



Published in final edited form as:

Rheum Dis Clin North Am. 2015 May ; 41(2): 225–236. doi:10.1016/j.rdc.2014.12.004.

Lung Disease in Rheumatoid Arthritis

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Keywords

Rheumatoid arthritis; Extra-articular disease; Pulmonary; Interstitial lung disease; Interstitial pneumonia; Bronchiolitis; Pleural effusion; Drug-induced lung disease

INTRODUCTION

Rheumatoid arthritis (RA) is a progressive, systemic autoimmune disorder characterized by articular and extra-articular manifestations. The lung is commonly a site of extra-articular disease. Within the lung, manifestations of RA vary and may include airways, parenchymal, vascular, and/or pleural disease (Box 1). Manifestations of lung disease in RA typically follow the development of articular disease, but in some instances lung involvement is the first manifestation of RA and is the most aggressive feature of the disease.¹ Clinicians should therefore remain alert to the possibility of lung disease in all patients with RA.

EPIDEMIOLOGY

RA is the most common connective tissue disease (CTD), with a prevalence of 0.5% to 2% in the general population.² The disease occurs more frequently in women than in men with a ratio of 3:1. Extra-articular disease occurs in approximately 50% of patients, with the lung being a common site of involvement.³ Lung involvement may occur in as many as 67% of patients, although some reports indicate a lower incidence (around 10%–20%).^{4–6} This wide variation reflects differences in study design, study populations, and the way that lung disease in RA is defined. Many patients with RA have no clinical symptoms of respiratory disease despite radiographic or physiologic evidence of lung abnormalities, often leading to a misrepresentation of disease prevalence. In a study of 52 patients with RA, high-resolution computed tomography (HRCT) abnormalities were identified in 67.3% with only 40% of patients having respiratory symptoms.⁴ In addition to respiratory involvement from RA, medication toxicity and secondary pulmonary infections are important sources of lung disease that must be considered in patients with RA.

Mortality is increased in patients with RA with extra-articular manifestations relative to those without extra-articular involvement, with cardiovascular disease, infection, and lung

disease being the leading causes. Mortality in RA is greatest within the first 5 to 7 years after diagnosis and risk may be slightly higher in men than in women, with a mortality ratio of 2.07:1.97 respectively.^{7,8} Lung disease alone accounts for 10% to 20% of deaths in patients with RA, and most of these are attributed to interstitial lung disease (ILD).⁹⁻¹¹

FORMS OF LUNG DISEASE IN RHEUMATOID ARTHRITIS

Interstitial Lung Disease

ILD refers to heterogeneous group of parenchymal lung disorders classified by distinct clinical, pathologic, and radiographic features. The 2013 American Thoracic Society/ European Respiratory Society official classification of the idiopathic interstitial pneumonias (IIPs) outlines the most recent histopathologic classifications of ILD, many of which may be seen in RA.¹² The most common forms of ILD associated with RA are usual interstitial pneumonia (UIP) and nonspecific interstitial pneumonia (NSIP); however, organizing pneumonia (OP), desquamative interstitial pneumonia, lymphocytic interstitial pneumonia, diffuse alveolar damage, and acute interstitial pneumonia have been reported.^{13,14} Smoking, advanced age, high-titer anticyclic citrullinated peptide antibodies, high-titer rheumatoid factor, family history of RA, and in some studies male gender are all risk factors for developing RA-ILD.¹⁵

Pathophysiology

The pathophysiologic basis for development of ILD in patients with RA remains elusive. Available data suggest a role for both environmental and genetic factors. Specific human leukocyte antigen (HLA) variants including HLA-B54, HLA-DQB1*0601, HLA-B40, and HLA-DR4 have been associated with RA-ILD.¹⁶⁻¹⁹ Similarly, cigarette smoking has been linked with both RA and RA-ILD.^{20,21} Some speculate that the lungs may be a site of initial immune dysregulation that leads to the development of RA.²² Citrullinated proteins have been identified in bronchoalveolar lavage fluid from cigarette smokers without RA, and RA-related autoantibodies are detectable in the sputum of patients identified to be at risk for RA.^{23,24}

It is hoped that investigations of biomarkers for RA-ILD will identify key molecules and thus provide more insight into disease immunopathogenesis and avenues for early diagnosis. To date, serum autoantibodies against multiple citrullinated proteins and peptides including fibrinogen, vimentin, and citrullinated isoforms of heat shock protein 90 and matrix metalloproteinase 1 (MMP-7) and interferon-gamma inducible protein 10²⁵⁻²⁷ have been associated with RA-ILD. The precise role of these proteins in tissue-specific disease manifestations is not known.

Prognosis and mortality

Information pertaining to the natural history of RA-ILD relies on data from a limited number of studies and more data are needed to confidently characterize prognosis and mortality within this population. The available studies indicate that patients with RA-ILD have a 3-fold increased risk of death relative to those without ILD. In addition, although overall mortality from RA seems to be decreasing, mortality from RA-ILD seems to be

increasing, particularly in women and in older age groups.^{28,29} A study of 582 patients with RA identified a median survival of 2.6 years in those with ILD compared with 10 years in age-matched patients with RA without ILD.²⁹ Within the category of RA-ILD, prognosis varies significantly depending on the precise histopathologic form of RA-ILD and from patient to patient. UIP is the most common subtype of RA-ILD and carries the worst prognosis,^{1,14,30} which differs from CTDs overall, in which the most common pattern of ILD is NSIP.¹ High-quality studies of additional factors that influence prognosis are lacking. A recent systematic review of current literature investigating predictors of mortality in RA-ILD included 10 studies and found that male gender, older age, lower lung diffusion capacity for oxygen (DLCO), a finding of UIP, and the extent of fibrosis were significant predictors of mortality.³¹

Clinical features

Exertional dyspnea and cough of insidious onset are the predominant clinical symptoms of RA-ILD. Fatigue and generalized weakness are also frequently seen. Radio-graphic evidence of ILD on HRCT precedes the development of respiratory symptoms in a significant number of patients with RA and time to development of symptoms for patients with subclinical ILD is not known. Given the prevalence of lung involvement in RA, clinicians should have a low threshold to pursue evaluation of new respiratory complaints in this population.²⁰ Once present, symptoms usually progress over time; however, the rate of progression is variable from patient to patient and within the different histopathologic forms of ILD. Studies indicate that patients with UIP may progress faster than other subtypes of ILD in RA and at rates similar to those reported for idiopathic pulmonary fibrosis (IPF).^{14,32}

Radiographic features

HRCT has increased the diagnostic sensitivity and accuracy for RA-ILD greatly compared with chest radiograph alone. In a study of 150 consecutive individuals with RA, HRCT evidence of ILD was seen in 19% of patients; however, bilateral inter-stitial infiltrates were seen on chest radiograph in less than 3%.⁶ The most common radiographic finding is a UIP pattern, which is characterized on HRCT by peripheral basilar predominant reticular abnormalities, honeycombing, traction bronchiectasis, and minimal to no ground-glass opacification (Fig. 1). NSIP is the other common pattern in RA-ILD and is characterized by reticulation and ground-glass with little or no architectural distortion or honeycombing (Fig. 2).

Diagnostic evaluation

Early symptoms of respiratory disease, particularly dyspnea on exertion, may be difficult to ascertain in patients with exercise-limiting joint disease. Clinicians should therefore remain alert to subtle symptoms, including new cough, change in activity level, or low resting oxygen levels. The initial diagnostic evaluation for patients with RA with respiratory symptoms includes an assessment of lung physiology with pulmonary function tests (PFTs), radiographic imaging with HRCT, and assessment of the patient's oxygenation both at rest and with activity. Initial PFTs should include components of lung volume, airflow with bronchodilator challenge, and DLCO measurements. For initial imaging, HRCT imaging is recommended rather than chest radiograph for its superior sensitivity in detecting early

parenchymal disease and small airways disease.^{6,33} Lung biopsy is not indicated in most cases of RA-ILD; however, if the diagnosis is uncertain or computed tomography findings are atypical, surgical lung biopsy may be useful. Transbronchial biopsies have low yield and are generally not performed, although they may be helpful for the purpose of ruling out drug-related disease or infection. For all patients with diffuse parenchymal disease, infection and drug-induced disease must be ruled out before making a diagnosis of ILD. Numerous medications used in the treatment of RA have reported pulmonary toxicities (Table 1).

Treatment

No randomized placebo-controlled therapeutic trials have been performed to date in RA-ILD. As such, no consensus therapeutic guidelines have been established. Our practice is to monitor these patients closely for progression of disease and initiate treatment when clinical symptoms manifest or when there is physiologic evidence of progressive disease. In all cases, risk of therapy must be weighed against threat of disease.

Current treatment regimens usually involve corticosteroid therapy with or without a cytotoxic agent; most commonly azathioprine, mycophenolate mofetil (MMF), or cyclophosphamide. Recent retrospective analyses centered on treatment of RA-ILD with MMF and rituximab have shown promising results. In a study of 125 patients with CTD-related ILD treated with MMF, subgroup analysis of 18 patients with RAILD identified a trend toward improved forced vital capacity following initiation of therapy.³⁴ Further, this drug has shown good patient tolerability and safety in patients with CTD-ILD.^{34,35} Retrospective studies with rituximab have recently shown success in cases of refractory CTD-ILD,^{36,37} although larger prospective studies are needed to validate these findings in patients with RA-ILD. Limited reports also exist for treatment with cyclosporine, methotrexate, and tumor necrosis factor (TNF) alpha inhibitors.³⁶⁻⁴¹ Response to therapy in RA-ILD seems to correlate with histopathologic form of disease. As in IIPs, NSIP shows better response to therapy and prognosis than a UIP pattern.^{1,14} Note that control of joint disease does not translate to control of lung disease, and optimal management requires a coordinated approach between an experienced pulmonologist and rheumatologist.

All patients with RA-ILD should be encouraged to abstain from smoking. Smoking-related lung disease should be treated if present. Oxygenation should be evaluated during rest, ambulation, and sleep and supplemental oxygen should be prescribed as indicated. Vaccinations for influenza and pneumococcal pneumonia are recommended for all patients. We also recommend prophylaxis against *Pneumocystis jiroveci* pneumonia for all patients on immunosuppressive therapy. In managing the articular manifestations in patients with RA-ILD, methotrexate use should generally be avoided because of well-documented pulmonary toxicity. TNF-alpha inhibitors should be used with caution in these patients following reports of increased rates of lung toxicity with these agents.^{42,43} In spite of these reports, a prospective observational study of 367 patients with RA-ILD showed no increase in mortality following treatment with anti-TNF agents compared with standard immunomodulatory agents.⁴⁴ Patients with progressive disease should be considered for lung transplant evaluation. Survival rates after transplant for RA-ILD are similar to those for IPF and with significant improvements in quality-of-life scores following transplantation.⁴⁵

Airways Involvement (Bronchiolitis, Bronchiectasis, and Cricoarytenoid Disease)

Prevalence of airways disease in RA is high; it occurs in 39% to 60% of patients.^{46–48} Any part of the airway may be involved, including the large airways (upper and lower) and distal small airways. The most common manifestations are bronchiectasis, bronchiolitis, airway hyperreactivity, and cricoarytenoid arthritis. PFTs and HRCT obtained with expiratory images are useful in making a diagnosis of airways involvement with HRCT, showing greater sensitivity for detection of small airways disease relative to PFTs.³⁴

Cricoarytenoid arthritis and bronchiectasis are the most common forms of large airway involvement. Cricoarytenoid abnormalities occur in as many as 75% of patients, although fewer have clinically significant symptoms.⁴⁹ Arthritis of the cricoarytenoid joints leads to midline adduction of the vocal cords with resultant hoarseness and in some cases inspiratory stridor. Bronchiectasis, defined as destruction and widening of the large airways, occurs in 16% to 58% of patients with RA.^{50,51} Most cases are not clinically significant but, when present, symptoms include cough and sputum production. Treatment of these patients with a biologic agent has been reported as an independent risk factor for lower respiratory tract infection.⁵²

Small airways disease refers to disease involving the distal airways (2 mm in diameter or less). Two forms of small airways disease (follicular bronchiolitis and constrictive bronchiolitis) have been described in association with RA. Follicular bronchiolitis is identified pathologically by the presence of hyperplastic lymphoid follicles with reactive germ cell centers within bronchiole walls. Constrictive bronchiolitis (also referred to as obliterative bronchiolitis) is identified by concentric narrowing of membranous and respiratory bronchioles caused by peribronchiolar inflammation and fibrosis without evidence of lymphoid hyperplasia.⁵³ There are limited reports regarding disease course and prognosis for RA-associated follicular and constrictive bronchiolitis. Prognosis is thought to be poor; however, in a recent prospective study in CTD-associated bronchiolitis (in which 50% of patients had RA), the forced expiratory volume in 1 second showed stability over time in both forms, suggesting that bronchiolitis associated with CTD may have a less aggressive course than idiopathic disease.^{54,55}

Rheumatoid Nodules

Rheumatoid necrobiotic nodules are pulmonary lesions histologically composed of a central fibrinoid necrotic region surrounded by mononuclear cells, granulation tissue, lymphocytes, plasma cells, and fibroblasts. The nodules may be single or multiple and are typically found in pleural or subpleural regions, occasionally with cavitation.^{56,57} Rheumatoid nodules carry good prognosis and may come and go over time. Neoplasm and infection should be ruled out, but once a diagnosis is made no specific therapy is typically required.

Vascular Disease

Pulmonary arterial hypertension is exceedingly rare in RA. It is more commonly seen in other CTDs such as scleroderma and systemic lupus erythematosus.⁵⁸ The most common form of vascular involvement in RA is rheumatoid vasculitis, which is characterized pathologically by the presence of a destructive inflammatory infiltrate within small and

medium-sized blood vessel walls. This condition carries significant morbidity and mortality, but primary involvement of the lung is rare.⁵⁹

Pleural Involvement

Pleuritis and pleural effusions are the most common forms of pleural disease in RA. RA effusions are exudative and sterile, often with low glucose (80%) and low pH (71.4%).⁶⁰ A cytologic finding of elongated macrophages and multinucleated giant cells alongside granulomatous debris is pathognomonic for rheumatoid effusions.⁶¹ These findings mirror those in rheumatoid synovitis or rheumatoid nodules. Occasionally, pleural involvement may precede joint disease. Pleural effusions often resolve spontaneously over time. As with rheumatoid lung nodules, infection and malignancy should be considered and ruled out, if appropriate.

FUTURE CONSIDERATIONS/SUMMARY

RA is a common disorder with a myriad of pulmonary manifestations. Although any compartment of the respiratory system is at risk, the ILDs cause the greatest concern. In its most severe form, affected patients can develop a fibrotic ILD with progression similar to that seen in IPF. Treatment is based on expert opinion and there are no placebo-controlled trials. In order to effectively care for these patients, a better understanding is needed of the link between synovitis and pulmonary disease. Predictors of lung involvement, biomarkers to clinically phenotype patients, and well-designed treatment trials are urgently needed.

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Box 1 Pulmonary manifestation of RA

Interstitial lung disease

- Usual interstitial pneumonia
- Nonspecific interstitial pneumonia
- Organizing pneumonia
- Lymphocytic interstitial pneumonia
- Acute interstitial pneumonia

Airways disease

- Follicular bronchiolitis
- Constrictive bronchiolitis (obliterative bronchiolitis)
- Bronchiectasis
- Cricoarytenoid arthritis

Rheumatoid nodules

Pleural disease

- Pleuritis
- Pleural effusion
- Pneumothorax
- Empyema

Vascular disease

- Pulmonary hypertension
- Vasculitis

Rheumatoid pneumoconiosis (Caplan syndrome)

Drug toxicity

Infection

Amyloidosis

Fibrobullous disease

KEY POINTS

- Rheumatoid arthritis commonly affects the lungs and can involve any compartment of the respiratory system.
- Usual interstitial pneumonia and nonspecific interstitial pneumonia are the most common patterns seen with interstitial involvement in rheumatoid arthritis.
- Treatment consists of long-term therapy with immunomodulatory agents.
- Further studies are needed to better characterize patients, predict progression, and determine optimal therapeutic regimens.

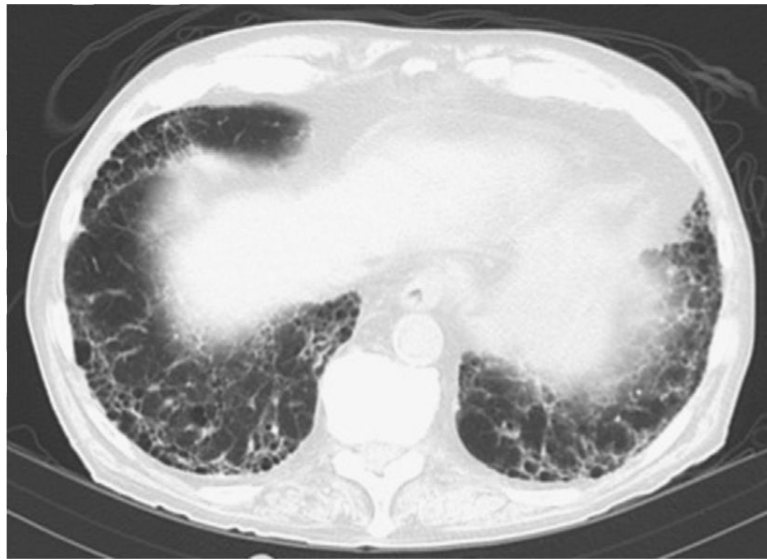


Fig. 1. UIP in RA. The UIP pattern consists of peripheral basilar predominant reticular abnormalities, honeycombing, traction bronchiectasis, and minimal to no ground-glass opacification.

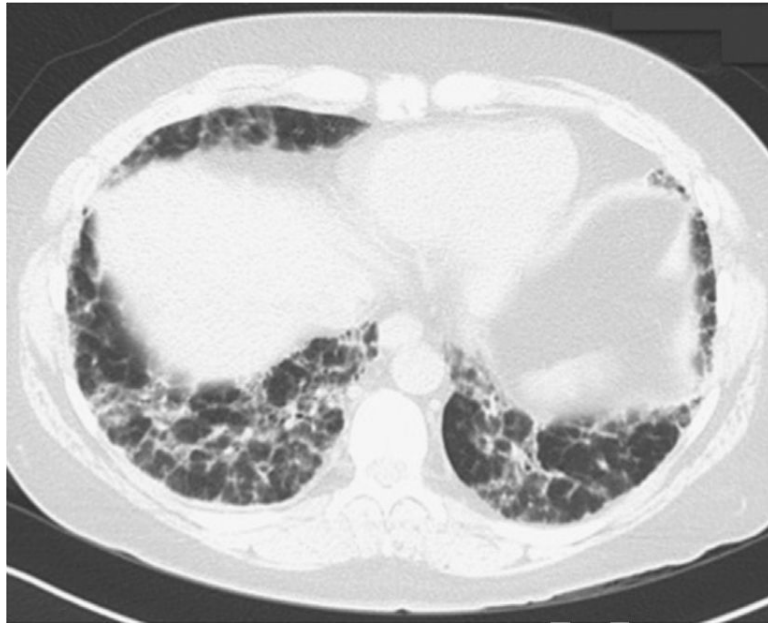


Fig. 2. Nonspecific interstitial pneumonia in RA. The nonspecific interstitial pneumonia pattern consists of reticulation and ground-glass with little or no architectural distortion or honeycombing.

Table 1

Lung toxicity of rheumatoid therapies

Medication	Symptoms	Radiopathologic Findings	Incidence
Methotrexate	Dyspnea, cough, fever ⁶²	Common: bilateral interstitial granulomatous infiltrates with ground-glass opacification on chest CT ⁶² Uncommon: unilateral infiltrates, pleural effusions, reticulonodular disease, hilar lymphadenopathy ⁶³⁻	0.3%-11.6% ⁶⁷ Most cases occur within 2 y of drug initiation and may occur after a single dose ⁶⁸
Anti-TNF	Dyspnea	Aseptic granulomatous pulmonary nodules, both noncaseating and necrotizing ^{69,70} Accelerated interstitial lung infiltrates ^{42,43} Bronchospasm ⁷¹	ILD, 0.5%-3% ⁷²
Leflunomide	Dyspnea, fever, cough ⁷³	Diffuse or patchy ground-glass opacities. Often with septal thickening ⁷⁴	ILD, <1% ⁷³ 2-fold increased risk of new ILD seen in those with prior methotrexate use ⁷⁵
Rituximab	Dyspnea	Acute/subacute OP ⁷⁶ Acute respiratory distress syndrome ⁷⁶	Unknown
Sulfasalazine	Dyspnea, cough	Variable. Most commonly, eosinophilic pneumonia and peripheral eosinophilia ⁷⁷ Interstitial fibrosis ⁷⁸	Unknown
Tocilizumab	—	OP ⁷⁹ Exacerbation of ILD ⁸⁰ Allergic pneumonitis ⁸¹	Unknown

Abbreviations: CT, computed tomography; TNF, tumor necrosis factor.