Rheumatoid Arthritis-Associated Lung Diseases

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Introduction

Rheumatoid arthritis (RA) is the second most prevalent autoimmune condition, affecting 1% of the world population. It is a chronic, inflammatory, autoimmune disease that primarily involves the peripheral synovial joints with high morbidity and enhanced mortality, and is associated with autoantibodies targeting various molecules including modified self-epitopes. The basic pathogenesis of RA is connected with pathogenic humoral and cellular immunity to citrullinated proteins. Therefore, a significant proportion of RA patients exhibits RA-related autoantibodies, which include rheumatoid factor and antibodies to citrullinated protein antigens (ACPAs)\(^1\). The subclinical phase of RA where ACPAs are detected before the onset of clinically apparent disease may persist from 3 to 5 years\(^2-5\). ACPA reactivity is directed against various citrullinated intracellular and extracellular antigens, including vimentin, histones, fibrinogen, and enolase. Reactivity to citrullinated antigens correlates with the presence of the HLA-DRB1*04:01 shared epitope, which includes HLA-DRB1*04:01, HLA-DRB1*04:04, and HLA-DRB1*01:01, haplotypes associated with risk of developing RA\(^6,7\). Citrullination of specific anchor residues enhances the ability of peptides to bind and be presented by the major histocompatibility complex class II (MHC II)–shared epitope alleles, allowing the activation and expansion of citrulline-specific CD4+ T cells, and the subsequent promotion of ACPA generation\(^8-12\).

Genetic factors clearly play a critical role in RA risk, severity, and progression. The most important genetic risk allele for RA resides in the class II major histocompatibility (MHC) locus, accounting for about 40% of the genetic influence\(^13\). The odds ratio of developing RA in individuals with MHC class II HLA-DR4 alleles is about 5:1. A so-called shared “susceptibility epitope” (SE) was identified in amino acids 70 through 74 in the third hypervariable region of the DR\(\beta\) chain. The sequence associated with disease is generally glutamine-leucine-arginine-alanine-alanine (QKRAA), which is present in some DR4 and DR14, in addition to DR1\(\beta\) chains\(^13\). The SE is also associated with increased disease severity, such as extra-articular manifestations and progression of erosions\(^14\). The SE region predominantly faces away from the antigen binding groove that binds processed peptides for presentation to T cells, which has raised some questions about their precise contributory role\(^15\). RA-specific peptides that bind to QKRAA-containing molecules have been difficult to identify\(^16\). This observation led to the notion that SE might also partially contribute by shaping the T cell repertoire in the thymus, altering intracellular HLA-DR trafficking and antigen loading, or serving as an autoantigen. RA-associated alleles present citrullinated peptides efficiently to T cells, which, in turn, produce higher amounts of cytokines.
IL-17 and IFN-γ than to native peptide. Adaptive immune responses to citrullinated peptides are also characterized by the presence of “anti-citrullinated peptide antibodies” (ACPAs), observed in 80%-90% of RA patients. Together these data support the hypothesis that HLA-DR risk for RA is based at least in part on the increased efficiency of antigen presentation for altered peptides rather than native proteins. Citrullination of peptides in the presence of environmental stress is ubiquitous in mammalian cells and is not a unique feature of RA. Instead, the production of antibodies recognizing citrullinated peptides differentiates individuals at risk. The emergence of numerous other post-translationally modified protein targets, e.g., via carbamylation or acetylation, recognized by autoantibodies in RA is consistent with the notion of altered presentation of post-translationally modified peptides; other families of altered peptides could be implicated in discrete subsets of patients.

There are two potential models for the sequence of events leading to the development of clinically detectable RA. In the first model, a pre-RA phase comprises the early generation of autoantibodies (ACPAs) that can bind post-translationally modified self-proteins, particularly via citrullination. This is followed by amplification of the range of specificities of ACPA and by the elaboration of cytokines and chemokines, complement, and metabolic disturbance in the months prior to clinical development of disease. A transition event that requires a “second hit” (as yet poorly understood) permits the development of synovitis. The latter is characterized by frank inflammation, stromal compartment changes, and tissue modification leading to articular damage. In the second model, which is not mutually exclusive, there is an early interaction between innate immune activation and stromal factors that lead to stromal cell alteration, including epigenetic modifications that initiate a cycle of inflammatory stromal-mediated damage. Autoimmunity can arise as a result of these interactions that in turn can contribute directly or in an amplification loop to disease perpetuation.

Rheumatoid arthritis produces destructive joint inflammation that is a key feature. The normal knee is a synovial joint that encloses a space containing a clear, viscous, largely acellular fluid filtrate of plasma and is bordered by synovium, a tissue consisting of lining cells, stromal matrix molecules, and blood vessels. Traditionally, platelets and rheumatoid arthritis do not go together. A recent study has reported that they do. Microparticles, vesicles shed by activated platelets and their presence in knee joint fluid in rheumatoid arthritis, may be incendiary devices in the conflagration of a hot, swollen, and painful rheumatoid joint. A mouse model demonstrated that activation of glycoprotein VI, a platelet-specific receptor for collagen, induces microparticle shedding. In addition, fibroblast-like cells that line the synovial cavity of the joint can also trigger microparticle release. Because these fibroblast-like synoviocytes and collagen are present in the inflamed synovium, platelet interactions in this milieu could lead to local release of microparticles and their translocation into the joint space. Confirmation in humans showed that microparticles from the joint fluid of patients with rheumatoid arthritis can reciprocally activate fibroblast-like synoviocytes, and this interaction induces synoviocytes to secrete inflammatory chemokines and cytokines. Interleukin-1—a pleiotropic cytokine that is rapidly synthesized by activated human platelets and is packaged into microparticles—accounted for much of this stimulatory activity. Thus, a vicious cycle ensues: Fibroblast-like synoviocytes induce the formation of platelet-derived microparticles. The microparticles then
deliver interleukin-1, which triggers synoviocytes to synthesize other cytokines and chemokines, some of which attract polymorphonuclear leukocytes and thereby fan the fire of inflammation.

In addition to the involvement of synovial joints, pulmonary complications are an important extra-articular feature of RA and a major cause of morbidity and mortality\textsuperscript{21-22}. The underlying pathogenesis probably involves multiple cellular compartments, including epithelium, lung fibroblasts, and the innate and adaptive immune system. Heterogeneity in the extent and progression of lung fibrosis probably reflects differences in underlying pathogenic mechanisms. A growing understanding of the key pathogenic drivers of lung fibrosis might lead to the development of more effective targeted therapies.

**Lung involvement in RA**

The commencement of pulmonary symptoms usually occurs within 5 years after the initial RA diagnosis. The multiplicity of pulmonary disease processes exists across lung structures as shown in table 1, including airway disease, interstitial lung disease, pulmonary vasculopathy and extrapulmonary restriction. The most common form of RA-associated lung disease is interstitial lung disease\textsuperscript{23}. The diagnostic evaluation of pulmonary abnormalities is complexed by underlying risk for infection, the use of therapeutic drugs with known pulmonary toxicity, and the frequency of lung disease related to rheumatoid arthritis itself. Therefore, the assessment and management of RA-associated lung diseases necessarily requires a multidisciplinary approach.

**Table 1** Pulmonary manifestations of rheumatoid arthritis

<table>
<thead>
<tr>
<th>Parenchymal</th>
<th>Interstitial lung disease (i.e. UIP, NSIP, acute interstitial pneumonia/ diffuse alveolar damage and organizing pneumonia)</th>
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<tbody>
<tr>
<td>Pleural disease</td>
<td>Pleural effusion</td>
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<td>Pneumothorax</td>
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<td>Bronchopleural fistula</td>
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<td>Trapped lung syndrome</td>
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<td>Airway obstruction</td>
<td>Cricoarytenoid arthritis</td>
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<td>Bronchiectasis</td>
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<td>Follicular bronchiolitis</td>
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<td>Obliterative (constrictive) bronchiolitis</td>
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<td>Nodules</td>
<td>Rheumatoid nodules</td>
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<tr>
<td>Vascular disease</td>
<td>Rheumatoid vasculitis</td>
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<td></td>
<td>Pulmonary hypertension</td>
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**Interstitial lung disease (ILD)**

Interstitial lung disease (ILD) can occur in any of the connective tissue diseases (CTD) with varying frequency and severity and has now been appreciated to be a major cause of morbidity and mortality of patients with connective tissue diseases (CTDs). With improved overall survival in these disorders, clinicians are required to evaluate and manage a rapidly increasing number of patients with clinically important ILD.

The prevalence of ILD is varying depending on the diagnostic tools and population studied. Original studies using simple chest radiography estimated the prevalence of ILD at 5 %\textsuperscript{24}. However, when assessed by High Resolution Computed Tomography (HRCT), lung abnormalities have been found in 50–70 % of unselected
RA patients\textsuperscript{25}. ILD is the most common manifestation among other forms of RA lung involvement and may be an early feature of RA. The diagnosis of ILD in RA portends a poor prognosis.

**Epidemiology and risk factors**

The epidemiology of parenchymal lung disease occurring in the context of autoimmune rheumatic disease is difficult to determine for several reasons. First, the classification criteria for individual diseases are not always well defined and many current criteria have limitations in specificity or sensitivity\textsuperscript{26}. In addition, overlap syndromes and undifferentiated CTD is frequent and pose both a clinical and epidemiological challenge\textsuperscript{27}. Although the overlap between the pathology and clinical features of parenchymal lung disease across the spectrum of CTDs is clear, differences in the pattern and frequency of lung involvement, and also in the rate of progression and long-term outcome can be observed\textsuperscript{28-29}. The disease that is most often associated with lung fibrosis is systemic sclerosis (SSc) and studies have defined the timing and frequency in the major SSc subsets. Thus, patients with diffuse SSc are roughly twice likely to be affected by moderate-to-severe lung fibrosis than patients with limited SSc\textsuperscript{27,30}. However, as limited SSc is at least twice as common as diffuse disease the number of cases with lung fibrosis in the two subsets is similar in most reported cohorts. A nonspecific interstitial pneumonia (NSIP) pattern is most often seen in SSc, but a usual interstitial pneumonia (UIP) pattern is more frequent in RA than in the other CTDs\textsuperscript{31}. Indeed, the occurrence of clinically significant lung fibrosis in the context of poorly defined or undifferentiated conditions has led to the concept of lung-dominant CTD\textsuperscript{32}.

RA can have a UIP or NSIP pattern of lung disease, with UIP more common\textsuperscript{31}. Although rheumatoid arthritis associated-ILD (RA-ILD) and rheumatoid nodule are more common in males, with a male to female ratio as high as 2:1\textsuperscript{33-34} Saag KG et al. found that history of smoking is a major risk factor, odd ratio 3.5 for smoke >25 pack-years\textsuperscript{35}. A high level of rheumatoid factor is a risk factor for extra-articular manifestations of RA, including ILD\textsuperscript{36}.

**Pathogenesis**\textsuperscript{13, 37 - 38}

Cellular pathogenesis of fibrosis in CTD involves multiple cell types and the interplay between the various cellular components probably determines the pattern and severity of fibrosis. Key cellular interactions might determine the development and pattern of lung fibrosis through fibrotic lung injury. Cells in the epithelial, endothelial and interstitial compartments, together with components of the innate and adaptive immune system, interact with the ECM and with each other to produce architectural disruption and collagen-rich ECM. Inflammation and fibrosis can co-exist, especially at early stages, the former of which will be delineated in detail later. A plausible model of pathogenesis for parenchymal lung involvement in connective tissue disease includes initial alveolar epithelial injury triggered by environmental pathogens or inflammation. These processes result in damage to lung tissue and initiation of repair pathways, including the recruitment of fibroblasts and myofibroblasts. Close anatomical and functional interactions between alveolar epithelial and endothelial compartments result in the recruitment of circulating cellular components and mediators including platelets and progenitor cells. Myofibroblasts are critical profibrotic cells that persist in affected lung tissue. The extent of this persistence determines the pattern and type of fibrotic reaction. Interplay with ECM components via matricellular proteins including integrins and microfibrils together with soluble factors such as CTGF drive the process, and the degree
of irreversible destruction and architectural disruption probably determine the progression or reversibility of the lung condition.

Inflammation is likely to be one of the earliest events in CTD-ILD pathogenesis, leading to the influx of inflammatory cells into the interstitial and alveolar airspaces. Resultant epithelial damage occurs to some extent and studies focusing on this aspect suggest that the degree of alveolar epithelial damage at this stage is a major determinant of the likelihood of progression of the disease\textsuperscript{39-40}. A variety of methods have been used to assess the extent of alveolar epithelial damage including diethylenetriamine penta-acetate (DTPA) clearance and serum levels of surfactant D or KL-6 glycoprotein\textsuperscript{41-42}. Inflammation disintegrates lung tissue with loss of normal architecture. The extent to which this process occurs and the degree of disruption to the normal lung extracellular matrix, especially the basal matrix layers that delineate the alveolar structure, probably determines the extent to which recovery and resolution of the process occurs and, ultimately, the potential for recovery of lung structure and function\textsuperscript{14}.

Once inflammation and epithelial damage have been established, resident interstitial pulmonary fibroblasts that are normally present in the connective tissue spaces of the lung and are located in the alveolar wall become activated\textsuperscript{43}. These resident pulmonary fibroblasts seem to be activated through a variety of pathways and mediators, including transforming growth factor (TGF)\textbeta\textsuperscript{-}-dependent pathways critical to their normal function\textsuperscript{44}. These cells then regulate and control other cellular processes that lead to the development of a profibrotic microenvironment in the damaged lung tissue; one consequence of the activation of resident fibroblasts is the activation and recruitment of active TGF-\textbeta from the lung tissue\textsuperscript{45}. The activation of latent matrix-bound TGF-\textbeta is probably a conserved and important injury response process requiring initiation to minimize and localize pathology and might be especially important for some forms of infectious pathogen. That infection, environmental or chemical stimuli for lung epithelial damage and inflammation has an important role in initiation, amplification or persistence of these processes and might determine the progression of lung fibrosis in CTD is plausible\textsuperscript{43-44}.

The developmental process of lung fibrosis requires activated fibroblasts and myofibroblasts to produce increased amounts of extracellular matrix proteins and populate fibrogenic cellular scarring within the lung\textsuperscript{43}. This population of activated fibroblasts and myofibroblasts has three potential sources and all might be highly relevant in the development of interstitial fibrosis. There is a generation of profibrotic myofibroblasts after lung injury. Experimental evidence indicates that the profibrotic myofibroblast population is a key inducer of the fibrotic response to injury that develops and persists at sites of fibrosis. In the lung, these cells probably arise from resident fibroblasts, transdifferentiation of epithelial cells and from circulating progenitor cells including fibrocytes. Resident fibroblasts seem to influence this process, probably controlling recruitment, differentiation and persistence in a TGF-\textbeta\textsuperscript{-} dependent manner via regulation of the local microenvironment in the injured lung tissue. Experimental work in transgenic mice suggests that the resident interstitial pulmonary fibroblasts are critical to the retention and/or differentiation of these circulating cells as they are recruited to sites of injury in mutant mice in which TGF-\textbeta signaling in resident fibroblasts is genetically attenuated, but they do not develop into a population of fibrogenic myofibroblasts\textsuperscript{46-48}. Pulmonary epithelial cells might contribute to the profibrotic mesenchymal cell population.
in lung fibrosis. Multiple reports demonstrate epithelial–mesenchymal transdifferentiation, although the precise importance and role of the process remain unclear.

The overall model of the development of lung fibrosis supports the concept that minor injury and possibly chronic disease processes lead to the development of a lung microenvironment that favors fibrosis. The lung is primed to develop fibrosis in response to injury and in certain contexts, which is likely to be more severe and persistent than in individuals who do not have CTD. SSc and other autoimmune rheumatic diseases, therefore, provide a scenario in which lung fibrosis or parenchymal lung disease occurs and it is likely that intrinsic differences in the pathogenic mechanisms of associated disease are reflected in the different patterns of lung fibrosis and inflammation. In addition, subtypes of individual disease are relevant and might have other surrogate markers such as the hallmark autoantibodies of SSc. For example, patients with anti-topoisomerase antibodies are more likely to develop clinically significant lung fibrosis and those with anti-RNA polymerase III antibodies less likely. Other minor antibodies are also associated with increased risk of lung fibrosis in SSc, including anti-U11/U12 ribonucleoprotein (RNP) antibodies or anti-Th/To RNP antibodies. Similarly, there is an upregulation of the citrullination pathway in RA-ILD.

Despite considerable studies, mostly in systemic sclerosis, there are quite a few researches particularly focusing on RA-ILD-associated pathogenesis of lung fibrosis that possibly can be assumed comparable to other CTDs. The pathogenesis of RA-ILD is unknown but may be related to genetic susceptibility, immune dysregulation, and impair wound healing. Autoimmunization provides a source of antigenic stimulation in RA, and reaction of the rheumatoid factor with immune complexes produces insoluble complexes, which might occur in the capillaries. First large capillary bed is in the lungs. IgM and rheumatoid factor deposit in rheumatoid lung tissue. Alveolar macrophage dysfunction results in the recruitment of inflammation and immune effector cell such as neutrophil and lymphocyte to lungs. T lymphocyte abnormality in RA may be predicted that patients will have clinical progression and evolution to ILD. HLA-DRB1 alleles were found having a high binding affinity to citrullinated proteins. Smoking may contribute to RA-ILD development by promoting the citrullination of lung proteins, thus leading to the development of anti-CCP antibody. Aubart and colleagues found that high anti-CCP antibody levels were associated with RA-related lung disease. Several lines of data support the concept in which the lung represents the site for immune tolerance breakdown. Many studies are demonstrating the presence of RF and anti-CCP antibodies in the airways of patients with preclinical RA, which are not associated with corresponding changes in serum. This discordant phenomenon is even markedly enhanced in RA-ILD bronchoalveolar lavage fluid (BALF) relative to matched serum. The association of RA-ILD with citrullinated autoantigen targets in the lung is supported by studies demonstrating the relationship between RA-ILD and anti-PAD3/PAD4 antibodies capable of activating protein deimination, suggesting that alternative post-translational modifications of lung-derived proteins may generate "cryptic" epitopes capable of driving autoimmune/inflammatory responses which culminate in interstitial lung abnormalities. Collectively, these data support the conceptual pathogenesis in which environmental insults (such as smoking) lead to oxidative stress which, in conjunction with posttranslational modifications and associated autoimmune responses, triggers inflammatory processes characterized by cellular...
infiltration and release of selected cytokines, chemokines, and growth factors. In cooperation with growth factors such as PDGF, many of these cytokines (IL-4, IL-13, and TGF-β) promote fibroblast differentiation and proliferation, providing a potential link between inflammation and fibrosis. Simultaneously, matrix metalloproteinases (MMPs) elaborated from damaged epithelia promote cellular recruitment (through breakdown of tissue barriers) as well as activation of cytokines and pro-fibrotic mediators (through cleavage of molecular precursors), thereby contributing to the cross-talk between inflammatory cascades and tissue remodeling pathways.

RA-ILD is most commonly classified as UIP, overlapping mechanistically and phenotypically with IPF. However, subclinical disease can radiographically resemble NSIP, raising the question of whether RA-ILD encompasses a spectrum of temporally linked histopathologic subtypes or is comprised of pathogenically distinct subsets. These paradigms suggest at least two possible pathways that could explain the coexistence of RA and ILD: (1) RA-ILD with an NSIP pattern may occur as a result of an immune response against posttranslationally modified proteins (e.g., citrullinated proteins) taking place in another site (such as the joints) that subsequently cross-react with similar antigen targets in the lungs; (2) RA-ILD may represent a disease process in which interstitial lung abnormalities (including UIP) trigger an immune response against posttranslationally modified proteins (generated in response to smoking or other oxidative stressors) that promotes articular disease indicative of RA. This leads to a considerable number of studies as to whether biomarkers in serum and bronchoalveolar fluid could differentiate between IPF and RA-ILD.

**Clinical manifestation**

RA-ILD can present unique challenges to diagnosis and management, often leading to delays that may augment morbidity and mortality as some patients may remain asymptomatic even the presence of significantly abnormal radiologic findings suggestive of RA-associated ILD (RA-ILD). In addition, despite recent advances in our diagnostic armamentarium with high-resolution CT scans and digital quantification schemes, for example, there is still a significant lack of comprehension regarding the natural history of RA-ILD—limiting our ability to predict which patients will have a progressive disease pattern warranting more aggressive treatment. In view of the potential mechanistic and epidemiological overlap between RA-ILD and idiopathic pulmonary fibrosis (IPF), understanding factors that determine the risk of disease progression is clearly important.

Dyspnea on exertion and nonproductive cough are the most common pulmonary symptoms. Pleuritic and nonpleuritic chest pain, fever and hemoptyis are rare. Physical signs might be absent despite abnormal radiographic findings. Tachypnea and basilar crackles are common. If the disease is severe, cyanosis, peripheral edema and sign of pulmonary hypertension may be detected.

Pulmonary symptoms usually occur 5 years after arthritic symptoms. Although pulmonary symptoms often follow the arthritis, simultaneous onset or exacerbation may occur. The severity of pulmonary disease does not correlate with the severity of underlying arthritis.

The presence of ILD has been largely ignored in the management of RA, mainly because more typical symptoms of cough and dyspnea are subclinical in most patients. Given that early recognition and treatment of RA-ILD is of paramount importance to potentially slow/alter disease course, the discovery and validation of biomarkers that can enhance our ability to diagnose early stage RA-ILD and/or predict response to treatment in
clinical trials has garnered significant attention. Although the pathogenesis of RA-ILD remains poorly defined, early identification and institution of anti-fibrotic therapy in other models of fibrosing disorders has actually led to amelioration of disease progression, exemplifying the importance of this strategic approach in conditions such as RA-ILD, in which early disease may be a precursor to pulmonary fibrosis.

Radiographic Features

The chest radiograph findings include bibasilar ground-glass opacities, reticular and nodular opacities. In advanced disease, finding of pulmonary hypertension may be found. With new exacerbation, new opacities can become superimposed on fibrotic areas.

Computed tomography (CT) can detect abnormalities earlier than chest radiography. HRCT pattern is thought to mirror the histopathology pattern. The most common is usual interstitial pneumonia pattern, HRCT scans show subpleural, basal predominant, reticular abnormalities with honeycombing, and traction bronchiectasis but a relative absence of ground-glass opacities. Nonspecific interstitial pneumonia is the second most common pattern that is characterized by basilar predominant ground-glass opacities and the absence of honeycombing.

Pulmonary function test

Abnormalities associated with RA-ILD are identical to other fibrosing lung diseases. There are reductions in lung volumes and diffusing capacity for carbon monoxide, oxygen desaturation during exercise and, in late disease, resting hypoxemia. Abnormal pulmonary function may be found in patients with normal chest radiography.

Bronchoalveolar lavage (BAL)

Patients with RA-ILD tend to have alveolitis characteristics by an increase in macrophages and neutrophils whereas those without lung disease have BAL lymphocytosis. Abnormal BAL findings can also be seen in patients with RA and subclinical ILD and elevated lymphocyte counts in these patients may help to distinguish them from those with normal physiology and chest radiographs. However, bronchoalveolar lavage (BAL) findings are not specific for the diagnosis of RA-ILD, but do play an important role in the exclusion of infection (e.g. Pneumocystis jirovecii pneumonia), drug reactions, co-existing disease or malignancy. Quantification of alveolar proteins has provided further insight regarding potential pathogenic mechanisms distinguishing RA patients with various stages of ILD. Bronchoalveolar lavage fluid (BALF) levels of platelet-derived growth factor isoforms AB and BB were higher in RA patients with subclinical ILD relative to RA patients without radiographic evidence of ILD. More importantly, elevated BALF levels of IFN-γ and TGF-β were associated with an increased risk of radiographic progression in patients with subclinical RA-ILD.

Histopathology

Usual interstitial pneumonia

UIP is more common in RA-ILD, which is different from other types of connective tissue disease that nonspecific interstitial pneumonia is most common. Lee et al found the UIP pattern in RA-ILD patients (56%). This was followed by NSIP (33 %) and organizing pneumonia (11 %). In UIP, a characteristic heterogeneous pattern of fibroblast foci amid regions of normal tissue is seen. More extensive disease and rapid decline of pulmonary function during follow-up were found to associate with poor prognosis.
**Nonspecific interstitial pneumonia**

Fibrotic NSIP may occur often than cellular NSIP. The lesions are often characterized by, relatively uniform appearance at low magnification due to a cellular interstitial infiltrate of mononuclear inflammatory cells associated with varying degrees of interstitial fibrosis.\(^6\)

**Lymphocytic interstitial pneumonia**

LIP is a spectrum of pulmonary lymphoid proliferation ranging from follicular bronchitis/bronchiolitis to low-grade malignant lymphoma. It is characterized by infiltration of the interstitium and alveolar spaces of the lung by lymphocytes, plasma cells. Although LIP is commonly seen in Sjögren’s syndrome, it has also been reported in RA and is associated with autoantibody production (especially with dysproteinemias).

**Organizing pneumonia**

Characteristics of OP include excessive proliferation of granulation tissue, which consists of loose collagen-embedded fibroblasts and myofibroblasts, within small airway, and alveolar duct, along with chronic inflammation in surround alveoli. OP has a better prognosis than other RA-ILD.

**Prognosis and management**

The treatment for RA-ILD is quite empirical because there have been no randomized placebo-controlled trials. Patients with non-UIP histopathologic patterns are more likely to respond to steroid and/or immunosuppressive agents.

Asymptomatic patients can be monitored though clinical assessment, pulmonary function test, and chest radiography at 6-12 months interval or whenever the symptoms get worse.

Treatments should be considered in the following patients: younger age, histopathologic patterns other than UIP, and worsening of symptoms, pulmonary function test or HRCT over the preceding 3-6 months.

For symptomatic patients who have evidence of progressive respiratory impairment or have non-UIP histopathologic types (based on HRCT or biopsy), initial treatment should be prednisolone 0.5 mg/kg/day after excluding infection. The maximum dose is 60 mg/day as a higher dose carries a significant risk of infection without providing additional benefit. If response occurs (usually within 1-3 months), prednisolone should be slowly tapered to the maintenance dose of 10 mg/day.

For patients who fail to response to initial treatment with glucocorticoid, immunosuppressive agents such as azathioprine (3 mg/kg orally up to 200 mg/day), mycophenolate mofetil (250 mg given twice a day initially with a target dose of 1.5 to 2 g/day), or cyclophosphamide (100 to 120 mg orally/day as a single daily dose) could be added.\(^3\)

For patients who develop rapidly progressive acute interstitial lung disease (Hamman-Rich syndrome) or organizing pneumonia after excluding infection, high-dose intravenous glucocorticoids (methylprednisolone 1-2 g/day) should be given. If those patients develop impending or ongoing respiratory failure, immunosuppressive agents may be added at the same time.

**Airway Disease in Rheumatoid Arthritis**

Along with interstitial lung disease, airway disease is now regarded as one of the major lung complications in RA. Both upper and lower airway diseases can be involved.

**Upper airway involvement**

The prevalence of laryngeal involvement in RA ranges from 13-75 % in different series.\(^6\)

Cricoarytenoid arthritis is the most common cause
of upper airway obstruction. Other causes are less common such as rheumatoid nodules on the vocal cord or vasculitis involving the recurrent laryngeal or vagus nerves, causing vocal cord paralysis. Upper airway disease is frequently found in females with longstanding and severe RA\textsuperscript{67}. Early manifestation includes hoarseness of voice, dysphagia, odynophagia, tenderness of the throat, pain on coughing or speaking, and exertional dyspnea. Acute stridor or obstructive respiratory failure might occur from sudden subluxation or superimposed airway edema from infection or recent endotracheal intubation. However, symptoms usually are absent until significant obstruction occurs.

HRCT is more sensitive than direct laryngoscopy and can detect abnormalities before symptoms develop. These HRC findings include prominent hyperdense intra-articular sclerotic foci in the arytenoid and cricoid cartilages, increased spacing between the arytenoid and cricoid cartilages due to joint effusion, and subluxation of the joint\textsuperscript{68}.

Mild symptoms may be treated with non-steroidal anti-inflammatory drugs (NSAIDs) and other medications to control RA joint inflammation. For more severe obstruction, surgical intervention with mobilization of the cricoarytenoid joints and lateral fixation of one of the cords may be required in addition to immediate airway management\textsuperscript{33}.

**Lower airway involvement**

The prevalence of small airway obstruction and bronchial hyperresponsiveness remains uncertain as studies have been confounded by smoking or RA-ILD. Mori et al found that the prevalence of obstructive small airway disease was 30.3 % in RA patients without RA-ILD or bronchiolitis on HRCT. However, 17.4 % of the participants in this study were former or current smokers. Factors that were significantly associated with abnormal FEF\textsubscript{25–75} include respiratory symptoms, smoking history, and disease duration more than 10 years\textsuperscript{69}. The prevalence of small airways abnormalities detected from HRCT is greater than physiologic airway obstruction detected from PFT\textsuperscript{70}.

**Bronchiectasis**

Bronchiectasis is the feature of permanent irreversible dilatation of cartilage-containing airways. Symptoms typically include recurrent cough, sputum production, and respiratory infections. The prevalence in case series has varied from 0 % to 10 %. HRCT can detect bronchiectasis up to 30 % in RA without I LD\textsuperscript{71,72}. The most common radiographic abnormalities are bibasilar diffusely interstitial marking and focal opacities. However, cysts and air-fluid levels can be found. Obstructive and restrictive patterns can be found in PFT.

Shared genetic risk factors in terms of share epitope (SE) might contribute to the association between bronchiectasis and RA. In RA patients with bronchiectasis, more protease inhibitor phenotype MM and HLADR4- antigen positive were observed\textsuperscript{52}. Remy et al found that CFTR abnormalities may predispose to the development of bronchiectasis in RA\textsuperscript{72}. RA patients with bronchiectasis, recurrent pulmonary infections, and respiratory failure could have a mortality rate of 7.3 times of the general population, 5 times of RA patients alone, 2.4 times of bronchiectasis patients alone\textsuperscript{73}. Treatment is similar to other forms of bronchiectasis.

**Obliterative bronchiolitis**

Obliterative bronchiolitis (OB) is rare but fatal, characterized by progressive concentric narrowing of membranous bronchioles that associated with previous penicillamine treatment. OB is more common in women and patients with positive rheumatoid factor tests.
The clinical manifestations include abrupt onset of dyspnea and dry cough. Its rapid onset allows us to distinguish this condition from other pulmonary diseases in RA.

Physical examination may find inspiratory rales and mid-inspiratory squeak. Chest radiography can be normal but may show signs of air trapping. HRCT often shows bronchial wall thickening, centrilobular emphysema, areas of low attenuation with a mosaic pattern, and bronchiectasis. PFT may reveal airflow obstruction, normal or reduced diffusing capacity (DLCO), and mild to moderate arterial hypoxemia as well as respiratory alkalosis in arterial blood gases. BAL may show an increase in the percentage of neutrophils (range 60 to 78%).

Constrictive bronchiolitis is the most common histopathologic finding that shows lymphoplasmacytic infiltration of airway walls that are confined to small bronchi and bronchioles. Bronchiolar lumens are obliterated and bronchial walls are destroyed by granulation tissue. Parenchymal involvement may be affected only to the surrounding bronchiolitis.

The initial treatment of RA-associated OB is to discontinue the offending agent such as penicillamine, gold, or sulfasalazine. The use of antibiotics and bronchodilators is usually ineffective. The prognosis is generally poor due to the lack of satisfactory response to immunosuppressive agents. High-dose corticosteroids are often used. Azathioprine, cyclophosphamide, etanercept (a TNF-inhibitor), erythromycin, could be used. However, data from large series or randomized trials are lacking. In severe cases, a lung transplant may be necessary.

**Follicular bronchiolitis**

Follicular bronchiolitis is defined as lymphoid hyperplasia of bronchus-associated lymphoid tissue. The obstruction is caused by external compression of bronchioles which is different from direct luminal occlusion seen in OB. In the study of Tansey and colleagues, follicular bronchiolitis (23%) was most commonly seen in RA patients.

Clinical presentations include dyspnea (100%), both fever and cough infrequently occur. High level (1:640 to 1:2560) of rheumatoid factor is usually seen. Chest radiography shows bilateral reticular or nodular opacities. The most common findings in HRCT are bilateral, diffuse centrilobular nodule (less than 3 mm.), and glound-glass opacity. Mosaic patterns and honeycombing are usually not seen. PFT shows both obstructive and restrictive pattern, but restrictive is more common.

The optimal treatment of follicular bronchiolitis in RA is not known. Patients with mild symptoms may be observed without treatment. For symptomatic patients, corticosteroid and macrolide may be used.

**Rheumatoid Nodules**

Rheumatoid nodule is the only pulmonary manifestation specifically for RA. Prevalence of pulmonary rheumatoid nodules in RA patients depends on methods used for detection such as chest radiography can detect lung nodules approximately 0.2% of RA patients. HRCT increases the yield of detection to 22%. Rheumatoid nodules often occur in patients with longstanding disease and with concomitant subcutaneous rheumatoid nodules. The HLA-DR4 haplotype (including the heterogeneous group of DRB1 alleles) is predictive of the risk of developing subcutaneous nodules in RA.
Patients are usually asymptomatic, but hemoptysis (from cavitation lesion), pleural effusion, pyopneumothorax and pneumothorax (from erosion pleural space) can occur.71

The nodules in the lung could be recurrent or appearing first in one lung then the other lung later. These nodules may be solitary or multiple and may enlarge, remain static or shrink to scar. They are round and vary in size from 0.5-7 cm. They are located in subpleural areas or interlobular septa in the middle and upper lung zones78. The central necrosis may occur in some of pulmonary nodules. Histopathology of the nodules is a central area of necrosis surrounded by palisading macrophages and then inflammatory cells including lymphocytes and plasma cells. The radiographic finding may mimic malignancy.

The etiology of rheumatoid nodule is unknown. It is hypothesized that repeated trauma including local vascular damage resulting in neoangiogenesis and granulation formation. Endothelial injury causes accumulation of IgM immune complex on small vessel walls. The deposit of RF induces the activation of monocytes and macrophages. These cells secrete interleukin-1, prostaglandin E2 and angiogenic factors. Chemotactic factors and fibronectin are responsible for the necrotic matrix and formation of palisading granuloma. This can suggest that rheumatoid nodules may result from vasculitis process79.

Differentiation of rheumatoid nodules from lung cancer is essential, especially in patients with a history of smoking. Prognosis of rheumatoid nodules is good, with spontaneous resolution. Complications are rare.

**Pleural disease**

Pleural disease is one of the most common pulmonary complication of RA. In autopsy studies, 38-73% of RA patients had pleural involvement; however, symptomatic pleurisy was less frequent80-81. Biopsy reveals nonspecific chronic inflammation and fibrosis. The incidence of clinical pleural effusion in RA is 2-5%. Male and subcutaneous nodules are thought to be at high risk of pleural involvement, usually at the age of 45 years31. Pleural disease is common in longstanding RA but can precede joint disease. A high prevalence of HLA-B8 and Dw3 is associated with rheumatoid pleural effusion82.

Mechanisms of pleural effusion include impaired fluid resorption in pleura, necrosis of subpleural rheumatoid nodules, and local production of cytokines and immune complexes leading to endothelial injury and capillary permeability33.

The patients may be asymptomatic with effusion discovered in routine chest radiographs. When symptoms occur, chest pain and fever are common. These symptoms may mimic bacterial pneumonia. Usually, pleural effusion is small-moderate volume and unilateral.

Pleural effusion can be diagnosed on chest radiography, with blunting of the costophrenic angles in the upright position. Further evaluation of possible comorbid ILD, subpleural cavitating rheumatoid nodules, pleural thickening, or unexpandable lung might require HRCT to aid in diagnosis.

Thoracentesis should be performed for any effusion with >1 cm of layering on decubitus films. Rheumatoid effusion is a sterile exudative fluid with low pH (<7.3), low glucose (<60 mg/dl) and high lactate dehydrogenase (may be >700 IU/L).

This low glucose level is secondary to impaired membrane transport of glucose (due to pleural
thickening) and increased utilization by inflammatory cell\textsuperscript{83}.

A low level of pH reflects ongoing inflammation in the pleural cavity with a high rate of glucose metabolism and lactate and carbon dioxide accumulation\textsuperscript{82}. Infection should be ruled out as low pH, low glucose, and high LDH level seen in rheumatoid effusion is also typical for bacterial empyema.

Sterile empyematous effusion is pus-like appearance with a very high WBC content (>50,000/mm\textsuperscript{3}), low pH (<7.2) and glucose content (<40 mg/dl), and massive cellular debris without organisms found. This may be caused by rupture necrotic subpleural rheumatoid nodule into pleural space and subsequent formation of bronchopleural fistula\textsuperscript{78}. Long-standing chronic pleural inflammation may result in the formation of fibrous peel causing trapped lung. Chronic pleural inflammation may cause pseudochylous pleural, milky appearance due to elevated cholesterol level (>200 mg/dl). Among the causes for pseudochylous pleural exudates, long-standing TB and rheumatoid pleural effusion were the most common.

The rheumatoid factor is increased in pleural effusion and is usually greater than 1:320 and greater than found in serum. A finding of RF in the pleural effusion is strongly suggestive of a rheumatoid origin for the pleural exudate. RA cell or ragocytes (WBC with phagocytic intracellular inclusions and ability to liberate RF) are seen but are not diagnostic because they can be found in tuberculous pleurisy and malignant pleural effusions\textsuperscript{84}. There are giant multinucleated macrophages, elongated macrophages, and background of granular debris in cytology examination\textsuperscript{33}.

Rheumatoid pleuritis and rheumatoid effusion usually resolve spontaneously (within an average of 14 months) or with treatment of RA joint disease. However, symptomatic patients may require thoracentesis. When diseases do not resolve spontaneously, corticosteroid and immunosuppressive drugs may be beneficial. Complete resolution of pleural effusion with high doses of oral corticosteroid was reported\textsuperscript{82}.

**Pulmonary hypertension**

Pulmonary arterial hypertension (PAH) is extremely rare in RA. This may be associated with vasculitis, symptoms and sign of systemic vasculitis should occur simultaneously. Secondary pulmonary hypertension has also been reported in patients with RA. Dawson et al found that 6\% of RA patients had pulmonary hypertension due to lung disease\textsuperscript{85}.

**Lung cancer**

The risk of developing lung cancer may be slightly greater in patients with RA than in the general population. In one cohort study of 8768 patients with diagnosis RA, patients with RA were 43\% (odds ratio 1.43) more likely to develop lung cancer than patients without RA\textsuperscript{86}.

**Conclusion**

Pulmonary involvement is common among patients with rheumatoid arthritis. Almost all components of the lung structure are targets of injury, especially ILD. The presence of ILD is important because it leads to significant morbidity and mortality. The mechanism of lung injury is caused by genetic, environmental exposure and drug use. Some patients may develop pulmonary disease before arthritis symptoms, however, some patients with pulmonary involvement may be asymptomatic. Advanced screening tools allow us to detect and treat at an early stage.
References


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