Published in final edited form as:

Clin Chest Med. 2019 September ; 40(3): 545–560. doi:10.1016/j.ccm.2019.05.003.

Thoracic Manifestations of Rheumatoid Arthritis

Anthony J. Esposito, MD,

Division of Pulmonary and Critical Care Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts

Sarah G. Chu, MD,

Division of Pulmonary and Critical Care Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts

Rachna Madan, MD,

Department of Radiology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts

Tracy J. Doyle, MD,

Division of Pulmonary and Critical Care Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts

Paul F. Dellaripa, MD

Division of Rheumatology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts

Keywords

bronchiectasis; bronchiolitis; drug-induced lung toxicity; rheumatoid arthritis; rheumatoid arthritis-associated interstitial lung disease; rheumatoid nodule

INTRODUCTION

Rheumatoid arthritis (RA) is a destructive, systemic, inflammatory disorder that characteristically affects small, diarthrodial joints in a progressive, symmetric, and erosive fashion.¹ This connective tissue disease (CTD) occurs in approximately 1% of the adult population in developed countries and is associated with decreased quality of life, poor functional status, and increased mortality.² It is the 42nd highest etiology of global disability and contributes an estimated \$19.3 billion in excess annual US health costs.^{3,4} There is evidence that the incidence and prevalence of RA has been increasing over the past 20 years, further increasing the burden of disease.⁵

Although joint disease is the main presentation, RA has a plethora of extraarticular manifestations that contribute to the substantial morbidity and excess mortality observed

corresponding author: pdellaripa@bwh.harvard.edu, Mailing Address: 60 Fenwood Road, Boston, MA 02115.

Disclosure Statement:

PFD participates in clinical trials for Genentech and Bristol-Myers Squibb without income support or fees paid. AJE, SGC, RM, and TJD have nothing to disclose.

with this disease.⁶ While cardiac disease is responsible for a majority of RA-related deaths, pulmonary disease is also a major contributor, accounting for approximately 10–20% of all mortality. Pulmonary complications occur in 60–80% of RA patients, many of whom are asymptomatic.^{7–10} RA directly affects all anatomic compartments of the thorax, including the lung parenchyma, large and small airways, pleura, and less commonly the vasculature (Box 1).^{11,12} In addition, pulmonary infection and drug-induced lung disease associated with immunosuppressive agents utilized for the treatment of RA can occur.

RA-associated lung disease typically occurs within 5 years of RA diagnosis and may even precede joint disease in up to 20% of patients.^{13–16} Respiratory symptoms may be masked by the patient's poor functional status from chronic joint and systemic inflammation, which may lead to delays in diagnosis.¹⁷ It is therefore imperative for clinicians to regularly assess RA patients for signs and symptoms of pulmonary disease and, reciprocally, to consider CTD, including RA, when evaluating a patient with pulmonary disease of unknown etiology.

INTERSTITIAL LUNG DISEASE

Epidemiology:

Interstitial lung disease (ILD) is characterized by fibrosis and inflammation of the pulmonary interstitium. It is the most common manifestation of RA-associated lung disease, as patients with RA are approximately 9 times more likely to develop ILD than the general population.¹⁸ Its prevalence, however, has been difficult to estimate due to the extensive heterogeneity among studies that vary by the study population, diagnostic criteria, and imaging method used to establish the diagnosis. The most robust population studies to date estimate the cumulative incidence of clinically significant ILD in the US to be 5% at 10 years,¹⁹ 6.3% at 15 years,²⁰ and 6.8% at 30 years of follow-up,²¹ with an estimated lifetime risk of 7.7%.²² Moreover, RA patients who undergo screening with high-resolution computed tomography (HRCT) regardless of symptoms commonly have pulmonary abnormalities that vary in studies from 19 to 67% depending on the population screened.^{8,10,23,24} Despite decreasing mortality rates from RA alone, age-adjusted mortality rates from RA-ILD have been increasing over the past 25 years.^{25,26} In one study, patients with RA-ILD had a median survival of 2.6 years after diagnosis, which is a threefold increased risk of death compared to RA patients without ILD.²²

HRCT is more sensitive than chest radiograph in the detection of ILD and has led to the identification of subclinical disease in patients with RA.²⁷ In one study, HRCT abnormalities compatible with ILD were described in 33% of patients with recently diagnosed RA compared to 6% by chest radiograph alone.²⁸ A significant number of those subjects had mild, subclinical interstitial lung abnormalities (ILA). Accordingly, ILA in RA patients without pulmonary symptoms have been described in up to 44% of subjects.^{28–30} Of the patients with ILA, progression of disease has been described in up to 57% over a two-year follow-up period.^{29,31} These data suggest that although ILD is already known to be a common extra-articular manifestation of RA, it is still underrecognized.

Risk Assessment:

Risk factors for RA-ILD, which may identify susceptible individuals at risk for poorer outcomes and increased mortality, have been identified that overlap with known risk factors for idiopathic pulmonary fibrosis (IPF). The strongest evidence exists for factors that describe RA patients' demographics, which include RA disease severity, functional status, and tobacco exposure. Older age and male gender are associated with increased risk of RA-ILD,^{32–34} with older age specifically associated with the presence of ILD at the time of RA diagnosis.²² Although RA is more common in females,⁵ RA-ILD is about four times more common in men,^{22,32–34} also similar to the male-predominant disease of IPF.³⁵ Furthermore, RA disease activity, decreased functional status, and the presence of other non-pulmonary extra-articular disease are risk factors for RA-ILD.^{22,36} Smoking is not only a well-established risk factor for RA in general but also for RA-ILD.^{24,37,38} The incidence of ILD in an ever-smoker RA patient has a dose response relationship, with the highest incidence in those with ≥ 25 pack-years cumulative history.²⁴ Low baseline percentage predicted forced vital capacity (FVC) or diffusion capacity of the lung for carbon monoxide (DLCO) and a significant decline in lung function at follow-up (defined as a >10% decrease in FVC or >15% decrease in DLCO) have all been associated with disease progression and increased mortality.^{31–33,39}

Autoantibody profiles as well as genetic variants have also been implicated in the development of RA-ILD. Positive serologies for either rheumatoid factor (RF) or anti-cyclic citrullinated protein (anti-CCP) antibodies are significant predictors for the development of ILD in RA patients,^{33,40,41} with some suggestion that higher anti-CCP titers correlate with extent of disease.⁴² Recent evidence has also associated specific genetic mutations implicated in endoplasmic reticulum stress, telomere shortening, and airway microbial defense. In targeted whole exome sequencing of 101 patients with RA-ILD, increased frequency of mutations in several telomere maintenance-associated and surfactant protein genes were identified compared to control.⁴³ Furthermore, a gain-of-function promoter variant in the mucin 5B (*MUC5B*) gene was recently associated with RA-ILD and was particularly associated with usual interstitial pneumonia (UIP), the prototypical radiographic and histologic pattern of IPF.⁴⁴

ILD Subtypes:

HRCT is the imaging modality of choice for evaluating ILD in RA patients. RA-ILD has a variety of radiographic and histopathologic subtypes that are well-described and shared with the idiopathic interstitial pneumonias (Fig. 1).^{45,46} The most frequently encountered are the UIP (Fig. 1A) and non-specific interstitial pneumonia (NSIP; Fig. 1B) patterns of disease.^{47–49} Other less common patterns of disease include organizing pneumonia (Fig. 1C), diffuse alveolar damage, lymphocytic interstitial pneumonia (LIP; Fig. 1D), and desquamative interstitial pneumonia. The majority of patients with clinically apparent disease have a UIP pattern, which distinguishes RA from other CTDs in which NSIP is more frequently seen. A UIP pattern on HRCT obviates the need for a surgical lung biopsy to secure the diagnosis, as numerous studies have demonstrated a positive predictive value of 90–100% for a pathologic diagnosis of UIP.^{50–53} There is increasing evidence that RA patients with UIP possess a different phenotype, clinical evolution, and prognosis compared

to RA patients with a non-UIP pattern of disease. Notably, UIP pattern is more frequent in older, male RA patients with a history of smoking and confers a poorer prognosis with survival rates that parallel those seen in IPF.^{48–50,54,55} Moreover, RA-ILD patients with UIP have been reported to have more respiratory-related hospitalizations than other ILD subtypes.⁵⁶

Clinical Presentation:

While ILD is usually diagnosed early in the clinical course of RA,¹⁴ it can develop at any time. It has been described in long-standing RA and has even been shown to precede the onset of articular symptoms.^{15,16,57,58} Patients with RA-ILD commonly report non-specific symptoms of dyspnea (most common), exercise limitation, and/or dry cough although symptoms can be masked by functional impairment.^{16,17,24,59} Less frequent symptoms include chest pain, wheezing, and productive cough.⁶⁰ Patients who have abnormal pulmonary function tests (PFTs) are more likely to report symptoms.⁶⁰

As noted previously, up to 44% of RA patients without pulmonary symptoms may have subclinical ILD or ILA on HRCT.^{28–30} These patients are more likely to have lower percent predicted forced expiratory volume in 1 second (FEV1) and FVC than patients without ILA.³⁴ Some data suggest that ILA progress over time in a subset of patients;^{28,29,31} however, the clinical significance of subclinical ILD in RA remains to be determined.

Evaluation and Diagnosis:

Development of otherwise unexplained respiratory symptoms in an RA patient or the presence of articular symptoms in a patient undergoing evaluation for ILD should raise suspicion for RA-ILD, especially if risk factors are present. In patients with known RA, other types of RA lung disease should be considered as well as drug toxicity and opportunistic infections.

Initial evaluation of patients with suspected RA-ILD should include a complete history and physical examination, imaging with HRCT, and PFTs. Patients may report non-specific respiratory symptoms such as dyspnea, cough, wheeze, or pleuritic chest pain on history,^{16,24,56,59,60} and physical examination may reveal rales, clubbing, wheezing, or signs of right heart failure.^{23,29} HRCT is essential to characterize the radiologic pattern and to assess disease severity. The most common findings are ground-glass opacities, honeycombing, and reticulation in the aforementioned disease patterns.^{47,61} PFTs assess the physiologic severity of RA-ILD and are useful to monitor disease activity. Up to 30% of patients with RA have abnormal PFTs commonly in the form of restrictive ventilatory deficits and/or a reduced DLCO.^{24,34,60}

Other diagnostic studies are rarely indicated for evaluation of RA-ILD. Bronchoscopy with bronchoalveolar lavage adds little value other than to exclude infection when clinically suspected.⁶² Surgical lung biopsy is also rarely indicated as identification of the histopathologic pattern is not currently part of the algorithm to diagnose and treat RA-ILD.¹⁷ Nonetheless, biopsy may be indicated when the etiology of lung disease is unclear. Currently no biomarkers have been identified that are either sensitive or specific for RA-ILD disease activity or progression; however, emerging biomarkers are being investigated beyond

the known demographic and serologic variables and include MMP7, SP-D, and PARC. These may enhance our ability to predict the presence and potential progression of RA-ILD.

40

Treatment and Disease Monitoring:

Treatment of RA has changed dramatically over the past few decades, catalyzed by the introduction of new classification criteria that identify patients with early disease and the expansion of therapeutic options for disease management. While numerous medications have been described as potential therapies for RA-ILD, there are no large randomized controlled trials (RCTs) to help guide management. Many of the recommendations for treating RA-ILD have been extrapolated from studies of other CTD-associated ILDs such as scleroderma-ILD.

In general, treatment of RA-ILD consists of supportive measures and anti-inflammatory therapies that target the inflammatory processes putatively responsible for the disease. Supportive treatment is recommended for patients with mild disease or contraindications to pharmacologic therapy. This strategy consists of nonpharmacologic measures that should be implemented in the care of every patient with RA-ILD and include smoking cessation, oxygen supplementation when indicated, age-appropriate vaccinations for pneumonia and influenza, education, exercise rehabilitation, and prophylaxis for *Pneumocystis jirovecii* pneumonia in the profoundly immunosuppressed.⁶³ In patients with moderate or severe disease, cautious use of immunosuppressive therapy may be considered although prospective trials are lacking. Features predictive of treatment response include histopathologic patterns other than UIP, younger age, and worsening of symptoms, PFTs, or HRCT findings over the preceding 3–6 months.^{63–65}

Glucocorticoids are often used as first-line therapy to stabilize and improve the disease course of RA-ILD when the radiographic or histologic pattern suggests a more inflammatory process such as NSIP, LIP, or organizing pneumonia.⁶³ Treatment of UIP with immunosuppression may be harmful, as it can increase patients' susceptibility to serious infections in a dose-dependent manner.^{66,67} This was exemplified by the PANTHER trial in which treatment of IPF with a combination of prednisone, n-acetylcysteine, and azathioprine was associated with increased mortality, hospitalizations, and serious adverse events compared to placebo.⁶⁸ The results of this trial raised the concern about use of these agents in RA patients with UIP though it admittedly did not specifically address UIP in CTD.

Mycophenolate mofetil (MMF) has been used in the management of scleroderma-ILD and other CTDs with a majority of the evidence derived from one large prospective trial, small prospective case series, and retrospective reviews.^{69–71} In a study of MMF in CTD-ILD that included 18 patients with RA-ILD, MMF was associated with modest improvements in FVC and DLCO and with reduced prednisone dosing;⁷¹ however, it is worth noting that MMF is ineffective for treatment of active articular disease, requiring concomitant use of other immunosuppressive agents that may limit its tolerability. Cyclophosphamide has been commonly used as a second-line agent to treat ILD unresponsive to steroids although no RCTs have been performed for its use in RA-ILD. Its use in scleroderma-ILD has moderate benefit for those with early disease although a prior meta-analysis concluded that there was

no improvement in pulmonary function following 12 months of treatment.^{72,73} Therefore, its use is not recommended for mild/moderate or stable RA-ILD. Cyclosporine and other calcineurin inhibitors have limited experience for treatment of RA-ILD and are currently not recommended due to their poor safety profile and lack of proven benefit for joint disease.^{74,75}

There is limited data to support the use of biologic agents in the treatment of RA-ILD despite small case series/reports and one prospective trial using rituximab in RA-ILD.^{76–78} The role of rituximab in UIP-related disease is unknown although it may play a role in more inflammatory processes such as NSIP or LIP. There is early clinical evidence suggesting that abatacept—an inhibitor of T cell co-stimulation—may be an effective treatment for RA-ILD.^{79–81} In a large retrospective study, abatacept was associated with stabilization or improvement in symptoms, PFTs, or HRCT findings in up to 12 months of follow-up.⁸¹ Although these studies are promising, current evidence does not support routine switching therapy to a biologic in all patients with RA-ILD regardless of disease severity or active joint disease.

In end-stage RA-ILD, lung transplantation may be considered although there are limited data on long-term outcomes. Survival at 1 year seems to be similar to IPF lung transplant recipients (67% and 69%, respectively).⁸²

Evidence to guide screening strategies, management, and monitoring of treatment of RA-ILD is of low quality or absent. Many practice patterns have been extrapolated from scleroderma-ILD or IPF.⁸³ Here, we provide a suggested algorithm for identification of ILD in at-risk RA patients (Fig. 2). In RA patients with symptoms of dyspnea or cough not explained by other causes like infection or heart disease, assessment for underlying RA-ILD with HRCT and pulmonary function testing including ambulatory oximetry is reasonable. Recommendation for baseline screening of all patients with RA for ILD is the subject of ongoing prospective evaluation. For RA patients with known risk factors for ILD, risk assessment with PFTs may be a sensible and low risk approach. Patients with a history of smoking may be appropriate candidates for low dose CT scanning, where surveillance for lung cancer could be coupled with an assessment for ILA or ILD (Fig. 2). Patients at highest risk for progression (those with >10% decrease in FVC or >15% in DLCO) are those that should be considered for therapy and be monitored with serial PFTs every 3–6 months.⁸³

AIRWAY DISEASE

RA can affect both the upper and lower airways in multiple forms with or without airflow obstruction, including cricoarytenoid arthritis, mucosal edema, myositis, vasculitis, and airway/vocal cord rheumatoid nodules or bamboo nodes.^{84–86} Laryngeal involvement is likely underestimated but may involve over 30% of patients with RA⁸⁷ and may be the sole manifestation of this disease.⁸⁸ In a series of 32 patients with RA, cricoarytenoid joint (CJ) involvement was detected in up to 70% of subjects by direct laryngoscopy and HRCT.⁸⁹ CJ arthritis results from accumulation of synovial fluid in the CJ capsule, leading to erosion and subluxation of the cartilage that may ultimately result in fixation.⁸⁶ While laryngeal disease is often clinically silent, patients can present with a globus sensation, hoarseness, dysphagia,

odynophonia, dysphonia—which may mistakenly be attributed to laryngopharyngeal reflux or environmental allergies⁸⁶—or with dyspnea and stridor from airway obstruction. Local or systemic corticosteroids as well as non-steroidal anti-inflammatory drugs have been used for milder cases, although surgical excision of laryngeal nodules or laryngoplasty for fixation may be necessary. Several case reports of acute airway obstruction requiring emergent tracheostomy have also been described.^{90,91}

In the lower airways, RA has been associated with airway hyperresponsiveness, small airway disease, and bronchiectasis. The attributable risk of RA has been difficult to define due to confounding factors, particularly smoking. In a series of 50 patients with RA and no ILD, 18% were found to have airway obstruction, 8% had small airway disease (defined by a decreased FEF_{25–75}), and 32% had air trapping on PFTs and HRCT.⁹² Increased prevalence was noted in women and smokers. While airflow obstruction is typically diagnosed via PFTs, HRCT abnormalities—particularly with inspiratory/expiratory images (Fig. 3)—may precede physiologic findings.⁹²

The reported prevalence of bronchiolar disease varies widely and includes constrictive bronchiolitis obliterans, follicular bronchiolitis, and, infrequently, diffuse panbronchiolitis. Pathologically, RA-associated bronchiolitis is indistinguishable from other causes. Among 25 non-smokers with severe fixed airflow obstruction, bronchial wall thickening was the most common radiographic finding, followed by centrilobular emphysema, ground-glass opacification, mosaic attenuation (Fig. 3B), and bronchiectasis. Among the eight available biopsies in this study, there were six cases of constrictive bronchiolitis and one case of follicular bronchiolitis. Outcomes were overall poor, with approximately half experiencing progression of their symptoms and acute respiratory failure despite most patients receiving oral corticosteroids.⁹³ Other immunomodulatory agents, including cyclophosphamide, azathioprine, methotrexate, and tissue necrosis factor (TNF)-alpha inhibitors, have also been used with varying degrees of success.^{93–95} Despite unclear efficacy, many clinicians will often trial standard treatments for obstructive lung disease such as inhaled and systemic steroids. Macrolide therapy with azithromycin, which has been shown to attenuate lung function decline in post-lung transplant bronchiolitis obliterans,⁹⁶ or erythromycin, which may improve symptoms in RA-associated bronchiolitis,⁹⁷ is a reasonable option.

Follicular bronchiolitis, characterized by hyperplasia of bronchial associated lymphoid tissue (BALT), has been associated with CTDs including RA, Sjögren's syndrome, and systemic lupus erythematosus as well as immunodeficiency disorders.⁹⁸ HRCT may demonstrate centrilobular and peribronchial nodularity in addition to features of small airway disease.⁹⁹ It is pathologically related to other lymphoproliferative conditions such as LIP, and immunohistochemistry may be considered to rule out malignancy. Management may involve corticosteroids and in some cases rituximab when there is evidence of exuberant lymphoid aggregates in the airways.^{97,98} Outcomes for follicular bronchiolitis are generally more favorable than for constrictive bronchiolitis.

The prevalence of bronchiectasis in RA is higher than the general population, occurring in up to 30% of RA patients with no ILD;⁹² in a series of individuals with RA-associated airflow obstruction, 40% had bronchiectasis.⁹³ Although often asymptomatic, patients with

bronchiectasis and RA have been found to have increased bronchiectasis severity index scores and mortality compared to those with idiopathic bronchiectasis.^{100,101} Interestingly, among a group of RA patients with diffuse bronchiectasis, 15.4% were found to be heterozygous for the CFTR gene delta F508 mutation.¹⁰² In patients with symptomatic disease, management usually consists of standard treatment of bronchiectasis, including bronchodilators, mucus clearance, and antibiotics. The presence of bronchiectasis may complicate the use of anti-inflammatory therapies for RA, which augment the risk of respiratory infections.

PLEURAL DISEASE

Inflammation of the pleurae, manifesting as pleural thickening and/or effusions (Fig. 4A), is a common extraarticular manifestation of RA. In postmortem studies, pleural involvement is described in over 70% of patients, but less than 3–5% of patients are symptomatic.^{103–107} In earlier studies, pleural thickening and/or effusion was reported on chest radiograph in 24% of men and 16% of women.¹⁰⁸ Most effusions are unilateral, are more commonly found in male patients over the age of 35 with rheumatoid nodules, and have been associated with HLA-B8.^{103,109} If the patient is symptomatic, the most common presenting complaints are fever and pleuritic chest pain. Cough is uncommon unless parenchymal disease is present.

A “rheumatoid effusion” is classically described as a sterile exudative effusion with a low pH (<7.3), low glucose (<60 mg/dL), and elevated lactate dehydrogenase (as high as >700 IU/L).^{103,104} In instances of chronic pleural inflammation, the fluid can appear “pseudochyloous” due to the presence of cholesterol crystals in the fluid, which importantly differs from a true chylothorax by the absence of triglycerides and/or chylomicrons.¹⁰³ Rheumatoid factor is often positive. White cell count and differential is variable but is more commonly lymphocytic predominant; however, neutrophil- and eosinophil-predominant cell counts are also described.¹¹⁰

Thoracentesis should be performed for any pleural effusion >1 cm on decubitus imaging. Infection must always be ruled out, as low pH, low glucose, and elevated lactate dehydrogenase are also typical of empyema. Tuberculous and malignant effusions can also mimic rheumatoid effusions. Pleural biopsy is rarely indicated but should be performed when the diagnosis is unclear.

Most effusions resolve with management of the underlying RA. If small and asymptomatic, no therapy is indicated; however, longstanding pleural inflammation can result in trapped lung physiology.^{103,111}

RHEUMATOID LUNG NODULES

Rheumatoid nodules develop primarily in the subcutaneous tissue over articular joints but can occur in the upper airways, lungs (Fig. 4B), heart, and, rarely, in the sclerae.^{84,112–114} Pathologically, they consist of necrobiotic lesions of giant cells within palisaded foci, which produce pro-inflammatory cytokines similar to those of synovial membrane.^{115,116} The presence of nodules is associated with increased severity of RA and an elevated risk of vasculitis, hospitalization, and mortality.^{117–119} In a series of 40 patients with RA and open

lung biopsy, 32% were found to have rheumatoid nodules,¹¹³ although prevalence varies widely across studies.¹²⁰ In the lungs, they often occur in the subpleural regions and fissures,¹²¹ ranging in size from a few millimeters to greater than 7 cm.¹²² Infection, particularly with fungal and mycobacterial organisms, and malignancy should be considered in the differential. While most pulmonary RA nodules are asymptomatic and do not require treatment, larger nodules may cavitate and cause hemoptysis, pleural effusions, spontaneous pneumothoraces (Fig. 4B), or bronchopleural fistulae.¹²¹ B-cell therapies such as rituximab may decrease the size and number of pulmonary rheumatoid nodules.¹²³ Disease modifying anti-rheumatic drugs (DMARDs) including methotrexate and anti-TNF-alpha inhibitors have been associated with increased pulmonary nodulosis though it is unclear that these therapies should be stopped for this reason.^{124,125}

The occurrence of multiple, predominantly peripheral pulmonary nodules in a large cohort of coal miners with RA was first described in 1953 and came to be known as Caplan syndrome; as this was later broadened to include exposure to other inorganic dusts—silica in particular—the term rheumatoid pneumoconiosis is also used. Lung nodules may be detected in exposed subjects more than ten years prior to the development of arthritis.¹²⁶ Radiographically, nodules tend to form rapidly and persist over years, with approximately 10% developing cavitations or calcifications.¹²⁷ A causal link between RA and dust exposure has not been established, but it has been hypothesized that the exposure to foreign particles leads to chronic immune activity that might facilitate the formation of autoantibodies. Indeed, pneumoconiosis has been associated with increased immune complexes and rheumatoid factor positivity even without an apparent autoimmune diagnosis.^{127,128}

PULMONARY VASCULAR DISEASE

Pulmonary vascular disease is associated with RA but is regarded as a rare manifestation. Pulmonary hypertension in RA patients can occur as primary pulmonary arterial hypertension—thought to be due to an underlying vasculitis due to concomitant signs of systemic vasculitis that are often present—or secondary to severe parenchymal lung disease. Estimates of the prevalence of asymptomatic, isolated pulmonary hypertension by cross-sectional echocardiography (defined as a pulmonary artery systolic pressure ≥ 30 mmHg on echocardiography) in RA patients are between 21–28%, which is significantly higher than age-matched controls (4.5%).^{129–132} This finding is especially applicable to older patients, those with longer disease duration, and those with joint deformities.^{130,131} However, these echocardiographic studies are limited by the absence of right heart catheterization to confirm imaging observations and by liberal definitions of abnormal right-sided pressures, increasing the false positive rate and therefore the reported prevalence. Patients with RA are also at slightly increased risk for venous thromboembolism, even when controlling for other risk factors such as age, sex, comorbid diseases, and recent hospitalization.^{133,134} In a Taiwanese study, the risks of deep venous thrombosis and pulmonary embolism were increased about 3.5- and 2-fold, respectively, in RA patients compared to healthy age-matched controls.¹³³

DRUG-INDUCED LUNG TOXICITY

Drug-induced lung disease should be considered when an RA patient presents with new respiratory complaints, new findings on HRCT, or unexpected worsening of ILD. Almost all DMARDs and biologic therapies have been associated with lung toxicity in addition to an increased risk of infection.¹³⁵ The incidence of drug-induced lung disease in RA is not well characterized although one systematic review reported a relatively low overall risk of about 1% but with high mortality.¹³⁶ It is often a diagnosis of exclusion. Empiric drug discontinuation is an important diagnostic step, as noninfectious drug-related toxicity tends to regress upon withdrawal of the offending agent and, if disease is significant, treatment with steroids. Other diagnostics include laboratory testing (e.g., complete blood count with differential, b-type natriuretic peptide, c-reactive protein, cultures, and serologic studies), imaging, PFTs, and bronchoscopy. Lung biopsy rarely establishes the diagnosis, as there are no pathognomonic findings for drug-induced lung toxicity.¹³⁷ The differential includes rheumatoid-associated lung disease, infection, and heart failure, which may be hard to differentiate due to significant overlap of these clinical syndromes.

Methotrexate (MTX):

MTX is the most commonly prescribed DMARD for management of RA. Interstitial pneumonitis is the most common noninfectious pulmonary complication although it is regarded as a rare adverse event in RA patients. Its incidence, however, is difficult to determine due to diagnostic uncertainty and lack of a gold standard. Estimates vary between 0.43–1% of treated patients in up to 3 years of follow-up; however, mortality rates of up to 17% have been reported.^{138–140} MTX pneumonitis is thought to represent a unique hypersensitivity reaction. Onset typically occurs early in the course of MTX therapy (often within the first year),¹⁴¹ resolves after discontinuation of the drug and administration of corticosteroids,¹⁴² and has been reported in other conditions treated with MTX such as psoriatic arthritis.¹⁴³ It is unclear if pre-existing RA-ILD increases the risk of MTX pneumonitis as some studies have found up to 7.5 times increased risk^{144,145} while others suggest no association.^{146,147} There is currently no conclusive evidence that pulmonary disease progresses in patients with RA-ILD on MTX who do not develop pneumonitis.^{140,148} Less commonly, rheumatoid lung nodulosis, asthma, or air trapping can occur with MTX treatment, but it is unclear if these manifestations are drug-related or are due to underlying RA.¹⁴⁰ Given data that show a clear mortality benefit with use of MTX for RA in general,¹⁴⁹ the decision to withhold or withdraw MTX in RA patients with underlying lung disease can be difficult. Nonetheless, it may be justified to continue MTX in some cases in the face of stable joint disease and suppression of systemic inflammation.

Biologic Agents/Synthetic DMARDs:

TNF-alpha inhibitors, anakinra, rituximab, abatacept, and now Janus kinase inhibitors improve symptoms, joint disease, and possibly pulmonary disease in RA patients;¹⁵⁰ however, rare cases of pulmonary toxicity, including provocation or exacerbation of ILD, have been described.^{83,151} A systematic review estimated the overall risk of drug-induced ILD with biologic agents to be 1% in RA patients.¹³⁶ Data regarding morbidity and mortality associated with ILD due to anti-TNF-alpha therapy is conflicted and is most often

associated with infliximab.^{136,152,153} However, a study of post marketing surveillance of TNF-alpha inhibitors failed to identify any significant difference in the risk of ILD or its related complications compared to other biologics.⁸⁰ Drug-induced ILD has been reported with TNF-alpha inhibitors and anakinra, though not abatacept, and is more common in patients with preexisting ILD or who are aged 65 or older.^{154,155} Only a few cases of ILD have been described for rituximab therapy in RA patients.^{78,156} Several of these agents have also been associated with granulomatous lung disease and an increased risk of serious infections, particularly with TNF-alpha inhibitors.^{125,157} Although the frequency is thought to be low, development of new or worsening cough, dyspnea, or radiographic abnormalities in RA patients on biologic therapies should alert the physician to the possibility of drug-induced ILD.

Sulfasalazine:

Sulfasalazine has been associated with pneumonitis, with nearly half of affected patients presenting with pulmonary infiltrates and eosinophilia.^{136,158} Clinical improvement usually occurs with cessation of the drug although respiratory failure and death have been described. Other disorders associated with sulfasalazine include NSIP, organizing pneumonia, granulomatous disease, bronchiolitis obliterans, and pleural effusion.¹⁵⁸⁻¹⁶⁰

EMERGING DIAGNOSTIC APPROACHES AND TREATMENT MODALITIES

Our understanding of pulmonary complications in RA, especially RA-ILD, is still hampered by limited data regarding the natural history of disease and by imperfect diagnostic tools that are not sufficiently precise to identify which patients are at the greatest risk for progressive disease. There is promise, however, that emerging biomarkers, genomics, and computer-generated quantified CT assessments, amongst other newer technologies, may offer better tools to identify high-risk patients and thus candidates for treatment and clinical trials.^{161,162}

At this time, there are no formalized recommendations regarding screening for lung disease in RA. In light of potential therapeutic options that may become available, early assessment for ILD either with baseline physiologic testing or by CT in the context of lung cancer screening for high risk patients may be reasonable to identify ILD or early airway changes that are associated with RA (Fig. 2).¹³

Therapeutically, efforts to attenuate the development of fibrosis via the many identified pathways leading to fibrosis are being employed in clinical trials of IPF and may offer promise for RA-associated disease, though it is unclear whether these approaches may be equally applicable to RA-ILD. As of this publication, there are two trials in progress utilizing FDA-approved antifibrotic therapy in RA and other CTD-ILD. Newer insights into the mechanisms of RA, including the role of specific cytokines like IL-17, may demonstrate that the mechanisms important in the development of articular disease also play a role in lung disease and fibrosis.¹⁶³ In summary, our understanding of lung disease in RA and its treatment is at an inflection point of discovery and potential therapy, making lung health a priority in the care of patients with RA.

REFERENCES

1. Firestein GS. Evolving concepts of rheumatoid arthritis. *Nature*. 2003;423(6937):356–361. [PubMed: 12748655]
2. Gabriel SE, Crowson CS, O’Fallon WM. The epidemiology of rheumatoid arthritis in Rochester, Minnesota, 1955–1985. *Arthritis Rheum*. 1999;42(3):415–420. [PubMed: 10088762]
3. Birnbaum H, Pike C, Kaufman R, Marynchenko M, Kidolezi Y, Cifaldi M. Societal cost of rheumatoid arthritis patients in the US. *Curr Med Res Opin*. 2010;26(1):77–90. [PubMed: 19908947]
4. Cross M, Smith E, Hoy D, et al. The global burden of rheumatoid arthritis: estimates from the global burden of disease 2010 study. *Ann Rheum Dis*. 2014;73(7):1316–1322. [PubMed: 24550173]
5. Myasoedova E, Crowson CS, Kremers HM, Therneau TM, Gabriel SE. Is the incidence of rheumatoid arthritis rising?: results from Olmsted County, Minnesota, 1955–2007. *Arthritis Rheum*. 2010;62(6):1576–1582. [PubMed: 20191579]
6. Turesson C, O’Fallon WM, Crowson CS, Gabriel SE, Matteson EL. Extra-articular disease manifestations in rheumatoid arthritis: incidence trends and risk factors over 46 years. *Ann Rheum Dis*. 2003;62(8):722–727. [PubMed: 12860726]
7. Cortet B, Perez T, Roux N, et al. Pulmonary function tests and high resolution computed tomography of the lungs in patients with rheumatoid arthritis. *Ann Rheum Dis*. 1997;56(10):596–600. [PubMed: 9389220]
8. Bilgici A, Ulusoy H, Kuru O, Celenk C, Unsal M, Danaci M. Pulmonary involvement in rheumatoid arthritis. *Rheumatol Int*. 2005;25(6):429–435. [PubMed: 16133582]
9. Demir R, Bodur H, Tokoglu F, Olcay I, Ucan H, Borman P. High resolution computed tomography of the lungs in patients with rheumatoid arthritis. *Rheumatol Int*. 1999;19(1–2):19–22. [PubMed: 10651076]
10. Kanat F, Levendoglu F, Teke T. Radiological and functional assessment of pulmonary involvement in the rheumatoid arthritis patients. *Rheumatol Int*. 2007;27(5):459–466. [PubMed: 17028857]
11. Brown KK. Rheumatoid lung disease. *Proc Am Thorac Soc*. 2007;4(5):443–448. [PubMed: 17684286]
12. Yunt ZX, Solomon JJ. Lung disease in rheumatoid arthritis. *Rheum Dis Clin North Am*. 2015;41(2):225–236. [PubMed: 25836639]
13. Demoruelle MK, Weisman MH, Simonian PL, et al. Brief report: airways abnormalities and rheumatoid arthritis-related autoantibodies in subjects without arthritis: early injury or initiating site of autoimmunity? *Arthritis Rheum*. 2012;64(6):1756–1761. [PubMed: 22183986]
14. Wilsher M, Voight L, Milne D, et al. Prevalence of airway and parenchymal abnormalities in newly diagnosed rheumatoid arthritis. *Respir Med*. 2012;106(10):1441–1446. [PubMed: 22795504]
15. Fischer A, Solomon JJ, du Bois RM, et al. Lung disease with anti-CCP antibodies but not rheumatoid arthritis or connective tissue disease. *Respir Med*. 2012;106(7):1040–1047. [PubMed: 22503074]
16. Gizinski AM, Mascolo M, Loucks JL, et al. Rheumatoid arthritis (RA)-specific autoantibodies in patients with interstitial lung disease and absence of clinically apparent articular RA. *Clin Rheumatol*. 2009;28(5):611–613. [PubMed: 19252818]
17. Hamblin MJ, Horton MR. Rheumatoid arthritis-associated interstitial lung disease: diagnostic dilemma. *Pulm Med*. 2011;2011:872120. [PubMed: 21660199]
18. Saag KG, Teng GG, Patkar NM, et al. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. *Arthritis Rheum*. 2008;59(6):762–784. [PubMed: 18512708]
19. Myasoedova E, Crowson CS, Turesson C, Gabriel SE, Matteson EL. Incidence of extraarticular rheumatoid arthritis in Olmsted County, Minnesota, in 1995–2007 versus 1985–1994: a population-based study. *J Rheumatol*. 2011;38(6):983–989. [PubMed: 21459933]
20. Koduri G, Norton S, Young A, et al. Interstitial lung disease has a poor prognosis in rheumatoid arthritis: results from an inception cohort. *Rheumatology (Oxford)*. 2010;49(8):1483–1489. [PubMed: 20223814]

21. Turesson C, O'Fallon WM, Crowson CS, Gabriel SE, Matteson EL. Occurrence of extraarticular disease manifestations is associated with excess mortality in a community based cohort of patients with rheumatoid arthritis. *J Rheumatol*. 2002;29(1):62–67. [PubMed: 11824973]
22. Bongartz T, Nannini C, Medina-Velasquez YF, et al. Incidence and mortality of interstitial lung disease in rheumatoid arthritis: a population-based study. *Arthritis Rheum*. 2010;62(6):1583–1591. [PubMed: 20155830]
23. Dawson JK, Fewins HE, Desmond J, Lynch MP, Graham DR. Fibrosing alveolitis in patients with rheumatoid arthritis as assessed by high resolution computed tomography, chest radiography, and pulmonary function tests. *Thorax*. 2001;56(8):622–627. [PubMed: 11462065]
24. Saag KG, Kolluri S, Koehnke RK, et al. Rheumatoid arthritis lung disease. Determinants of radiographic and physiologic abnormalities. *Arthritis Rheum*. 1996;39(10):1711–1719. [PubMed: 8843862]
25. Olson AL, Swigris JJ, Sprunger DB, et al. Rheumatoid arthritis-interstitial lung disease-associated mortality. *Am J Respir Crit Care Med*. 2011;183(3):372–378. [PubMed: 20851924]
26. Raimundo K, Solomon JJ, Olson AL, et al. Rheumatoid Arthritis-Interstitial Lung Disease in the United States: Prevalence, Incidence, and Healthcare Costs and Mortality. *J Rheumatol*. 2018.
27. Padley SP, Hansell DM, Flower CD, Jennings P. Comparative accuracy of high resolution computed tomography and chest radiography in the diagnosis of chronic diffuse infiltrative lung disease. *Clin Radiol*. 1991;44(4):222–226. [PubMed: 1959296]
28. Gabbay E, Tarala R, Will R, et al. Interstitial lung disease in recent onset rheumatoid arthritis. *Am J Respir Crit Care Med*. 1997;156(2 Pt 1):528–535. [PubMed: 9279235]
29. Gochuico BR, Avila NA, Chow CK, et al. Progressive preclinical interstitial lung disease in rheumatoid arthritis. *Arch Intern Med*. 2008;168(2):159–166. [PubMed: 18227362]
30. Chen J, Shi Y, Wang X, Huang H, Ascherman D. Asymptomatic preclinical rheumatoid arthritis-associated interstitial lung disease. *Clin Dev Immunol*. 2013;2013:406927. [PubMed: 23983768]
31. Dawson JK, Fewins HE, Desmond J, Lynch MP, Graham DR. Predictors of progression of HRCT diagnosed fibrosing alveolitis in patients with rheumatoid arthritis. *Ann Rheum Dis*. 2002;61(6):517–521. [PubMed: 12006324]
32. Assayag D, Elicker BM, Urbania TH, et al. Rheumatoid arthritis-associated interstitial lung disease: radiologic identification of usual interstitial pneumonia pattern. *Radiology*. 2014;270(2):583–588. [PubMed: 24126367]
33. Kelly CA, Saravanan V, Nisar M, et al. Rheumatoid arthritis-related interstitial lung disease: associations, prognostic factors and physiological and radiological characteristics--a large multicentre UK study. *Rheumatology (Oxford)*. 2014;53(9):1676–1682. [PubMed: 24758887]
34. Doyle TJ, Dellaripa PF, Batra K, et al. Functional impact of a spectrum of interstitial lung abnormalities in rheumatoid arthritis. *Chest*. 2014;146(1):41–50. [PubMed: 24305643]
35. Esposito DB, Lanes S, Donneyong M, et al. Idiopathic Pulmonary Fibrosis in United States Automated Claims. Incidence, Prevalence, and Algorithm Validation. *Am J Respir Crit Care Med*. 2015;192(10):1200–1207. [PubMed: 26241562]
36. Turesson C Extra-articular rheumatoid arthritis. *Curr Opin Rheumatol*. 2013;25(3):360–366. [PubMed: 23425964]
37. Bergstrom U, Jacobsson LT, Nilsson JA, Berglund G, Turesson C. Pulmonary dysfunction, smoking, socioeconomic status and the risk of developing rheumatoid arthritis. *Rheumatology (Oxford)*. 2011;50(11):2005–2013. [PubMed: 21859698]
38. Hassan WU, Keaney NP, Holland CD, Kelly CA. High resolution computed tomography of the lung in lifelong non-smoking patients with rheumatoid arthritis. *Ann Rheum Dis*. 1995;54(4):308–310. [PubMed: 7763110]
39. Solomon JJ, Chung JH, Cosgrove GP, et al. Predictors of mortality in rheumatoid arthritis-associated interstitial lung disease. *Eur Respir J*. 2016;47(2):588–596. [PubMed: 26585429]
40. Doyle TJ, Patel AS, Hatabu H, et al. Detection of Rheumatoid Arthritis-Interstitial Lung Disease Is Enhanced by Serum Biomarkers. *Am J Respir Crit Care Med*. 2015;191(12):1403–1412. [PubMed: 25822095]
41. Mori S, Koga Y, Sugimoto M. Different risk factors between interstitial lung disease and airway disease in rheumatoid arthritis. *Respir Med*. 2012;106(11):1591–1599. [PubMed: 22867979]

42. Giles JT, Danoff SK, Sokolove J, et al. Association of fine specificity and repertoire expansion of anticitrullinated peptide antibodies with rheumatoid arthritis associated interstitial lung disease. *Ann Rheum Dis*. 2014;73(8):1487–1494. [PubMed: 23716070]
43. Juge PA, Borie R, Kannengiesser C, et al. Shared genetic predisposition in rheumatoid arthritis-interstitial lung disease and familial pulmonary fibrosis. *Eur Respir J*. 2017;49(5).
44. Seibold MA, Wise AL, Speer MC, et al. A common MUC5B promoter polymorphism and pulmonary fibrosis. *N Engl J Med*. 2011;364(16):1503–1512. [PubMed: 21506741]
45. American Thoracic S, European Respiratory S. American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001 and by the ERS Executive Committee, June 2001. *Am J Respir Crit Care Med*. 2002;165(2):277–304. [PubMed: 11790668]
46. Raghu G, Collard HR, Egan JJ, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med*. 2011;183(6):788–824. [PubMed: 21471066]
47. Tanaka N, Kim JS, Newell JD, et al. Rheumatoid arthritis-related lung diseases: CT findings. *Radiology*. 2004;232(1):81–91. [PubMed: 15166329]
48. Lee HK, Kim DS, Yoo B, et al. Histopathologic pattern and clinical features of rheumatoid arthritis-associated interstitial lung disease. *Chest*. 2005;127(6):2019–2027. [PubMed: 15947315]
49. Solomon JJ, Ryu JH, Tazelaar HD, et al. Fibrosing interstitial pneumonia predicts survival in patients with rheumatoid arthritis-associated interstitial lung disease (RA-ILD). *Respir Med*. 2013;107(8):1247–1252. [PubMed: 23791462]
50. Swensen SJ, Aughenbaugh GL, Myers JL. Diffuse lung disease: diagnostic accuracy of CT in patients undergoing surgical biopsy of the lung. *Radiology*. 1997;205(1):229–234. [PubMed: 9314990]
51. Raghu G, Margeto YN, Lockhart D, Schmidt RA, Wood DE, Godwin JD. The accuracy of the clinical diagnosis of new-onset idiopathic pulmonary fibrosis and other interstitial lung disease: A prospective study. *Chest*. 1999;116(5):1168–1174. [PubMed: 10559072]
52. Hunninghake GW, Zimmerman MB, Schwartz DA, et al. Utility of a lung biopsy for the diagnosis of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*. 2001;164(2):193–196. [PubMed: 11463586]
53. Mathieson JR, Mayo JR, Staples CA, Muller NL. Chronic diffuse infiltrative lung disease: comparison of diagnostic accuracy of CT and chest radiography. *Radiology*. 1989;171(1):111–116. [PubMed: 2928513]
54. Assayag D, Lee JS, King TE, Jr. Rheumatoid arthritis associated interstitial lung disease: a review. *Medicina (B Aires)*. 2014;74(2):158–165. [PubMed: 24736263]
55. Kim EJ, Elicker BM, Maldonado F, et al. Usual interstitial pneumonia in rheumatoid arthritis-associated interstitial lung disease. *Eur Respir J*. 2010;35(6):1322–1328. [PubMed: 19996193]
56. Nurmi HM, Purokivi MK, Karkkainen MS, Kettunen HP, Selander TA, Kaarteenaho RL. Variable course of disease of rheumatoid arthritis-associated usual interstitial pneumonia compared to other subtypes. *BMC Pulm Med*. 2016;16(1):107. [PubMed: 27461264]
57. Mori S, Cho I, Koga Y, Sugimoto M. A simultaneous onset of organizing pneumonia and rheumatoid arthritis, along with a review of the literature. *Mod Rheumatol*. 2008;18(1):60–66. [PubMed: 18159567]
58. Brannan HM, Good CA, Divertie MB, Baggenstoss AH. Pulmonary Disease Associated with Rheumatoid Arthritis. *JAMA*. 1964;189:914–918. [PubMed: 14174328]
59. Mohd Noor N, Mohd Shahrir MS, Shahid MS, Abdul Manap R, Shahizon Azura AM, Azhar Shah S. Clinical and high resolution computed tomography characteristics of patients with rheumatoid arthritis lung disease. *Int J Rheum Dis*. 2009;12(2):136–144. [PubMed: 20374331]
60. Pappas DA, Giles JT, Connors G, Lechtzin N, Bathon JM, Danoff SK. Respiratory symptoms and disease characteristics as predictors of pulmonary function abnormalities in patients with rheumatoid arthritis: an observational cohort study. *Arthritis Res Ther*. 2010;12(3):R104. [PubMed: 20507627]

61. Skare TL, Nakano I, Escuissiato DL, Batistetti R, Rodrigues Tde O, Silva MB. Pulmonary changes on high-resolution computed tomography of patients with rheumatoid arthritis and their association with clinical, demographic, serological and therapeutic variables. *Rev Bras Reumatol.* 2011;51(4):325–330, 336–327. [PubMed: 21779709]
62. Biederer J, Schnabel A, Muhle C, Gross WL, Heller M, Reuter M. Correlation between HRCT findings, pulmonary function tests and bronchoalveolar lavage cytology in interstitial lung disease associated with rheumatoid arthritis. *Eur Radiol.* 2004;14(2):272–280. [PubMed: 14557895]
63. Krause ML, Zamora AC, Vassallo R, Ryu JH, Matteson EL. The lung disease of rheumatoid arthritis. *Curr Respir Med Rev.* 2015;11(2):119–129.
64. Lake F, Proudman S. Rheumatoid arthritis and lung disease: from mechanisms to a practical approach. *Semin Respir Crit Care Med.* 2014;35(2):222–238. [PubMed: 24668537]
65. Raghu G, Rochwerg B, Zhang Y, et al. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline: Treatment of Idiopathic Pulmonary Fibrosis. An Update of the 2011 Clinical Practice Guideline. *Am J Respir Crit Care Med.* 2015;192(2):e3–19. [PubMed: 26177183]
66. Zamora-Legoff JA, Krause ML, Crowson CS, Ryu JH, Matteson EL. Risk of serious infection in patients with rheumatoid arthritis-associated interstitial lung disease. *Clin Rheumatol.* 2016;35(10):2585–2589. [PubMed: 27448151]
67. Dixon WG, Abrahamowicz M, Beauchamp ME, et al. Immediate and delayed impact of oral glucocorticoid therapy on risk of serious infection in older patients with rheumatoid arthritis: a nested case-control analysis. *Ann Rheum Dis.* 2012;71(7):1128–1133. [PubMed: 22241902]
68. Idiopathic Pulmonary Fibrosis Clinical Research N, Raghu G, Anstrom KJ, King TE Jr., Lasky JA, Martinez FJ. Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. *N Engl J Med.* 2012;366(21):1968–1977. [PubMed: 22607134]
69. Mendoza FA, Nagle SJ, Lee JB, Jimenez SA. A prospective observational study of mycophenolate mofetil treatment in progressive diffuse cutaneous systemic sclerosis of recent onset. *J Rheumatol.* 2012;39(6):1241–1247. [PubMed: 22467932]
70. Shenoy PD, Bavaliya M, Sashidharan S, Nalianda K, Sreenath S. Cyclophosphamide versus mycophenolate mofetil in scleroderma interstitial lung disease (SSc-ILD) as induction therapy: a single-centre, retrospective analysis. *Arthritis Res Ther.* 2016;18(1):123. [PubMed: 27255492]
71. Fischer A, Brown KK, Du Bois RM, et al. Mycophenolate mofetil improves lung function in connective tissue disease-associated interstitial lung disease. *J Rheumatol.* 2013;40(5):640–646. [PubMed: 23457378]
72. Nannini C, West CP, Erwin PJ, Matteson EL. Effects of cyclophosphamide on pulmonary function in patients with scleroderma and interstitial lung disease: a systematic review and meta-analysis of randomized controlled trials and observational prospective cohort studies. *Arthritis Res Ther.* 2008;10(5):R124. [PubMed: 18937831]
73. Tashkin DP, Elashoff R, Clements PJ, et al. Cyclophosphamide versus placebo in scleroderma lung disease. *N Engl J Med.* 2006;354(25):2655–2666. [PubMed: 16790698]
74. Ogawa D, Hashimoto H, Wada J, et al. Successful use of cyclosporin A for the treatment of acute interstitial pneumonitis associated with rheumatoid arthritis. *Rheumatology (Oxford).* 2000;39(12):1422–1424. [PubMed: 11136888]
75. Chang HK, Park W, Ryu DS. Successful treatment of progressive rheumatoid interstitial lung disease with cyclosporine: a case report. *J Korean Med Sci.* 2002;17(2):270–273. [PubMed: 11961317]
76. Eissa K, Palomino J. B-Cell Depletion Salvage Therapy in Rapidly Progressive Dermatomyositis Related Interstitial Lung Disease. *J La State Med Soc.* 2016;168(3):99–100. [PubMed: 27389378]
77. Keir GJ, Maher TM, Hansell DM, et al. Severe interstitial lung disease in connective tissue disease: rituximab as rescue therapy. *Eur Respir J.* 2012;40(3):641–648. [PubMed: 22282550]
78. Matteson EL, Bongartz T, Ryu JH, Crowson CS, Hartman TE, Dellaripa PF. Open-label, pilot study of the safety and clinical effects of rituximab in patients with rheumatoid arthritis associated interstitial pneumonia. *Open J Rheumatol Autoimmune Dis.* 2012;2:53–58.
79. Mera-Varela A, Perez-Pampin E. Abatacept therapy in rheumatoid arthritis with interstitial lung disease. *J Clin Rheumatol.* 2014;20(8):445–446. [PubMed: 25417684]

80. Curtis JR, Sarsour K, Napalkov P, Costa LA, Schulman KL. Incidence and complications of interstitial lung disease in users of tocilizumab, rituximab, abatacept and anti-tumor necrosis factor alpha agents, a retrospective cohort study. *Arthritis Res Ther*. 2015;17:319. [PubMed: 26555431]
81. Fernandez-Diaz C, Loricera J, Castaneda S, et al. Abatacept in patients with rheumatoid arthritis and interstitial lung disease: A national multicenter study of 63 patients. *Semin Arthritis Rheum*. 2018;48(1):22–27. [PubMed: 29422324]
82. Yazdani A, Singer LG, Strand V, Gelber AC, Williams L, Mittoo S. Survival and quality of life in rheumatoid arthritis-associated interstitial lung disease after lung transplantation. *J Heart Lung Transplant*. 2014;33(5):514–520. [PubMed: 24630861]
83. Jani M, Hirani N, Matteson EL, Dixon WG. The safety of biologic therapies in RA-associated interstitial lung disease. *Nat Rev Rheumatol*. 2014;10(5):284–294. [PubMed: 24366321]
84. Friedman BA. Rheumatoid nodules of the larynx. *Arch Otolaryngol*. 1975;101(6):361–363. [PubMed: 1131102]
85. Webb J, Payne WH. Rheumatoid nodules of the vocal folds. *Ann Rheum Dis*. 1972;31(2):122–125. [PubMed: 4111640]
86. Hamdan AL, Saredidine D. Laryngeal manifestations of rheumatoid arthritis. *Autoimmune Dis*. 2013;2013:103081. [PubMed: 23864939]
87. Lawry GV, Finerman ML, Hanafee WN, Mancuso AA, Fan PT, Bluestone R. Laryngeal involvement in rheumatoid arthritis. A clinical, laryngoscopic, and computerized tomographic study. *Arthritis Rheum*. 1984;27(8):873–882. [PubMed: 6466395]
88. Guerra LG, Lau KY, Marwah R. Upper airway obstruction as the sole manifestation of rheumatoid arthritis. *J Rheumatol*. 1992;19(6):974–976. [PubMed: 1404138]
89. Brazeau-Lamontagne L, Charlin B, Levesque RY, Lussier A. Cricoarytenoiditis: CT assessment in rheumatoid arthritis. *Radiology*. 1986;158(2):463–466. [PubMed: 3941873]
90. Chen JJ, Branstetter BFT, Myers EN. Cricoarytenoid rheumatoid arthritis: an important consideration in aggressive lesions of the larynx. *AJNR Am J Neuroradiol*. 2005;26(4):970–972. [PubMed: 15814955]
91. Erb N, Pace AV, Delamere JP, Kitas GD. Control of unremitting rheumatoid arthritis by the prolactin antagonist cabergoline. *Rheumatology (Oxford)*. 2001;40(2):237–239. [PubMed: 11257171]
92. Perez T, Remy-Jardin M, Cortet B. Airways involvement in rheumatoid arthritis: clinical, functional, and HRCT findings. *Am J Respir Crit Care Med*. 1998;157(5 Pt 1):1658–1665. [PubMed: 9603152]
93. Devouassoux G, Cottin V, Liote H, et al. Characterisation of severe obliterative bronchiolitis in rheumatoid arthritis. *Eur Respir J*. 2009;33(5):1053–1061. [PubMed: 19129282]
94. Pommepuy I, Farny M, Billey T, Olivier P, Lassoued S. Bronchiolitis obliterans organizing pneumonia in a patient with rheumatoid arthritis. *Rev Rhum Engl Ed*. 1998;65(1):65–67. [PubMed: 9523389]
95. Cortot AB, Cottin V, Miossec P, Fauchon E, Thivolet-Bejui F, Cordier JF. Improvement of refractory rheumatoid arthritis-associated constrictive bronchiolitis with etanercept. *Respir Med*. 2005;99(4):511–514. [PubMed: 15763460]
96. Vos R, Vanaudenaerde BM, Verleden SE, Van Raemdonck DE, Dupont LJ, Verleden GM. Azithromycin in posttransplant bronchiolitis obliterans syndrome. *Chest*. 2011;139(5):1246. [PubMed: 21540223]
97. Hayakawa H, Sato A, Imokawa S, Toyoshima M, Chida K, Iwata M. Bronchiolar disease in rheumatoid arthritis. *Am J Respir Crit Care Med*. 1996;154(5):1531–1536. [PubMed: 8912776]
98. Tashtoush B, Okafor NC, Ramirez JF, Smolley L. Follicular Bronchiolitis: A Literature Review. *J Clin Diagn Res*. 2015;9(9):OE01–05.
99. Howling SJ, Hansell DM, Wells AU, Nicholson AG, Flint JD, Muller NL. Follicular bronchiolitis: thin-section CT and histologic findings. *Radiology*. 1999;212(3):637–642. [PubMed: 10478225]
100. De Soyza A, McDonnell MJ, Goeminne PC, et al. Bronchiectasis Rheumatoid Overlap Syndrome Is an Independent Risk Factor for Mortality in Patients With Bronchiectasis: A Multicenter Cohort Study. *Chest*. 2017;151(6):1247–1254. [PubMed: 28093268]

101. Swinson DR, Symmons D, Suresh U, Jones M, Booth J. Decreased survival in patients with co-existent rheumatoid arthritis and bronchiectasis. *Br J Rheumatol*. 1997;36(6):689–691. [PubMed: 9236680]
102. Puechal X, Fajac I, Bienvenu T, et al. Increased frequency of cystic fibrosis deltaF508 mutation in bronchiectasis associated with rheumatoid arthritis. *Eur Respir J*. 1999;13(6):1281–1287. [PubMed: 10445602]
103. Balbir-Gurman A, Yigla M, Nahir AM, Braun-Moscovici Y. Rheumatoid pleural effusion. *Semin Arthritis Rheum*. 2006;35(6):368–378. [PubMed: 16765714]
104. Corcoran JP, Ahmad M, Mukherjee R, Redmond KC. Pleuro-pulmonary complications of rheumatoid arthritis. *Respir Care*. 2014;59(4):e55–59. [PubMed: 23962501]
105. Fingerman DL, Andrus FC. Visceral Lesions Associated with Rheumatoid Arthritis. *Ann Rheum Dis*. 1943;3(3):168–181. [PubMed: 18623696]
106. Horler AR, Thompson M. The pleural and pulmonary complications of rheumatoid arthritis. *Ann Intern Med*. 1959;51:1179–1203. [PubMed: 14403114]
107. Hyland RH, Gordon DA, Broder I, et al. A systematic controlled study of pulmonary abnormalities in rheumatoid arthritis. *J Rheumatol*. 1983;10(3):395–405. [PubMed: 6887163]
108. Jurik AG, Davidsen D, Graudal H. Prevalence of pulmonary involvement in rheumatoid arthritis and its relationship to some characteristics of the patients. A radiological and clinical study. *Scand J Rheumatol*. 1982;11(4):217–224. [PubMed: 7178857]
109. Hakala M, Tiilikainen A, Hameenkorpi R, et al. Rheumatoid arthritis with pleural effusion includes a subgroup with autoimmune features and HLA-B8, Dw3 association. *Scand J Rheumatol*. 1986;15(3):290–296. [PubMed: 3492039]
110. Avnon LS, Abu-Shakra M, Flusser D, Heimer D, Sion-Vardy N. Pleural effusion associated with rheumatoid arthritis: what cell predominance to anticipate? *Rheumatol Int*. 2007;27(10):919–925. [PubMed: 17294192]
111. Walker WC, Wright V. Rheumatoid pleuritis. *Ann Rheum Dis*. 1967;26(6):467–474. [PubMed: 6066230]
112. Ojeda VJ, Stuckey BG, Owen ET, Walters MN. Cardiac rheumatoid nodules. *Med J Aust*. 1986;144(2):92–93. [PubMed: 3941651]
113. Yousem SA, Colby TV, Carrington CB. Lung biopsy in rheumatoid arthritis. *Am Rev Respir Dis*. 1985;131(5):770–777. [PubMed: 3873887]
114. Lyne AJ, Rosen ES. Still's disease and rheumatoid nodule of the sclera. *Br J Ophthalmol*. 1968;52(11):853–856. [PubMed: 5696915]
115. Patterson JW. Rheumatoid nodule and subcutaneous granuloma annulare. A comparative histologic study. *Am J Dermatopathol*. 1988;10(1):1–8. [PubMed: 2459983]
116. Wikaningrum R, Highton J, Parker A, et al. Pathogenic mechanisms in the rheumatoid nodule: comparison of proinflammatory cytokine production and cell adhesion molecule expression in rheumatoid nodules and synovial membranes from the same patient. *Arthritis Rheum*. 1998;41(10):1783–1797. [PubMed: 9778219]
117. Nyhall-Wahlin BM, Turesson C, Jacobsson LT, et al. The presence of rheumatoid nodules at early rheumatoid arthritis diagnosis is a sign of extra-articular disease and predicts radiographic progression of joint destruction over 5 years. *Scand J Rheumatol*. 2011;40(2):81–87. [PubMed: 20919947]
118. Turesson C, McClelland RL, Christianson T, Matteson E. Clustering of extraarticular manifestations in patients with rheumatoid arthritis. *J Rheumatol*. 2008;35(1):179–180. [PubMed: 18176994]
119. Voskuyl AE, Zwinderman AH, Westedt ML, Vandenbroucke JP, Breedveld FC, Hazes JM. Factors associated with the development of vasculitis in rheumatoid arthritis: results of a case-control study. *Ann Rheum Dis*. 1996;55(3):190–192. [PubMed: 8712883]
120. Walker WC, Wright V. Pulmonary lesions and rheumatoid arthritis. *Medicine (Baltimore)*. 1968;47(6):501–520. [PubMed: 5727884]
121. Chansakul T, Dellaripa PF, Doyle TJ, Madan R. Intra-thoracic rheumatoid arthritis: Imaging spectrum of typical findings and treatment related complications. *Eur J Radiol*. 2015;84(10):1981–1991. [PubMed: 26210094]

122. Sargin G, Senturk T. Multiple pulmonary rheumatoid nodules. *Reumatologia*. 2015;53(5):276–278. [PubMed: 27407259]
123. Glace B, Gottenberg JE, Mariette X, et al. Efficacy of rituximab in the treatment of pulmonary rheumatoid nodules: findings in 10 patients from the French AutoImmunity and Rituximab/Rheumatoid Arthritis registry (AIR/PR registry). *Ann Rheum Dis*. 2012;71(8):1429–1431. [PubMed: 22504557]
124. Akiyama M, Mawatari T, Nakashima Y, et al. Prevalence of dyslipidemia in Japanese patients with rheumatoid arthritis and effects of atorvastatin treatment. *Clin Rheumatol*. 2015;34(11):1867–1875. [PubMed: 26292631]
125. Toussiot E, Berthelot JM, Pertuiset E, et al. Pulmonary nodulosis and aseptic granulomatous lung disease occurring in patients with rheumatoid arthritis receiving tumor necrosis factor- α -blocking agent: a case series. *J Rheumatol*. 2009;36(11):2421–2427. [PubMed: 19797509]
126. Caplan A Certain unusual radiological appearances in the chest of coal-miners suffering from rheumatoid arthritis. *Thorax*. 1953;8(1):29–37. [PubMed: 13038735]
127. Schreiber J, Koschel D, Kekow J, Waldburg N, Goette A, Merget R. Rheumatoid pneumoconiosis (Caplan's syndrome). *Eur J Intern Med*. 2010;21(3):168–172. [PubMed: 20493416]
128. Jones RN, Turner-Warwick M, Ziskind M, Weill H. High prevalence of antinuclear antibodies in sandblasters' silicosis. *Am Rev Respir Dis*. 1976;113(3):393–395. [PubMed: 1083176]
129. Shahane A Pulmonary hypertension in rheumatic diseases: epidemiology and pathogenesis. *Rheumatol Int*. 2013;33(7):1655–1667. [PubMed: 23334373]
130. Udayakumar N, Venkatesan S, Rajendiran C. Pulmonary hypertension in rheumatoid arthritis--relation with the duration of the disease. *Int J Cardiol*. 2008;127(3):410–412. [PubMed: 17689710]
131. Keser G, Capar I, Aksu K, et al. Pulmonary hypertension in rheumatoid arthritis. *Scand J Rheumatol*. 2004;33(4):244–245. [PubMed: 15370720]
132. Dawson JK, Goodson NG, Graham DR, Lynch MP. Raised pulmonary artery pressures measured with Doppler echocardiography in rheumatoid arthritis patients. *Rheumatology (Oxford)*. 2000;39(12):1320–1325. [PubMed: 11136873]
133. Chung WS, Peng CL, Lin CL, et al. Rheumatoid arthritis increases the risk of deep vein thrombosis and pulmonary thromboembolism: a nationwide cohort study. *Ann Rheum Dis*. 2014;73(10):1774–1780. [PubMed: 23926057]
134. Bacani AK, Gabriel SE, Crowson CS, Heit JA, Matteson EL. Noncardiac vascular disease in rheumatoid arthritis: increase in venous thromboembolic events? *Arthritis Rheum*. 2012;64(1):53–61. [PubMed: 21905005]
135. Singh JA, Cameron C, Noorbaloochi S, et al. Risk of serious infection in biological treatment of patients with rheumatoid arthritis: a systematic review and meta-analysis. *Lancet*. 2015;386(9990):258–265. [PubMed: 25975452]
136. Roubille C, Haraoui B. Interstitial lung diseases induced or exacerbated by DMARDs and biologic agents in rheumatoid arthritis: a systematic literature review. *Semin Arthritis Rheum*. 2014;43(5):613–626. [PubMed: 24231065]
137. Flieder DB, Travis WD. Pathologic characteristics of drug-induced lung disease. *Clin Chest Med*. 2004;25(1):37–45. [PubMed: 15062595]
138. Salliot C, van der Heijde D. Long-term safety of methotrexate monotherapy in patients with rheumatoid arthritis: a systematic literature research. *Ann Rheum Dis*. 2009;68(7):1100–1104. [PubMed: 19060002]
139. Sathi N, Chikura B, Kaushik VV, Wiswell R, Dawson JK. How common is methotrexate pneumonitis? A large prospective study investigates. *Clin Rheumatol*. 2012;31(1):79–83. [PubMed: 21638023]
140. Dawson JK, Graham DR, Desmond J, Fewins HE, Lynch MP. Investigation of the chronic pulmonary effects of low-dose oral methotrexate in patients with rheumatoid arthritis: a prospective study incorporating HRCT scanning and pulmonary function tests. *Rheumatology (Oxford)*. 2002;41(3):262–267. [PubMed: 11934961]

141. Carroll GJ, Thomas R, Phatouros CC, et al. Incidence, prevalence and possible risk factors for pneumonitis in patients with rheumatoid arthritis receiving methotrexate. *J Rheumatol*. 1994;21(1):51–54. [PubMed: 8151587]
142. Imokawa S, Colby TV, Leslie KO, Helmers RA. Methotrexate pneumonitis: review of the literature and histopathological findings in nine patients. *Eur Respir J*. 2000;15(2):373–381. [PubMed: 10706507]
143. Ameen M, Taylor DA, Williams IP, Wells AU, Barkert JN. Pneumonitis complicating methotrexate therapy for pustular psoriasis. *J Eur Acad Dermatol Venereol*. 2001;15(3):247–249. [PubMed: 11683290]
144. Alarcon GS, Kremer JM, Macaluso M, et al. Risk factors for methotrexate-induced lung injury in patients with rheumatoid arthritis. A multicenter, case-control study. Methotrexate-Lung Study Group. *Ann Intern Med*. 1997;127(5):356–364. [PubMed: 9273826]
145. Saravanan V, Kelly CA. Reducing the risk of methotrexate pneumonitis in rheumatoid arthritis. *Rheumatology (Oxford)*. 2004;43(2):143–147. [PubMed: 12923285]
146. Cottin V, Tebib J, Massonnet B, Souquet PJ, Bernard JP. Pulmonary function in patients receiving long-term low-dose methotrexate. *Chest*. 1996;109(4):933–938. [PubMed: 8635373]
147. Carson CW, Cannon GW, Egger MJ, Ward JR, Clegg DO. Pulmonary disease during the treatment of rheumatoid arthritis with low dose pulse methotrexate. *Semin Arthritis Rheum*. 1987;16(3):186–195. [PubMed: 3823910]
148. Rojas-Serrano J, Gonzalez-Velasquez E, Mejia M, Sanchez-Rodriguez A, Carrillo G. Interstitial lung disease related to rheumatoid arthritis: evolution after treatment. *Reumatol Clin*. 2012;8(2):68–71. [PubMed: 22341526]
149. Wasko MC, Dasgupta A, Hubert H, Fries JF, Ward MM. Propensity-adjusted association of methotrexate with overall survival in rheumatoid arthritis. *Arthritis Rheum*. 2013;65(2):334–342. [PubMed: 23044791]
150. Furst DE, Keystone EC, So AK, et al. Updated consensus statement on biological agents for the treatment of rheumatic diseases, 2012. *Ann Rheum Dis*. 2013;72 Suppl 2:ii2–34. [PubMed: 23532441]
151. Ramos-Casals M, Perez-Alvarez R, Perez-de-Lis M, Xaubet A, Bosch X, Group BS. Pulmonary disorders induced by monoclonal antibodies in patients with rheumatologic autoimmune diseases. *Am J Med*. 2011;124(5):386–394. [PubMed: 21531225]
152. Dixon WG, Hyrich KL, Watson KD, et al. Influence of anti-TNF therapy on mortality in patients with rheumatoid arthritis-associated interstitial lung disease: results from the British Society for Rheumatology Biologics Register. *Ann Rheum Dis*. 2010;69(6):1086–1091. [PubMed: 20444754]
153. Watson K, Symmons D, Griffiths I, Silman A. The British Society for Rheumatology biologics register. *Ann Rheum Dis*. 2005;64 Suppl 4:iv42–43. [PubMed: 16239385]
154. Perez-Alvarez R, Perez-de-Lis M, Diaz-Lagares C, et al. Interstitial lung disease induced or exacerbated by TNF-targeted therapies: analysis of 122 cases. *Semin Arthritis Rheum*. 2011;41(2):256–264. [PubMed: 21277618]
155. Weinblatt ME, Moreland LW, Westhovens R, et al. Safety of abatacept administered intravenously in treatment of rheumatoid arthritis: integrated analyses of up to 8 years of treatment from the abatacept clinical trial program. *J Rheumatol*. 2013;40(6):787–797. [PubMed: 23588946]
156. Naqibullah M, Shaker SB, Bach KS, Bendstrup E. Rituximab-induced interstitial lung disease: five case reports. *Eur Clin Respir J*. 2015;2.
157. Leon L, Gomez A, Vadillo C, et al. Severe adverse drug reactions to biological disease-modifying anti-rheumatic drugs in elderly patients with rheumatoid arthritis in clinical practice. *Clin Exp Rheumatol*. 2018;36(1):29–35.
158. Parry SD, Barbatzas C, Peel ET, Barton JR. Sulphasalazine and lung toxicity. *Eur Respir J*. 2002;19(4):756–764. [PubMed: 11999006]
159. Boyd O, Gibbs AR, Smith AP. Fibrosing alveolitis due to sulphasalazine in a patient with rheumatoid arthritis. *Br J Rheumatol*. 1990;29(3):222–224. [PubMed: 1972634]

160. Ulubas B, Sahin G, Ozer C, Aydin O, Ozgur E, Apaydin D. Bronchiolitis obliterans organizing pneumonia associated with sulfasalazine in a patient with rheumatoid arthritis. *Clin Rheumatol*. 2004;23(3):249–251. [PubMed: 15168156]
161. Jacob J, Hirani N, van Moorsel CHM, et al. Predicting outcomes in rheumatoid arthritis related interstitial lung disease. *Eur Respir J*. 2019;53(1).
162. Inchingolo R, Varone F, Sgalla G, Richeldi L. Existing and emerging biomarkers for disease progression in idiopathic pulmonary fibrosis. *Expert Rev Respir Med*. 2019;13(1):39–51. [PubMed: 30526140]
163. Zhang J, Wang D, Wang L, et al. Pro-fibrotic effects of IL-17A and elevated IL-17RA in IPF and RA-ILD support a direct role for IL-17A/IL-17RA in human fibrotic interstitial lung disease. *Am J Physiol Lung Cell Mol Physiol*. 2019.

Key Points:

- Pulmonary disease is a common extraarticular complication of rheumatoid arthritis and its associated treatment that can affect any anatomic compartment of the thorax.
- The optimal screening, diagnostic, and treatment strategies for rheumatoid arthritis-associated pulmonary disease remain uncertain and are the focus of ongoing investigation.
- Clinicians should regularly assess patients with rheumatoid arthritis for signs and symptoms of pulmonary disease and, reciprocally, consider rheumatoid arthritis and other connective tissue diseases when evaluating a patient with pulmonary disease of unknown etiology.

Synopsis

Rheumatoid arthritis (RA) is commonly associated with pulmonary disease that can affect any anatomic compartment of the thorax. The most common intrathoracic manifestations of RA include interstitial lung disease, airway disease, pleural disease, rheumatoid nodules, and drug-induced toxicity. RA patients with thoracic involvement often present with non-specific respiratory symptoms although many are asymptomatic. Therefore, clinicians should routinely consider pulmonary disease when evaluating any RA patient, particularly one with known risk factors. The optimal screening, diagnostic, and treatment strategies for RA-associated pulmonary disease remain uncertain and are the focus of ongoing investigation.

Box 1**Pulmonary manifestations of rheumatoid arthritis**

Parenchyma

Interstitial lung disease

Usual interstitial pneumonia

Non-specific interstitial pneumonia

Organizing pneumonia

Diffuse alveolar damage

Lymphocytic interstitial pneumonitis

Desquamative interstitial pneumonia

Necrobiotic nodules

Caplan syndrome

Infection

Drug-induced pneumonitis

Airway

Cricoarytenoid arthritis

Bronchiectasis

Bronchiolitis

Follicular bronchiolitis

Bronchiolitis obliterans

Panbronchiolitis

Pleura

Pleural effusion

Pleuritis

Pneumothorax

Bronchopleural fistula

Vasculature

Pulmonary hypertension

Pulmonary vasculitis

Venous thromboembolism

Pulmonary hemorrhage

Fig. 1. Rheumatoid arthritis-associated interstitial lung disease subtypes. (A) Usual interstitial pneumonia with characteristic basilar-predominant honeycombing (solid arrow) and subpleural reticulation with traction bronchiectasis. (B) Non-specific interstitial pneumonia discernible by relatively symmetric subpleural ground glass opacities with immediate subpleural sparing (arrowheads). (C) Cryptogenic organizing pneumonia with bilateral mid-to-lower lung predominate consolidative opacities in a peripheral and peribronchovascular distribution (dashed arrows). (D) Lymphocytic interstitial pneumonia marked by scattered thin-walled cysts (double arrow) and ground-glass opacification.

Fig. 2.

Suggested algorithm to identify interstitial lung disease in patients with rheumatoid arthritis. Abbreviations: *CCP* cyclic citrullinated peptide; *CT* computed tomography; *DLCO* diffusion capacity of the lung for carbon monoxide; *HRCT* high resolution computed tomography; *ILD* interstitial lung disease; *PFTs* pulmonary function tests; *RA* rheumatoid arthritis; *RF* rheumatoid factor.

Fig. 3. Rheumatoid arthritis-associated small airway disease. Inspiratory (*A*) and expiratory (*B*) high-resolution computed tomography images of a patient with bronchiolitis. Solid arrows: bronchiectasis. Arrowheads: mosaic attenuation characteristic of air trapping and small airway disease is accentuated on expiratory images.

Fig. 4. Rheumatoid arthritis-associated pleural disease. (A) Bilateral pleural thickening and hyperenhancement (solid arrows) with associated loculated pleural effusions, indicating pleuritis. (B) Necrobiotic cavitory nodule (arrowhead) resulting in a spontaneous pneumothorax (dashed arrow).