airways, and the pulmonary vasculature. RA with pulmonary involvement, particularly RA-associated ILD (RA-ILD), is associated with significant morbidity and mortality. Pulmonary disease contributes to 10–20% of RA-related mortality.[1,2]

Pulmonary manifestations typically develop after the onset of articular symptoms; however, in some cases, lung involvement precedes joint manifestations. Evaluation of respiratory symptoms in RA patients is challenging due to multiple potential differential diagnoses, including ILD, chronic obstructive pulmonary disease (COPD), bronchiectasis, pulmonary infections related to immunosuppressive therapy, drug-induced pulmonary toxicity, and coronary artery disease. Currently, screening and diagnosis of RA-associated lung disease remain suboptimal. Careful evaluation of RA patients is required, with consideration of other connective tissue diseases when assessing lung disease of unknown etiology. This review discusses current diagnostic approaches to RA-ILD and the challenges clinicians face in establishing the diagnosis. [1–3]

Pulmonary Involvement in Rheumatoid Arthritis

In RA patients, the most frequently detected pulmonary abnormality on high-resolution computed tomography (HRCT)

is pleural effusion**.** Other HRCT findings associated with interstitial and airway abnormalities may also be present. Respiratory manifestations generally appear within the first five years of disease onset. [1] The prevalence and clinical features of pulmonary involvement in RA are summarized in **Table 1**.

Table 1. Prevalence and Clinical Findings of Pulmonary Involvement in Rheumatoid Arthritis[1]

Phenotype	Clinical Features	Prevalence
Parenchymal Abnormalities		
UIP Pattern	Radiologic features: subpleural distribution, basal-predominant reticulation, honeycombing, minimal ground-glass opacities (GGO), and traction bronchiectasis	8-66%
NSIP Pattern	Extensive ground-glass opacities, traction bronchiectasis, and subpleural sparing	19-57%
Organizing Pneumonia	Focal ground-glass opacities, consolidation, and reversed halo sign	0-11%
Other patterns (lymphocytic interstitial pneumonia (LIP) and desquamative interstitial pneumonia (DIP))	Cysts, centrilobular nodules, ground-glass opacities, and peribronchovascular septal thickening, predominantly in the upper lobes	Rare
Rheumatoid Nodules	Variable in size; may present as solitary or multiple nodules	<1% radiologically
Caplan Syndrome	Complications associated with pneumoconiosis are characterized by multiple nodules predominantly distributed in the peripheral lung regions	<1% in the United States based on autopsy studies
Airway Disease		
Upper Airway Disease		
Cricoarytenoiditis	Cricoarytenoid arthritis causing hoarseness to stridors	Laryngoscopic findings in 32–75% and CT findings in 54–72%
Lower Airway Disease		
Bronchiectasis	Associated with chronic infection	Approximately 30%; some cases are asymptomatic
Bronchiolitis	More common in women, associated with high RF titers and long-standing rheumatoid arthritis	8-30%
Pleural Disease		
Pleural Effusion	Typically occurs in young adult males with positive RF titers. Pleural fluid characteristics: generally sterile exudate with low pH (<7.3), glucose <60 mg/dL, and elevated LDH levels	Clinically 3–5%

Risk Factors for ILD in Rheumatoid Arthritis

Genetic, clinical, serological, and environmental factors have been associated with RA-ILD. The incidence of ILD in RA patients is five times higher than in control populations within five years of RA diagnosis. The reported risk of RA progressing to ILD ranges from 6% to 15%**.** ILD may precede articular manifestations. Hyldgaard et al. reported that 14% of RA-ILD patients were diagnosed with ILD 1–5 years before RA diagnosis**.**[3,4]

Genetic Factors

The human leuckocyte antigen (HLA)-DRB1 allele is the most significant genetic risk factor identified to date, particularly in patients who are positive for rheumatoid factor (RF) or anti–citrullinated protein antibodies (ACPA). RA patients carrying HLA-DR alleles share similar amino acid sequences in the HLA-DRB region, which are associated with anti–cyclic citrullinated peptide (anti-CCP) antibodies.[1,3]

Several genetic studies have identified variants associated with pulmonary fibrosis (PF). The MUC5B promoter variant, found in RA-ILD, familial idiopathic pulmonary fibrosis (IPF), and other fibrotic ILDs, represents the strongest genetic risk factor for IPF, present in up to 50% of patients. MUC5B plays a role in airway clearance and host defense. Additional mutations associated with RA-ILD include TERT, RTEL1, PARN, and SFTPC.[1,3].

Age and Sex

Age >65 years has been reported as a risk factor for RA-ILD. Although RA is more prevalent in women, RA-ILD is more common in men, with a male-to-female ratio of approximately **2:1**. RA-ILD patients have a threefold increased risk of early mortality compared with RA patients without ILD, with a median survival of three years after ILD diagnosis.[1,3]

Environmental Factors

Among environmental risk factors, cigarette smoking is the most significant contributor to RA-ILD. Long-term smoking exposure influences the severity of articular manifestations in RA. Patients with a smoking history of >25 pack-years have a 3.1-fold increased risk of RF positivity and a 2.4-fold increased risk of joint erosions.[1,3]

Proinflammatory particles in cigarette smoke stimulate protein citrullination in the lung. This process alters amino acid structure, rendering proteins immunogenic. A Swedish case-control study demonstrated that smoking combined with HLA-DR alleles increases the risk of RA by up to 21-fold. Exposure to silica and coal dust may also induce pulmonary inflammation, leading to progressive fibrosis.[1,3]

Pathogenesis of ILD in RA

Pulmonary involvement in RA results from interactions among genetic predisposition, environmental exposures, and autoimmune mechanisms, leading to abnormal responses in lung parenchyma and alveolar walls. Airways, alveolar epithelial cells, pulmonary fibroblasts, and extracellular matrix structures are involved in RA-ILD pathology. Restrepo et al. identified increased susceptibility to RA-ILD in smokers carrying the HLA-DRB1 shared epitope, which also increases the risk of RA and anti-CCP positivity. Other HLA variants associated with RA-ILD include HLA-DQB1 and HLA-A**.**(Figure 1)[1,3].

Smoking injures respiratory epithelium and vascular endothelial cells, stimulating protein citrullination in the lung. Citrullination converts arginine to citrulline, which is recognized as an antigen by the immune system. Genetically predisposed individuals produce ACPA, a hallmark antibody in RA. The lung may represent the initial site of immune dysregulation in smokers, leading to RA development.[1,3]

Paulin et al. proposed two pathways leading to RA-ILD. First, immune reactions in RA occur not only in joints but also in the lung due to protein citrullination, leading to fibroblast activation and fibrosis, typically manifesting as NSIP. Second, aging alveolar epithelial cells secrete profibrotic mediators in genetically predisposed individuals, resulting in a fibrotic-dominant phenotype such as UIP. ACPA produced in the lung may also affect other citrullinated tissues, including synovium.[1,3]

Some studies suggest that RA may originate at mucosal sites (oral cavity, airways, gastrointestinal tract) before joint involvement. This hypothesis is supported by the detection of IgA ACPA in sputum samples and higher ACPA concentrations in bronchoalveolar lavage (BAL) fluid compared with serum, along with immune activation in bronchial tissue.[1,3] Recent studies by Zhang et al. demonstrated the role of interleukin (IL)-17 in the pathogenesis of RA-ILD and IPF. Th17 cytokines such as IL-17A and transforming growth factor (TGF)-β1 promote fibrosis by inducing fibroblast proliferation and extracellular matrix production. Protein citrullination was observed in 44% of IPF and 46% of RA-ILD cases. However, genetic factors such as HLA-DR distinguish RA-ILD by promoting ACPA involvement and articular disease, making immune dysregulation central to RA-ILD pathogenesis.

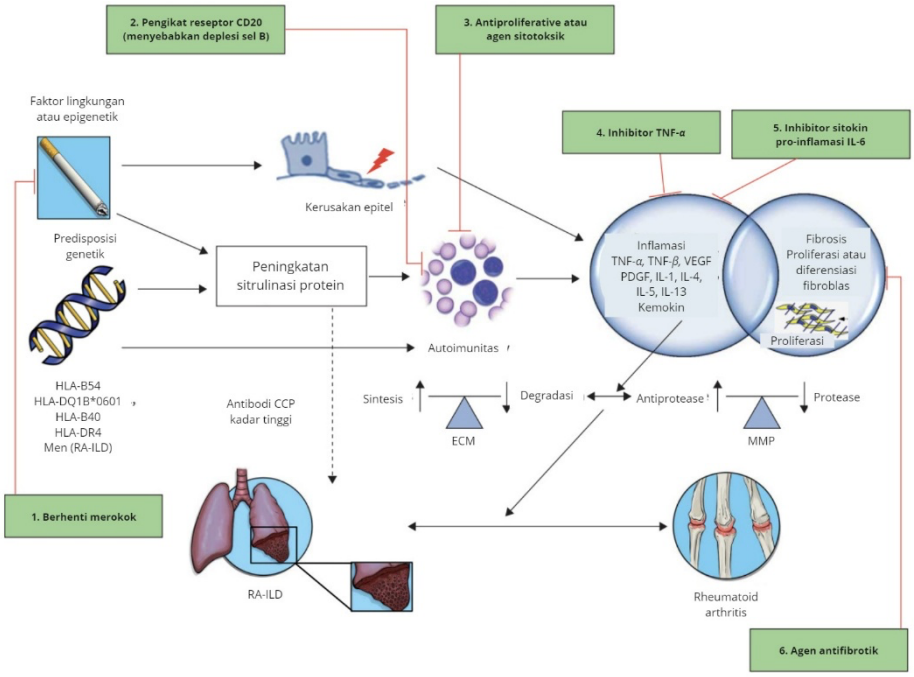

Figure 1. Pathogenesis of RA-ILD[1]

Diagnosis of Interstitial Lung Disease in RA

Diagnosis of ILD in patients with established or suspected RA requires a multidisciplinary approach involving radiologists, pathologists, rheumatologists, and pulmonologists. Potential etiologies such as hypersensitivity pneumonitis, pneumoconiosis, other connective tissue diseases, and environmental exposures must be excluded.(Figure 2)[1]

Imaging

RA evaluation, followed by HRCT, which is the gold standard. HRCT identifies interstitial pneumonia patterns, airway disease, pleural abnormalities, and other parenchymal changes, including nodules, bronchiectasis, and vascular abnormalities. HRCT is also essential for disease monitoring.[1,3]

Four ILD patterns are commonly identified on HRCT: UIP (37%), NSIP (30%), obliterative bronchiolitis (17%), and organizing pneumonia (OP) (8%). UIP typically shows subpleural basal predominance, reticulation, honeycombing, traction bronchiectasis, minimal GGO, and air trapping on expiration. NSIP is characterized by basal-predominant GGO without honeycombing. Rare patterns include OP, diffuse alveolar damage, lymphocytic interstitial pneumonia, and desquamative interstitial pneumonia. HRCT analysis reveals emphysema in 35% of IPF and 50% of RA-ILD patients with smoking history.[1,3] patients with respiratory symptoms should undergo chest radiography as an initial examination.

Pulmonary Function Testing

Pulmonary function tests, particularly diffusing capacity for carbon monoxide (DLCO), can detect lung involvement. Abnormal pulmonary function is observed in 45–65% of RA patients, with or without respiratory symptoms. Findings include airway obstruction, restriction (5–20%), and DLCO impairment (20–45%). Many abnormalities are clinically insignificant, and most patients are asymptomatic. There are no established screening recommendations for lung disease in RA, and management of mild pulmonary dysfunction remains challenging.[3]

Bronchoalveolar Lavage

BAL findings in RA-ILD are often abnormal but nonspecific. Lymphocytosis is commonly observed, whereas neutrophilia is more frequent in UIP. BAL is not a diagnostic tool but is useful to exclude infection in cases of acute deterioration.[1,3]

Histopathology

Lung biopsy should be considered after careful risk–benefit assessment and is generally reserved for cases with inconclusive HRCT findings. UIP can often be diagnosed radiologically, obviating the need for biopsy. UIP histology is found in 61% of RA-ILD cases. Biopsy may identify NSIP, OP, DIP, or LIP. Acute exacerbations may show superimposed diffuse alveolar damage.[1,3]

RA-UIP biopsies typically show fewer fibroblastic foci, abundant germinal centers, and increased $CD4^+$ lymphocytes compared with IPF. Recurrent follicular bronchiolitis, rheumatoid nodules, and chronic pleuritis may also be present.[1,3]

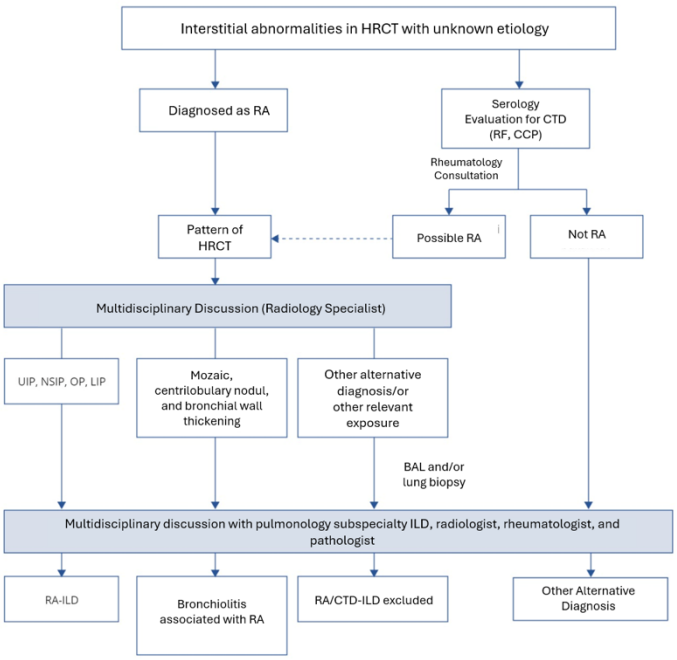

Figure 2. Diagnostic algorithm for RA with pulmonary involvement

Pulmonary Progressive Fibrosis (PPF) in RA

Definition of PPF

PPF is characterized by worsening interstitial lung disease despite adequate treatment, marked by progressive respiratory symptoms, declining quality of life, deteriorating lung function, progressive fibrosis, and premature mortality. In PPF, fibrosis progresses independently of the initial trigger or underlying disease.[5,6]

Epidemiology of PPF in RA-ILD

International surveys report that 18–32% of non-IPF ILD patients develop progressive fibrosing ILD (PF-ILD). Systematic reviews estimate that 24% of ILD patients develop a progressive fibrotic phenotype. In RA-ILD, approximately 40% of patients develop chronic progressive fibrosis. A multidisciplinary discussion is required for diagnosis. One study reported progressive RA-ILD in 20% of patients, while 40% of patients with honeycombing on HRCT developed progressive disease. Earlier studies reported progression rates of 23–52%.[5,7]

Challenges in Diagnosing RA-ILD

No validated screening program for RA-ILD currently exists. Pulmonary screening should be part of RA evaluation, and patients with respiratory symptoms should be promptly referred for further pulmonary assessment, including evaluation for COPD, bronchiectasis, and infection.[3] RA patients may exhibit HRCT abnormalities without respiratory symptoms, and not all parenchymal abnormalities progress to clinically significant ILD. Approximately 33–61% of patients with HRCT-detected ILD are asymptomatic. Poorly controlled RA may limit physical activity, mimicking respiratory symptoms. Acute exacerbations of RA-ILD occur at an incidence of 2.8% per year and may resemble severe respiratory infections, potentially exacerbated by environmental allergens. [3] Improved understanding of risk factors for progressive RA-ILD may facilitate early identification of high-risk patients, allowing closer monitoring and earlier initiation of antifibrotic therapy. [1–3]

Conclusion

Rheumatoid arthritis–associated interstitial lung disease remains a complex and clinically challenging condition. Pulmonary involvement in RA is common, heterogeneous, and often underrecognized, particularly in asymptomatic patients. RA-ILD arises from the interaction of genetic predisposition, environmental exposures such as smoking, and immune dysregulation, resulting in diverse radiologic and histopathologic patterns. HRCT is central to diagnosis and monitoring, while pulmonary function testing and invasive procedures play complementary roles in selected cases. The lack of standardized screening protocols and the potential for disease progression, including the development of progressive pulmonary fibrosis, contribute to diagnostic uncertainty and delayed management. Multidisciplinary collaboration is essential to distinguish RA-ILD from other pulmonary conditions and to identify patients at risk for progression. Improved understanding of risk factors and disease behavior may facilitate earlier recognition and closer monitoring of high-risk individuals.

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