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Diffuse lung involvement in rheumatoid arthritis: a respiratory physician's perspective

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Abstract

The lungs are one of the most common extra-articular organs involved in rheumatoid arthritis (RA), which is reported to occur in up to 60% to 80% of RA patients. Respiratory complications are the second leading cause of death due to RA. Although there is a wide spectrum of RA-associated respiratory diseases, interstitial lung disease is the most common manifestation and it impacts the prognosis of RA. There has been progress in understanding the management and progression of rheumatoid arthritis-associated interstitial lung disease (RA-ILD) and RA-associated respiratory diseases recently, for example, opportunistic pulmonary infectious diseases and toxicity from RA therapies. From a chest physicians' perspective, we will update the diagnosis and treatment of RA-associated ILD, methotrexate-associated lung disease, and the complication of *Pneumocystis jiroveci* pneumonia in RA in this review.

Keywords: Interstitial lung disease; Lung; Methotrexate pneumonitis; *Pneumocystis jiroveci* pneumonia; Rheumatoid arthritis

Introduction

Rheumatoid arthritis (RA) is a common autoimmune disease typically manifested by symmetric swelling and pain in the small joints of the hands and feet.[1] The lungs are one of the most common extra-articular organs involved in RA.[2,3] Lung involvement is reported to occur in up to 60% to 80% of RA patients. Most people develop pulmonary manifestations after or simultaneously with joint symptoms; however, up to 20% of cases present with thoracic disease followed by articular disease.[2,4] Respiratory complications are the second leading cause of death due to RA.[2]

There is a wide spectrum of RA-associated respiratory diseases [Table 1]. These include interstitial lung diseases (ILD), airway diseases, rheumatoid nodules, pleural diseases, and vasculitis. Thoracic involvement, especially ILD is a marker of poor prognosis in RA patients.[5] Secondary respiratory infection, for example, *Pneumocystis jirovecii* pneumonia (PJP) and drug-associated pulmonary disease are other common complications of RA patients, which also impact prognosis.[6-9] There has been recent progress in understanding the management and progression of rheumatoid arthritis-associated interstitial lung disease (RA-ILD) and RA-associated respiratory diseases. ILD, opportunistic pulmonary infectious diseases, and toxicity from medications are the common causes of diffuse pulmonary disease of RA. Although ILD is the most common manifestation of respiratory involvement of RA, it is important to differentiate RA-ILD from PJP and drug-induced pulmonary disease. Because pulmonologists play an important role during the treatment of RA-associated respiratory diseases, they should have an understanding of these challenging problems.

From a chest physician's perspective, we will update the diagnosis and treatment of diffuse lung diseases associated with RA, focusing on RA-associated ILD, methotrexate-associated lung disease, and the complication of PJP in RA.

RA-associated ILD

ILD is the most common manifestation of RA-associated lung disease, and it is a potentially life-threatening complication of RA. ILD is diagnosed in 5% to 63% of

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Table 1: Spectrum of RA-associated respiratory diseases.

Classifications	Diseases
Interstitial lung diseases	Usual interstitial pneumonia
	Non-specific interstitial pneumonia
	Organizing pneumonia
	Lymphocytic interstitial pneumonitis
	Desquamative interstitial pneumonia
	Diffuse alveolar hemorrhage
Pulmonary rheumatoid nodules	
Airway disease	Bronchiolitis
	Bronchiolitis obliterans
	Follicular bronchiolitis
	Bronchiectasis
Pleural disease	Pleuritis
	Pleural effusion
	Pleural rheumatoid nodules
	Pneumothorax
	Bronchopleural fistula
Vascular disease	Pulmonary hypertension
	Pulmonary vasculitis
	Thromboembolic diseases
Malignant diseases	Lung cancer
	Pulmonary lymphoproliferative disorders
Treatment-associated lung disease	Drug-induced lung diseases
	Methotrexate pneumonitis
	Opportunistic infectious pulmonary diseases

RA: Rheumatoid arthritis.

RA patients. The prevalence varies depending on whether ILD is defined by chest X ray (<5%), clinical symptoms (10%), pulmonary function tests (PFTs) (33%–41%), or high-resolution computed tomography (HRCT) (20%–63%).[10,11] The reported prevalence of ILD also differs among autopsy, hospital, and community-based studies.[12] For these reasons, it is difficult to definitively define the prevalence of RA-ILD.

Clinical manifestations

The symptoms of RA-ILD are non-specific and insidious and can be masked by joint manifestations that may limit activity. Subclinical ILD has been reported in 19% to 67% of cases.[13] Because of these limitations, early RA-ILD may be unrecognized by clinicians. Delayed diagnosis and treatment of RA-ILD is a poor prognostic factor for RA-ILD. The recognition of risk factors for RA-ILD, sensitive serum biomarkers, for example, anti-cyclic citrullinated peptide (CCP) and Krebs von den Lungen-6 (KL-6), and clinical examination may aid the diagnosis of RA-ILD in early stages.

Screening for ILD has been recommended for RA patients with factors reported to increase the risk for developing ILD. These include a history of current or past smoking, male, select human leukocyte antigen (HLA) variants (including HLA-B54, HLA-DQB1*0601, HLA-B40, and HLA-DR4), high titers of anti-CCP antibody, and presence of the mucin 5 subtype B (*MUC5B*) promoter variant (rs35705950).[14-16] Detailed inquiry about common ILD symptoms (dry cough, exertional dyspnea, exercise limitation, and auscultatory crackles) is central to the initial diagnostic workup. However, the velcro sound detector and/or transthoracic lung ultrasound could be suggested for rheumatologists to screen ILD in RA patients.[17-19] PFTs can be used to screen for RA-ILD as they are readily available. However, they are relatively insensitive to the presence of early ILDs. For example, it has been reported that 40 of 64 patients (62.5%) with significant ILD on HRCT had a normal forced vital capacity, and two showed normal values for all PFTs measures.[20] HRCT is more sensitive to screening ILDs and is a key test to evaluate ILDs. To identify ILDs, PFTs and chest HRCT are recommended for RA patients with suspected ILD after detailed clinical appraisal.[13,21,22] However, chest HRCT was a more sensitive and convincing examination than PFT to identify the ILD.

Morphological characters

The usual interstitial pneumonia (UIP) pattern and non-specific interstitial pneumonia (NSIP) pattern of ILD are the common pathological and chest radiological morphological patterns for the RA-ILD.[23-29] The chest HRCT of UIP and NSIP patterns are shown in Figure 1. The presence of honeycombing and a UIP pattern are also poor prognostic factors for RA-ILD.[28,30,31] An organizing pneumonia (OP) pattern is a less common morphological pattern of RA-ILD.[25,32] Rheumatoid nodules, lymphocytic interstitial pneumonia, diffuse alveolar hemorrhage, and desquamative interstitial pneumonia are rare morphological features of RA-ILD.[3,33] Compared with other connective tissue diseases (CTD), small airway diseases, including bronchiolitis obliterans, follicular bronchiolitis, and bronchiectasis, are more common in RA patients.[33,34] Some patients may have coexisting interstitial and small airways disease or diffuse bronchiectasis in RA[35,36]: a recent meta-analysis showed that the overall prevalence of bronchiectasis is between 18.7% and 22.6% among RA, and bronchiectasis is more common in RA-ILD (18.1%–30.0%) *vs.* RA without ILD (10.5%–20.0%). As ILD can be the first manifestation of RA, for patients with a UIP and/or NSIP pattern of ILD concomitant with bronchiectasis, screening for RA in the initial diagnostic algorithm and follow-up surveillance is recommended.

Evaluation and diagnosis

RA-ILD should be differentiated from drug-induced ILD and secondary pulmonary infections, especially opportunistic pulmonary infections (e.g., PJP, cytomegaovirus, and aspergillosis) in patients treated with immunosuppressants. Both non-biologic disease-modifying antirheumatic drugs (DMARDs) and biologic disease-modifying antirheumatic drugs can induce ILD during the RA treatment.[7,37,38] Drug-induced ILD usually has an acute/subacute course and is characterized by fever, dyspnea, with diffuse ground glass opacities (GGO) on HRCT in the context of medication use.[39] It should be differentiated from the opportunistic pulmonary infection,

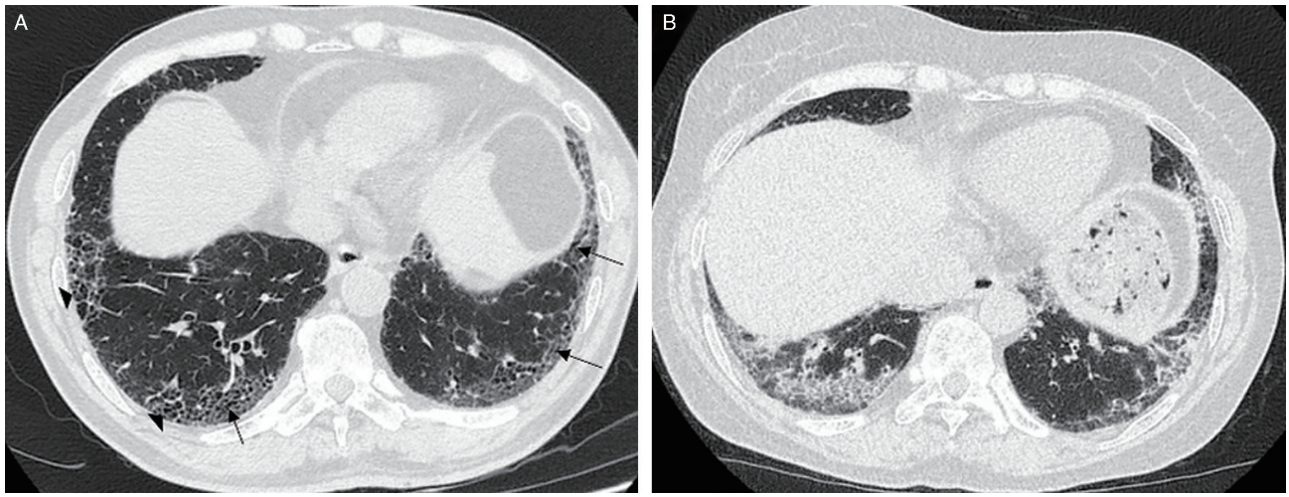

Figure 1: The chest high-resolution computed tomography characteristics of UIP and NSIP. (A) UIP: basal predominant subpleural reticulation with honeycombing (arrowheads) and traction bronchiectasis (arrows). (B) NSIP: interlobular septal thickening with subpleural GGO and the absence of honeycombing. GGO: Ground glass opacities; NSIP: Non-specific interstitial pneumonia; UIP: Usual interstitial pneumonia.

especially PJP. Bronchoalveolar lavage fluid (BALF) analysis and bacterial culture can be used to rule out infection in difficult cases.

Similar to the diagnostic algorithm of idiopathic pulmonary fibrosis (IPF),[40] a multidisciplinary discussion with input from pulmonologists, thoracic radiologists, pathologists, and rheumatologists (when available) is also recommended for the diagnosis of RA-ILD. Rheumatologists and pulmonologists often collaborate during management and follow-up of RA-ILD patients.

Treatment and prognosis

There are no randomized clinical trials guiding treatment of RA-ILD. Therefore, treatment decisions are currently based on clinical experience. For those with significant active RA-related inflammatory and joint symptoms, the rheumatologists typically take the main responsibility and DMARDs and/or glucocorticoids were the main medications for RA-ILD. However, for those with ILD-dominant RA, pulmonologists may lead the management of RA-ILD. The morphologic pattern of RA-ILD may be considered in the treatment protocol.[41] For patients with a UIP pattern, DMARDs and/or glucocorticoids might not be the first choice; however, anti-fibrotic medications, including nintedanib and pirfenidone, are preferred for management, especially in cases where physiologic progression is documented. Recent clinical trials using antifibrotic medications for progressive fibrosing ILD with variable causes (including RA-ILD) demonstrated that they may slow the decline of pulmonary function.[42-44] To explore the efficiency of pirfenidone for RA-ILD, a phase 2 clinical trial is ongoing.[45] For patients with an NSIP or OP pattern, both glucocorticoids and DMARDs may be useful. The initial doses and protocol of glucocorticoids treatment could refer to the treatment of cryptogenic organizing pneumonia or idiopathic NSIP or CTD-ILD[46-49]: start at a prednisone equivalent of 0.5 to 1.0 $mg \cdot kg^{-1} \cdot day^{-1}$ according to the activity and severity of the ILD. Non-anti-tumor necoris factor DMARDs may reduce the risk of lung disease progression.[50] As there is no randomized clinical trial investigating the efficacy of glucocorticoid-sparing immunosuppressants for RA-ILD, many different immunosuppressants including mycophenolate mofetil, cyclophosphamide, tacrolimus, and cyclosporine A, have been used for managing RA-ILD. Tocilizumab and abatacept may be effective for RA-ILD.[51-53] Lung transplantation may be considered for managing the end-stage RA-ILD. The one-year survival of RA-ILD patients managed with lung transplant is reportedly similar to IPF patients.[54]

Acute exacerbations, secondary pulmonary infections, and malignancy are additional complications of RA-ILD.[55-60] In the Izuka's retrospective study, RA-ILD in a UIP pattern was associated with the acute exacerbations and death.[57] Furthermore, patients with RA-ILD in a UIP pattern had a similar clinical phenotype and prognosis to patients with IPF.[30,61-63] Although the survival of RA-ILD has improved since the use of DMARDs, ILD remains a potentially life-threatening complication of RA.[64,65] Identifying potential future progression of RA-ILD can be challenging. The *MUC5B* rs35705950 promoter variant was not associated with the prognosis of RA-ILD.[66] A UIP pattern,[30,61-63] older age, male, smoking history, lower pulmonary function index,[67-69] and high serum KL-6 levels are poor prognostic factors for RA-ILD.[70]

Methotrexate (MTX) Pneumonitis in RA

MTX was the first conventional DMARD for RA. However, diffuse pulmonary disease had been reported to be an adverse effect of MTX. Since the first report of MTX pneumonitis in 1969, several hundred cases have been described. The frequency of MTX pneumonitis is reported as 0.3% to 11.6%. It typically presents as a subacute process of cough, dyspnea, and diffuse GGO and/or consolidation, frequently with fever and progression over several weeks. Although there are cases of late-onset pneumonitis, approximately 50% of cases are diagnosed within 32 weeks of starting MTX.[71]

Older age, diabetes, rheumatoid pleuropulmonary involvement, previous use of DMARDs, hypoalbuminemia, and HLA-A31:01 haplotype are reported risk factors for MTX pneumonitis.[72] Because of the potential for pneumonitis, MTX was not recommended for treatment of RA-ILD. However, this practice has been questioned because recent studies suggest that MTX might delay the onset or progression of ILD in RA patients,[73] and MTX has not been found to be a risk factor for RA-ILD.[73-75]

A hypersensitivity reaction, direct cytotoxic effect, and idiosyncratic immune reaction are proposed mechanisms of MTX pneumonitis.[39,76] Analysis of BALF from patients with MTX pneumonitis typically reveals a lymphocytosis with elevated CD4/CD8 ratio; however, some studies report a neutrophilic pattern and variable CD4/CD8 ratio.[77-79] Although the BALF analysis is not diagnostic, it may be useful for differentiating from opportunistic pulmonary infections. Histopathologically, an interstitial infiltrate by lymphocytes and granuloma formation are classic pathologic features of MTX-induced pneumonitis.[76] In addition, type II pneumocyte proliferation, tissue eosinophilia, organizing diffuse alveolar damage, and perivascular (predominantly perivenular) inflammation have all been described in MTX pneumonitis.[80-82] Chest imaging typically reveals diffuse ground-glass opacities, occasionally with regions of consolidation, septal thickening, and reticular shadows.[82,83] Traction bronchiectasis may be found in cases of chronic disease.[83]

Proposed diagnostic criteria for MTX pneumonitis include exposure to MTX preceding the onset of pulmonary symptoms (cough, dyspnea, and/or fever) with new or evolving opacities on chest radiographs, lung pathology consistent with drug-induced lung toxicity, and exclusion of pulmonary infections, especially PJP or alternative pulmonary diseases, including RA-ILD, pulmonary alveolar hemorrhage, or other drug-induced lung diseases.[82,84] Typically, RA-ILD is more chronic and insidious in onset than MTX pneumonitis and pulmonary infection. PJP is a serious complication to consider during MTX administration for RA patients because the clinical and radiological features of MTX pneumonitis and PJP may be similar.[8,85] Elevation of serum 1,3-β-D-glucan (βDG) and positive results of microbiological examinations with respiratory specimens including sputum or BALF are helpful to differentiate the presence of PJP.

Monitoring the pulmonary symptoms during follow-up for RA patients administrated with MTX, especially during the first year, is recommended. Early recognition and diagnosis of MTX pneumonitis may prevent progression of lung injury to a life-threatening adverse event. MTX pneumonitis typically resolves following discontinuation of MTX and glucocorticoids.[84] Immunosuppressants such as cyclophosphamide and tocilizumab may be used in severe or rapidly progressive cases where the mortality rate may be as high as 17.6%.[39] Although there are case reports of successful re-challenge of MTX for recovered RA-MTX pneumonitis patients, it is probably best to avoid re-introduction of MTX for those who have suffered from MTX pneumonitis.

PJP and RA-ILD

The incidence of PJP in RA patients (RA-PJP) treated with DMARDs is 0.1% to 0.4% and is associated with a relatively high mortality rate (10%–20%). Age >65 years, oral prednisolone ≥5 mg/day, use of DMARDs (both traditional and biological), preexisting lung disease, lower peripheral blood lymphocyte count, low serum immunoglobulin G levels, and asymptomatic carriers of *Pneumocystis jirovecii*, are risk factors for PJP in RA.[86-88] Although the prognosis of PJP has improved, it is worse for RA-PJP than non-RA-PJP.[89] Prophylactic administration of trimethoprim–sulfamethoxazole (TMP-SMX) is recommended for RA patients with more than one risk factor for PJP.[9]

Dry cough, dyspnea, hypoxia, and fever are common clinical manifestations of PJP. Radiographically, diffuse GGO, consolidations, and fine reticulation are chest CT manifestations of PJP.[8,9] Remarkably, these findings can be similar to RA-ILD. Thus, it may be challenging for physicians to differentiate the two conditions by clinical and/or radiological features alone. Symmetric, perihilar, and apical predominant distribution of GGO, usually with peripheral sparing, is the typical chest imaging of non-human immunodeficiency virus (HIV)-PJP.[90] The lung opacities typically resolve after treatment; however, progression to a mosaic pattern with architectural distortion or consolidation without effective management has been reported.[90] Focal or lower lobe predominant distribution, nodules, septal thickening, or cysts are unusual chest CT manifestations of non-HIV-PJP.

Traditionally, Gomori's methenamine silver (GMS) staining of sputum or BALF was used for PJP diagnosis; however, it has low sensitivity in non-HIV patients. Respiratory specimens polymerase chain reaction detection for PJP-DNA is more sensitive: the sensitivity ranges from 87% to 100%, with nearly a 100% negative predictive rate.[91] Anti-PJP monoclonal antibody with immunofluorescent stains is also reported to have a higher sensitivity and specificity than GMS staining. Elevated serum βDG and lactate dehydrogenase are useful biomarkers for the PJP diagnosis.[92]

Because a delay in the initiation of antimicrobial for PJP is associated with poor prognosis, anti-PJP treatment should be started for RA-PJP as soon as the disease is considered, even prior to diagnosis. TMP-SMX at a dose of trimethoprim 5 to 20 mg · kg^{-1} · day^{-1} is the standard treatment for PJP. Potential adverse events of TMP-SMX including skin rash, bone marrow suppression, or liver injury, should be monitored for carefully. As TMP-SMX may magnify the hematological toxicity of MTX, the combination of MTX with TMP-SMX should be avoided. Caspofungin, pentamidine, atovaquone, or clindamycin–primaquine are alternative therapeutic choices.[93] The adjunctive use of glucocorticoids and tapering protocol should be individualized for RA-PJP, considering the activity and severity of RA and RA-associated complications. Poor prognostic factors include older age, lymphopenia, pneumothorax or pneumomediastinum, intensive care unit admission, and concomitant ILD.

Conclusions

ILD is the most common respiratory complication of RA, and it is associated with poor prognosis. However, it is important to differentiate RA-ILD from opportunistic pulmonary infections and pulmonary toxicity from RA treatment medications. Individualized management is indicated once the final diagnosis is established. The activity and severity of RA and ILD should be considered during management of RA-ILD. For those with ILD-dominant RA, pulmonologists should consider the morphologic pattern of ILD. Antifibrotic medications might be used for those with progressive fibrosing ILD.

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Conflicts of interest

None.

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