The lung in rheumatoid arthritis

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Summary

Rheumatoid arthritis (RA) is a common inflammatory disease, affecting about 1% of the population. Although a major portion of the disease burden including excess mortality is due to its extra-articular manifestations, the prevalence of RA-associated lung disease is increasing. RA can affect the lung parenchyma, airways, and the pleura; and pulmonary complications are directly responsible for 10 to 20% of all mortality. Even though pulmonary infection and drug toxicity are frequent complications of RA, lung disease directly associated with the underlying RA is more common. The prevalence of a particular complication varies based on the characteristics of the population studied, the definition of lung disease used, and the sensitivity of the clinical investigations employed. An overview of lung disease associated with RA is presented here with an emphasis on parenchymal lung disease, pleural effusion, and airway involvement.
of RA-related deaths [2], pulmonary complications are common and directly responsible for 10 to 20% of all mortality [3–5]. Furthermore, while the prevalence of other serious extra-articular manifestations is declining, RA-associated lung disease is increasing [6]; both pulmonary infection and drug-induced lung disease are frequent [7,8]. Pulmonary abnormalities are common in patients with RA and may include RA-associated interstitial lung disease (ILD), pleural effusions, rheumatoid nodules, and airway complications (Box 1). The prevalence of a particular complication varies based on the characteristics of the population studied, the definition of lung disease used, and the sensitivity of the clinical investigations employed. In unselected populations, up to one-third of subjects describe important respiratory symptoms [9], but two-thirds or more may have significant radiographic abnormalities on high-resolution computed tomography (HRCT) [9,10]. An overview of lung disease associated with RA is presented here, with an emphasis on the clinical features of the different anatomic parts of the lung that may be involved in patients with RA.

Parenchymal involvement

Interstitial lung disease

Epidemiology

Interstitial lung disease (ILD) is a frequent extra-articular manifestation of RA and a significant cause of morbidity and mortality in the RA patient population [11]. The estimated prevalence of RA-ILD among patients with RA varies depending on the criteria used to define disease, the methods of detection such as high-resolution computerized tomography (HRCT) scanning, chest radiograph, or pulmonary function testing, and the population selected for study, whether it be symptomatic, asymptomatic, autopsy series, etc. Routine chest radiographs are not sensitive and the reported rate of ILD based on chest x-rays is 1–5% [12]. The estimated prevalence of RA-ILD using HRCT is 20–44% [13]. In unselected populations, specific features of ILD will be seen in up to two-thirds of individuals [9,10].

Clinical findings and risk factors

Symptoms, which are usually insidious in onset, include dyspnea on exertion and a nonproductive cough [14,15]. Recognition of exertional dyspnea may be delayed due to the exercise limitations associated with joint disease. Less common manifestations include fever and chest pain. Most patients have fine bibasilar crackles, but clubbing is less common than in patients with idiopathic pulmonary fibrosis [16]. Asymptomatic ILD often precedes the articular manifestations of RA by months.

Box 1

Pleuropulmonary manifestations of rheumatoid arthritis

Interstitial

RA-ILD

• Usual interstitial pneumonia
• Non-specific interstitial pneumonia
• Desquamative interstitial pneumonia
• Lymphocytic interstitial pneumonia

Bronchilitis obliterans with organizing pneumonia

Rheumatoid nodule

Apical fibrobullos disease

Rheumatoid pneumoconiosis (Caplan’s Syndrome)

Airway

Upper airway obstruction
• Cricoarytenoid arthritis
• Laryngeal obstruction

Bronchiolitis

• Follicular bronchiolitis
• Constrictive bronchiolitis
• Obliterative bronchiolitis

Bronchiectasis

Pleural

Pleuritis

Pleural effusion

Empyema

Pneumothorax

Chyliiform effusion

Chest wall

Thoracic cage abnormality

Vascular

Pulmonary hypertension

Vasculitis

Infection

Drug reaction

Glossary

BOOP bronchiolitis obliterans organizing pneumonia
CB constrictive bronchiolitis
CVD-IP collagen vascular disease-associated interstitial pneumonia
DIP desquamative interstitial pneumonia
DLCO decreased diffusion capacity for carbon monoxide
HRCT high-resolution computed tomography
ILD interstitial lung disease
LIP lymphocytic interstitial pneumonia
MTX methotrexate
NSIP nonspecific interstitial pneumonia
OB obliterative bronchiolitis
OP organizing pneumonia
OSA obstructive sleep apnea
RA rheumatoid arthritis
TNF tumor necrosis factor
UIP idiopathic interstitial pneumonia and include usual interstitial pneumonia
Pathology

The pathological findings of collagen vascular disease-associated interstitial pneumonia (CVD-IP) are similar to those of idiopathic interstitial pneumonia and include usual interstitial pneumonia (UIP), nonspecific interstitial pneumonia (NSIP), organizing pneumonia (OP) or bronchiolitis obliterans organizing pneumonia (BOOP), lymphocytic interstitial pneumonia (LIP), and desquamative interstitial pneumonia (DIP). However, a wide variety of histopathologic features have been observed in RA, not only various types of interstitial pneumonia, but also airway diseases with frequent overlap between different patterns of interstitial pneumonia in the same patient, making the pathological diagnosis more complicated [29,30]. Currently available data show that among RA-ILD patients, there is a higher proportion of patients with UIP pattern [31] compared to patients with other connective tissue diseases. Lee et al. [31] found UIP to be the most common histopathologic pattern in RA-ILD patients (56%). This was followed by NSIP (33%) and organizing pneumonia (11%). Flaherty et al. [32] demonstrated that patients with collagen vascular disease-associated UIP pattern had fewer fibroblastic foci and better survival compared to patients with the idiopathic type, which may be related to better prognosis of UIP associated with collagen vascular disease.

Pulmonary function tests

Pulmonary function tests frequently demonstrate reduced lung volumes and DLCO, even in the absence of symptoms [33]. Reduced DLCO was suggested to be the most sensitive marker for interstitial pneumonia on HRCT [34].

Radiology

The chest radiograph is often normal in patients with early RA-ILD. HRCT is highly sensitive for detecting the presence of interstitial pneumonia and is abnormal in up to 80% of patients with RA and clinically suspected interstitial pneumonia [35–39]. The prevalence of interstitial pneumonia on HRCT was approximately 33% in patients with early RA [26,38]. However in asymptomatic patients, abnormalities on HRCT had no relationship with symptoms or pulmonary function testing in most studies, and their significance and implications for therapy are not clear.

Four major radiographic patterns have been identified in patients with RA-ILD: a UIP-like pattern with bilateral subpleural reticulation with or without honeycombing; a NSIP-like pattern with predominant ground-glass opacities; an inflammatory airway disease pattern with centrilobular branching lines, with or without bronchial dilatation; and an organizing pneumonia-like pattern with patchy areas of consolidation [40,41]. The correlation between histopathologic and radiographic patterns in RA-ILD patients has not been rigorously studied, but it appears that HRCT scanning is reasonably specific for the presence of UIP pattern seen on surgical lung biopsy specimens in patients with RA-ILD [35–43]. A predominant ground-glass pattern on HRCT suggests inflammatory process such as DIP or NSIP. On the other hand, reticular changes and honeycombing reflect fibrosis and are more typical of UIP (figure 1) [42]. In general, HRCT findings accurately predict pathological findings. HRCT has replaced lung biopsy in many cases [43]; however, pathologic diagnosis may be required, especially when atypical features are present on HRCT.

Diagnosis

The diagnosis of RA-ILD is generally based on the combination of clinical presentation, pulmonary function testing, HRCT, and in some cases, lung biopsy [14]. A careful exposure history (including occupational, environmental and pharmaceutical) should be conducted to evaluate potential alternative causes. The most important differential diagnoses are infection and treatment-related drug toxicity. The risk of serious infection in patients with RA is two times higher than normal [44]. Bronchoalveolar lavage is not a routine part of the diagnostic approach to RA-ILD although neutrophil alveolitis is usually found in patients with clinical interstitial pneumonia [45–47]; it is useful to exclude other processes, such as an infection [45–47]. The pattern of radiographic abnormality seen on HRCT in RA has proved to be an excellent predictor of the underlying pathologic pattern. UIP, NSIP, and BOOP are strongly correlated with the underlying pathology [48,49]. Similar to the pathologic patterns, these radiographic patterns also appear to predict progression and outcome in RA-ILD. The most common pathologic
findings among patients with RA-ILD are those of UIP and NSIP. In patients with HRCT scan findings consistent with UIP pattern, the diagnosis of RA-ILD with UIP pattern can be made confidently [39–43]. Males and former smokers are prevalent among patients with RA-ILD who develop the UIP pattern [15]. Similarly, the HRCT scan appearance of isolated ground-glass opacity without honeycombing or reticulation appears to correlate well with histopathologic NSIP. RA patients with NSIP tend to be women and nonsmokers. Lymphocytic interstitial pneumonia (LIP) usually occurs when RA is complicated by Sjögren’s syndrome [31]. In addition to dyspnea and cough, these patients complain of dry eyes and mouth (xerophthalmia and xerostomia). In indeterminate cases, lung biopsy should be considered. A transbronchial biopsy (TBB) is usually inadequate for diagnosis. Therefore, lung biopsy is typically performed, usually by video-assisted thoracoscopy [14,41].

Treatment
For patients with RA-ILD, the decision to start therapy is influenced by the patient’s age, severity, speed of disease progression, and the presence of co-morbidities. It is important to document deterioration of lung function over a period of one to three months, which strengthens the case for intervention. Response to therapy varies according to the histopathologic abnormality, similar to the idiopathic interstitial pneumonias [14,41]. In general, more aggressive treatment is justified in patients with evidence of inflammation on HRCT, lymphocytes on bronchoalveolar lavage, or a non-UIP pattern on biopsy. Glucocorticoid therapy is the treatment of choice with variable subjective and objective improvement in the treatment of RA-ILD [14,15,21]. Other drugs reported to be beneficial include cyclophosphamide, azathioprine, hydroxychloroquine, D-penicillamine, and cyclosporine [50–52]. The impact of newer therapies for RA (e.g., anti-TNF-alpha regimens), which decrease inflammation and may interfere with fibrosis, is still unknown [53]. However, the potential benefit of anti-TNF-alpha therapy should be viewed in the context of several cases of rapid, occasionally fatal progression of lung disease in patients with RA-associated ILD treated with anti-TNF therapy [54,55]. About a third of patients with RA have their joint disease controlled by methotrexate. Methotrexate was reported to be effective in some patients with RA-ILD, although it has resulted in pulmonary toxicity in approximately 5% of patients [56]. Some have questioned whether this pulmonary toxicity is actually a reflection of progressive lung injury due to RA [57–59]. However, as approximately half of patients with methotrexate lung toxicity have preexisting interstitial pneumonia and may thus have poor lung reserve with a higher risk of respiratory failure in the event of pneumonitis, it appears to be better to avoid methotrexate in patients with established interstitial pneumonia [60].

Prognosis
The prognosis of RA-ILD is variable and studies comparing RA-ILD to idiopathic pulmonary fibrosis have yielded conflicting results. For many patients with RA-ILD, the pulmonary abnormalities do not progress and may remain subclinical; however, a small group of patients may have more rapid deterioration with worse prognoses. Low DLCO is considered a marker for a poor prognosis [61]. The pathologic patterns seen in RA-ILD may have prognostic significance as well. Park et al. reported that the prognosis for subjects with collagen vascular disease (CVD)-ILD, and particularly those with CVD-UIP, is better than that of patients with idiopathic UIP [62]. However, consistent with data from previous studies [29,31,63], subjects with RA and with UIP pattern pathology had a survival similar to matched subjects with idiopathic pulmonary fibrosis. Radiographic changes seen on HRCT in patients with RA-ILD correlate well with the underlying pathology [29,31], especially for UIP, NSIP, and BOOP. These radiographic patterns also appear to predict progression and outcome in RA-ILD [48,49].

Organizing pneumonia
Organizing pneumonia (OP), also known as bronchiolitis obliterans organizing pneumonia (BOOP), is a distinct clinical entity with predominant features of pneumonia, rather than a...
primary airway disorder [64–67]. Organizing pneumonia can also be seen in association with connective tissue diseases, a variety of drugs, malignancy, and other interstitial pneumonias [65,68].

**Epidemiology**

A number of studies have noted an association of OP with RA [69–71]. In a study of open lung biopsies from 40 patients with parenchymal lung disease and RA, OP was the second most common pathologic manifestation, following rheumatoid nodules [72]. In other series, it was the most common ILD after UIP and NSIP [69,72].

**Clinical findings**

The clinical presentation of OP often mimics that of community-acquired pneumonia. In about half of cases, the onset is heralded by a flu-like illness with fever, malaise, fatigue, and cough. The most common features at presentation include persistent nonproductive cough, dyspnea with exertion, malaise, weight loss, and fever. Crackles are noted on physical examination [73–75].

**Laboratory and pulmonary function testing**

Laboratory and pulmonary function testing reveal increased CRP and erythrocyte sedimentation rate with restrictive pattern and reduced DLCO, respectively [73,74].

**Radiology**

Bilateral, diffuse alveolar opacities in the presence of normal lung volumes are typically seen on chest x-ray [76]. Chest CT scan shows patchy air-space consolidation, ground-glass opacities, small nodular opacities with bronchial wall thickening, and dilation (figure 2) [48,77]. These patchy opacities occur more frequently in the periphery of the lung and are often in the lower lung zone.

**Pathology and diagnosis**

Histopathologic lesions characteristic of OP include excessive proliferation of granulation tissue within the small airways (proliferative bronchiolitis) and alveolar ducts, associated with chronic inflammation in the surrounding alveoli [29,78]. Diagnosis may occasionally be made with a transbronchial lung biopsy, but more commonly, an open or thoracoscopic lung biopsy is required.

**Treatment and prognosis**

RA patients with OP who receive treatment generally have a good prognosis. However, spontaneous improvement is rare and rapid progression has been reported [79]. Most patients with OP respond rapidly to oral glucocorticoid therapy with substantial improvement of respiratory symptoms [15,65]. If the patient is stable or improved, the prednisone dose is gradually tapered. The duration of treatment is three to six months. The patient should be followed routinely with chest radiographs and pulmonary function testing and therapy should be reinstated aggressively at the sign of any recurrence. Importantly, the chest radiograph may change before the patient develops significant symptoms. If the patient cannot tolerate glucocorticoid therapy, or deteriorates despite treatment, a cytotoxic agent, such as cyclophosphamide should be started [15]. Consolidation shows a tendency to improve in most patients and to evolve into honeycombing in the remaining patients on serial CT [37,48,80].
Rheumatoid nodules

The rheumatoid nodule is the most common cutaneous manifestation of rheumatoid arthritis (RA) [81]. Although nodules commonly are found on pressure points, they may involve other organs as well. Rheumatoid nodulosis is considered a benign variant of rheumatoid arthritis and is the only pulmonary manifestation specific for the disease.

Epidemiology

The prevalence of pulmonary rheumatoid nodules is not established. Chest x-rays revealed rheumatoid nodules in only 2 of 516 patients with RA in one clinical series [82]. However, on pathological series, rheumatoid nodules were the most common abnormality. A previous study reported that rheumatoid nodules were found in 13 out of 40 open lung biopsies from patients with RA and possible “rheumatoid lung disease”, and 8 of the 13 patients, had multiple nodules [29].

Pathology

Histologically, the pulmonary nodules are similar to nodules at other sites, with central necrosis, palisading epithelioid cells, a mononuclear cell infiltrate, and associated vasculitis [83].

Diagnosis and differential diagnosis

Nodules are generally located in subpleural areas or in association with interlobular septa (figure 3). Pulmonary rheumatoid nodules have to be differentiated from malignant and infectious processes, particularly when only a single nodule is present. Therefore, radiological follow-up and sometimes fine needle aspiration may be required to exclude malignancy.

Clinical findings and prognosis

Pulmonary rheumatoid nodules are usually asymptomatic and the prognosis is generally good, with spontaneous resolution and infrequent complications. Complications may include pleural effusion, pneumothorax, hemoptysis, and infection. Accelerated pulmonary nodulosis, which may mimic infection or malignancy, has been reported to follow anti-tumor necrosis factor (anti-TNF) therapy and leflunomide treatment [84–86].

Rheumatoid pneumoconiosis (Caplan’s syndrome)

In 1953, Caplan defined rheumatoid pneumoconiosis as characterized by rounded, peripheral pulmonary radiological images, 0.5–5.0 cm in diameter, with or without small opacities, consistent with pneumoconiosis or massive pulmonary fibrosis, found in patients with RA who were exposed to mineral, coal, or silica dust. The prevalence of this entity among patients with pneumoconiosis is low. Caplan found a prevalence of 0.4% and, more recently, Honma and Vallyathan showed that the incidence was 0.75% in Japan and 1.5% in the USA [87]. Although the syndrome was originally described in coal miners, several cases have since been diagnosed in individuals exposed to free silica or asbestos [41]. Histologically, the findings are similar to those with simple rheumatoid nodules, except that the nodules in Caplan’s syndrome are surrounded by pigmented cells [17]. There is no effective treatment for Caplan’s syndrome, but the prognosis is good.

Apical fibroblous disease

Fibroblous disease, similar to that seen in ankylosing spondylitis has been reported in RA and may precede the articular manifestations. Yue et al. described two patients with rheumatoid arthritis and fibrocutaneous lesions in the upper lobes of the lungs. Postmortem pathologic studies revealed necrobiotic nodules with cavitation, suggesting that apical fibrocutaneous disease is a clinically distinct pattern of lung involvement in RA [88].

Airway involvement

Upper airway obstruction

The cricoarytenoid joints are small diarthroidal joints that rotate with the vocal cords as they abduct and adduct to vary the pitch and tone of the voice. Though not disabling, the cricoarytenoid joints may become inflamed and immobilized with the vocal cords adducted to midline, causing inspiratory stridor and upper airway obstruction [89]. Laryngeal obstruction is usually related to arthritis of the cricoarytenoid joints, less commonly a rheumatoid nodule may develop on the vocal cords [90]. An erosive mass on the cricoid cartilage causing acute upper airway
obstruction with significant destruction of the surrounding structures was also described [91].

Epidemiology

Upper airway involvement is more common in woman and in patients with long-standing RA. Involvement of the larynx in RA was first described by Sir Morell Mackenzie in 1880 [92]. Jurik and Pedersen found arthritis of the cricoarytenoid joints in 55% of patients with RA [93]. The incidence was higher in females (65%) than in males (20%) [93]. When HRCT and fiberoptic laryngoscopy were used, cricoarytenoid abnormalities were seen in up to 75% of the patients [91,94] although symptoms were reported in only about half this number [95].

Clinical findings

Symptoms include hoarseness, foreign body sensation, dyspnea, odynophagia, coughing, sore throat, stridor, and acute airway obstruction causing inspiratory difficulties [91,92,94,96]. However, symptoms are usually absent until significant obstruction occurs. Thus, patients with previously unsuspected disease may present as an emergency when airway edema secondary to an infection or intubation causes a life-threatening obstruction. Cases of cardiopulmonary arrest and pulmonary edema following obstruction have also been described [97,98]. Chronic cricoarytenoid arthritis may be asymptomatic. Decompensation of the chronic state may occur because of laryngeal manipulation [89].

Pulmonary function tests

Pulmonary function tests may reveal blunting of the inspiratory loop in patients with variable extrathoracic obstruction and flattening of the inspiratory and expiratory loops in patients with fixed obstruction. However, these tests lack accuracy and are not highly sensitive or specific.

Radiology

CT scan is important for the evaluation of structural integrity. CT staging was proposed by Brazeau-Lamontagne as: grade I cricoarytenoid thickening, grade II cricoarytenoid erosion, grade III cricoarytenoid luxation, and grade IV sub-occlusion of the larynx [94]. No laryngeal symptoms predictive of CT findings were ascertained [91,94].

Diagnosis

Both laryngoscopy and CT imaging have been used to diagnose RA of the larynx. They appear to be complementary investigations, as laryngoscopy tends to allow better evaluation of mucosal and functional integrity, while CT scanning enables visualization of structural integrity [94,99].

Treatment

The management of tenderness of the throat or pain on coughing or speaking involves use of NSAIDs. A tracheostomy may be necessary to bypass the obstruction and can be reversed at a later date. Surgical intervention with mobilization of the cricoarytenoid joints and lateral fixation of one of the cords has been reported in cases of severe obstruction [94,95,100].

Preoperative evaluation

CT and laryngoscopic evaluation is important before general anesthesia is contemplated [94]. Acute obstruction can occur during intubation or extubation [89]. In an emergency, severe obstruction may respond to inhalation of helium-oxygen mixtures. Because RA can be complicated by cervical spine instability, intubation and invasive diagnostic and treatment procedures should be performed by experienced operators, avoiding excessive neck flexion [101,102].

Obstructive sleep apnea

Data on the frequency of sleep disturbances and obstructive sleep apnea (OSA) in patients with autoimmune diseases, including RA, are scarce. Holman and DePaso reported 45% prevalence of OSA in men with connective tissue diseases, including RA [103], regardless of BMI or the type of inflammatory disease. The large percentage of RA patients at high risk for sleep apnea is intriguing. In another study from Japan, more than half of 96 RA patients (mostly female) had OSA [104]. Interestingly, among patients treated with CPAP, a 40% reduction in RA disease activity and in CRP values at 6 months was found. The possible reasons for a high incidence of sleep apnea among patients with RA may include a reduction in the size of the upper airway due to temporomandibular joint destruction, spinal cord lesions or upper airway obstruction [105]. RA patients may be at higher risk for sleep apnea and a high index of suspicion is needed for proper evaluation and treatment.

Bronchiolitis

Bronchiolitis is a generic term that encompasses a group of diseases with diverse etiologies. In general, it indicates the presence of inflammation in the small airways, which by definition measure less than 2 mm in diameter.

Follicular bronchiolitis

Follicular bronchiolitis is characterized by the presence of abundant lymphoid tissue, situated in the walls of the bronchioles and, to some extent, in larger bronchi [106–108]. Follicular bronchiolitis can be idiopathic or associated with immunodeficiency diseases, hypersensitivity reactions, infection, or connective tissue disease, such as Sjögren’s syndrome, and particularly with RA [106,109].

In RA, follicular bronchiolitis probably represents lymphoid hyperplasia in response to an extrinsic immune stimulus or altered systemic immune response [110]. Rangel-Moreno et al. [111] found increased expression of molecules involved in the immunopathology of RA and chemokines in bronchus-associated lymphoid tissue with correlation to tissue damage, suggesting a role in local RA pathogenesis [111].
Epidemiology
Although in the past lymphocytic bronchiolitis was thought to be rare [112] and there are only few series and case reports in the literature, Tansey et al. [30] and Rangel-Moreno et al. [111] showed that in biopsies from patients with RA, most patients had follicular bronchiolitis as the main pattern of pulmonary disease, or as a minor finding occurring with another form of RA-associated pulmonary disease [30,111]. Another study reported that follicular bronchiolitis might even precede RA [113].

Clinical findings and pulmonary function tests
The most common clinical findings are progressive dyspnea and cough [110]. Peribronchial infiltrates consisting of lymphocytes and plasma cells may cause compression of the bronchi with airflow obstruction [107,112,114]. Initial reports suggested up to a 60% prevalence of airflow obstruction in patients with RA; later studies in non-smoking subjects noted a prevalence of 0 to 24% [115,116].

Radiology
The cardinal signs of follicular bronchiolitis in HRCT are a mixed pattern of small centrilobular nodules variably associated with patchy ground-glass opacity. Additional peribronchial nodules are also a frequent finding [55]. Nodules and ground-glass opacities are generally bilateral and diffuse in distribution. Mild bronchial dilatation with wall thickening is seen in some cases [55]. Interestingly, the prevalence of small airway abnormalities on HRCT is greater than that of airway obstruction detected by pulmonary function testing. In patients with RA, without evidence of ILD, changes of small airway disease were noted on HRCT in 35 of 50 patients and in 20 patients with an abnormal HRCT, no physiological abnormalities were found [115].

Treatment and prognosis
Treatment is similar to that used for airflow obstruction in other settings. No treatment is required in patients with mild disease, whereas inhaled bronchodilators, glucocorticoids, and occasionally a trial of oral glucocorticoids are used in those with symptomatic obstruction. The prognostic implications of follicular bronchiolitis are unclear [109].

Constrictive bronchiolitis-obliterrative bronchiolitis
Constrictive bronchiolitis (CB) or obliterative bronchiolitis (OB) is a rare, usually fatal, condition characterized by progressive concentric narrowing of membranous bronchioles [117–119]. Although Geddes et al. first reported CB with RA in 1977 [120], only a few years later, it became clear that the disease was related to RA [121]. The term “obliterative bronchiolitis” may be confusing because it is similar to a more widely established term, “bronchiolitis obliterans organizing pneumonia” (BOOP).

BOOP is defined pathologically as proliferating plugs of fibrous connective tissue within bronchiolar lumens (“bronchiolitis obliterans”) and alveolar ducts and lumens (“organizing pneumonia”), as opposed to inflammation and fibrosis occurring predominantly in the walls and contiguous tissues of membranous and respiratory bronchioles, with resultant narrowing of their lumens [117–119]. CB was reported in patients that were treated with penicillamine and gold salts [122–128], although in some cases, the description may be confusing and represent BOOP [129].

Clinical presentation
Constrictive bronchiolitis usually occurs after the diagnosis of RA, with an average of 7.8 ± 8.2 years between the diagnosis of RA and the onset of respiratory symptoms, [130] but it can also precede or be the only manifestation of RA [131,132]. The mean interval between respiratory symptoms and the diagnosis of CB was found to be 19 months (1–73 months). It is more common in women [121,131] but this may reflect the nature of RA disease. Patients typically present with a rapid onset of dyspnea and dry cough [131]. The rapidity of onset and severity of symptoms are unusual and should lead to suspicion of the diagnosis [121,131]. Inspiratory crackles and sometimes mid-inspiratory squeak can be found on physical examination [121,131].

Laboratory and pulmonary function tests
Pulmonary function tests demonstrate obstructive patterns with air trapping and normal DLCO. On arterial blood gas analysis, hypoxemia may occur during rest or after a six-minute walk test [121,131].

Radiology
Chest x-ray may be normal [120,121]. The most common findings are pulmonary hyperinflation (64%), diffuse lung infiltrates (44%) and bronchiectasis (40%). Diffuse alveolar opacities and nodular shadows were reported less frequently, in 32% and 16% of cases, respectively. The most frequent HRCT findings were bronchial wall thickening (96% of patients), centrilobular emphysema (56%), lobular areas of decreased attenuation with mosaic pattern indicative of air trapping (42%), and bronchiectasis (40%) [131,132].

Diagnosis
The constellation of rapid onset of dyspnea and dry cough and obstructive pattern with irreversibility on pulmonary function test, with typical HRCT findings, should raise the suspicion for CB. However, in most cases, open or thoracoscopic lung biopsy is required to make a definitive diagnosis; although tissue confirmation may not be necessary in patients with a clear predisposition and typical HRCT findings. Transbronchial lung biopsy is often inadequate for diagnosis, because these processes involve the respiratory and membranous bronchioles [133].

Treatment and prognosis
The prognosis and response to therapy are poor [131]. Although no therapy has proven consistently effective, a trial of high dose glucocorticoids (e.g., prednisolone 1–1.5 mg/kg per day) is warranted [109,134]. Macrolids have been shown to benefit
patients with RA and CB somewhat, although data are limited to case reports and case series [109,134,135]. One case report demonstrated successful treatment with etanercept—a tumor necrosis factor (TNF)-alpha inhibitor combined with methotrexate in a patient who did not respond to treatment with steroids and azathioprine [130]. Lung transplantation may be an option, although data are lacking.

**Bronchiectasis**

An association between bronchiectasis and RA has been noted and bronchiectasis may result from recurrent infections, retraction in interstitial lung diseases, traction bronchiectasis, or the progression of lymphocytic/constrictive bronchiolitis. The prevalence of bronchiectasis in HRCT among RA patients is 16.6–58% [136,137]. One study noted a significantly higher proportion of heterozygous for the CFTR gene deltaF508 mutation among patients with RA and bronchiectasis, than in a control group of patients with RA and no bronchiectasis in the general population. No alterations in sweat chloride concentration or nasal potential difference measurements were noted [138]. Bronchiectasis does not appear to be clinically significant in most patients with RA. In those that require therapy, treatment should be similar to that used for other forms of bronchiectasis.

**Pleural involvement**

**Epidemiology**

Pleural disease is common in patients with RA, but it is usually subclinical [139–141]. The annual incidence of rheumatoid pleural effusion in the RA population is 0.34% in women and 1.54% in men [142]. Many pleural effusions are found incidentally on chest radiography, with overt clinical evidence of pleural disease in less than 5% [143–146]. Whereas autopsy studies identified pleural disease in 38 to 73% of patients with RA, only about 20% had complained of pleurisy. Sequelae of pleurisy (pleural thickening and/or effusion) were found in RA, only about 20% had complained of pleurisy. Sequelae of pleurisy studies identified pleural disease in 38 to 73% of patients with RA, only about 20% had complained of pleurisy. Sequelae of pleurisy (pleural thickening and/or effusion) were found in 24% of men and 16% of women in 309 chest radiographs of RA patients [147].

**Risk factors and clinical findings**

Rheumatoid pleuritis can be transient, chronic, or relapsing. It is most common in patients with long-standing RA, middle-aged men with high rheumatic factor titers and rheumatoid nodules. In approximately 25% of RA patients, the appearance of pleural effusion preceded or occurred simultaneously with the onset of joint disease [142,144,148]. Usually there is no correlation between the appearance of pleural effusion and joint disease activity [149]; although in some patients, worsening arthritis was reported with the appearance of pleural effusion [150]. A genetic predisposition to rheumatoid pleurisy has also been reported, with a high prevalence of HLA-B8 and Dw3 associated with rheumatoid pleural effusion [151]. Most patients with rheumatoid pleural effusion are asymptomatic and have small amounts of pleural effusion [139–141]. Patients with large pleural effusion may complain of dyspnea, fever, and pleuritic chest pain. The reported frequency of pleuritic chest pain in RA patients varied from 30 to 50% [82]. Dyspnea out of proportion to the amount of pleural effusion reflects severe underlying lung pathology that can be found in about one-third of RA patients with pleural disease [82,152]. Pleural effusion may appear after several years of established RA [148,153]. In approximately 25% of RA patients it may precede or occur simultaneously with the onset of joint disease [82,149]. However, no correlation was found between the appearance of rheumatoid pleural effusion and joint disease activity [149]. In about 70% of patients, the effusion is unilateral [82,154].

**Pleural fluid examination**

Thoracocentesis should be performed in patients who have RA and pleural effusion. The fluid is exudative, nonnodular, and may be cloudy, greenish-yellow, or opalescent [155]. Glucose levels are typically low although in acute or recent rheumatoid pleurisy, glucose levels may be normal [156–159]. In a study of 76 patients with rheumatoid effusions, pleural glucose levels were less than 20 mg/dL in 63%, and less than 50 mg/dL in 83% [156], and a pleural fluid glucose to serum glucose ratio of less than 0.5 has been demonstrated in 80% of rheumatoid pleural effusions [156]. Therefore, glucose concentrations of 25 mg/dL or less, despite normal serum glucose concentrations, with no evidence of infection are virtually diagnostic of RA. pH levels are generally less than 7.3 and reflect ongoing inflammation in the pleural cavity, with a high rate of glucose metabolism. Further reduction in the pH below 7.2 raises the possibility of a concomitant infection [160]. High LDH levels (above 700 IU/L) are considered an indicator of the degree of pleural inflammation and may be useful in monitoring the effects of therapeutic intervention [161]. RF levels in the pleural fluid are usually equal to or even higher than serum RF titers [147,162]. A finding of RF in the pleural effusion is strongly suggestive of a rheumatoid origin for the pleural exudate [157]. Less commonly, patients with RA and a long-standing pleural effusion will have a pseudochylous or chyloform effusion diagnosed by the appearance and analysis of the pleural fluid [145,154,155,163]. Cholesterol effusions have the appearance of an empyema, but are sterile [154]. The milky appearance is due to elevated cholesterol and total lipid levels (always above 65 mg/dL and sometimes over 1000 mg/dL). Cholesterol crystals, identifiable with polarized light, may also be present. Demonstration of cholesterol crystals and lecithin-globulin complexes allow for distinguishing between pseudochylous rheumatoid pleural effusions and cholesterol-rich effusions due to ruptured lymphatics [161,164]. Chyloform effusion may result from rupture of a necrotic subpleural rheumatoid nodule. Whole complement activity and C3 and C4 levels are lower in RA pleural fluid than in non-rheumatoid effusions,
however, diagnostic and prognostic accuracy of complement measurements in rheumatoid pleural effusions is of limited clinical value [155,162,165]. On cytological examination, characteristic findings include slender or elongated multinucleated macrophages, round giant multinucleated macrophages, and necrotic background material in the absence of mesothelial cells, although their specificity has not been evaluated in large series of unselected patients [162,166,167].

**Diagnosis**

The combination of very low glucose levels (< 40 mg/dl), pleural fluid acidosis (pH < 7.20), high lactate dehydrogenase (LDH) levels (< 700 IU/L), high cholesterol levels (< 65 mg/dl), and negative bacterial smears or cultures are prominent features of rheumatoid sterile empyematosus pleural effusion [146]. Typical biochemical features of rheumatoid pleural effusions with no evidence of infection are diagnostic and pleural biopsy is not recommended [155,160].

In the case of rheumatoid pleuritis preceding joint manifestations or atypical cases of rheumatoid pleurisy, pleural biopsy may lead to a diagnosis. Thoracoscopic pleural biopsy is the recommended diagnostic approach. The thoracoscopic granular appearance of the parietal pleura and the histopathological changes are often diagnostic [148,168]. On histology, thickening of the visceral and parietal pleura is seen with the normal mesothelial cell covering replaced by epithelioid cells with multinucleated giant cells. Neither granulomas nor necrotic tissue is routinely seen, but several foci of palisade or radial-oriented fibroblastic cells and lymphocytes with microscopic necrotic centers may be found, resembling rheumatoid pulmonary nodules [14,98,169,170].

**Treatment**

The course of rheumatoid pleurisy is variable. In most cases, the effusion is small and asymptomatic and does not require specific therapy [149,155,161]. Data on the efficacy of therapy in rheumatoid pleural disease are scarce. Initial treatment of pleuritis with nonsteroidal anti-inflammatory drugs may suffice and some patients respond to systemic corticosteroids [155,160]. In patients with persistent symptomatic effusions, repeated aspirations have been used to control effusions. The effectiveness of repeated intrapleural corticosteroid installations in refractory rheumatoid pleural effusion has not been established.

**Prognosis**

Usually rheumatoid effusions resolve within four weeks in 50% of patients and within four months in two-thirds [82], but it may persist for years in approximately 20% [18]. Unresolved rheumatoid effusion may result in marked pleural thickening, trapped lung with progressive restriction of lung volume, necessitating pleural decortication and even lung resection, or occasionally may be complicated by bacterial empyema [155,160,171,172].

**Complications**

Empyema may complicate rheumatoid pleural disease. The reported prevalence is variable, but it seems to be higher in the post-steroid era [150,173]. Empyema in RA patients usually results from microbial colonization of necrotizing subpleural rheumatoid nodules and formation of a bronchopleural fistula and pyopneumothorax, but may also occur in the absence of other pleuropulmonary complications [155,173]. RA patients treated with TNF-α blockers are prone to TB infection [174]. The pleural fluid in this subgroup of patients should always be tested for mycobacteria. Mortality from empyema ranges from 1 to 19% and is especially high in immunocompromised patients [175]. Early diagnosis and corresponding treatment for infective empyema are crucial.

Pneumothorax is a relatively rare complication of RA. It is thought to occur in approximately 5% of patients with rheumatoid lung [150,176] and probably results from perforation of cavitating rheumatoid nodules into the pleural space, creating continuous leakage [155,160].

**Vascular involvement**

**Pulmonary hypertension**

Pulmonary arterial hypertension (PAH) can be associated with various connective tissue diseases such as systemic sclerosis, systemic lupus erythematosus, RA, and mixed connective tissue disease. Although PAH is found rarely in RA [177], subclinical pulmonary hypertension may be more common. Dawson et al. [178] reported that 21% of all rheumatoid arthritis patients had pulmonary hypertension identified by echocardiography, without significant cardiac disease or lung disease evident upon pulmonary function testing. Since inflammation may play a significant role in PAH, particularly in association with connective tissue disease, anti-inflammatory treatment may have beneficial effects. Treatment with corticosteroids and/or immunosuppressive therapy in patients with severe PAH associated with some forms of CTD, such as systemic lupus erythematosus resulted in a significant improvement of pulmonary vascular disease with corticosteroids and/or immunosuppressive therapy [179,180]. However, since PAH is rare in patients with RA, we can only suggest, based on case studies, that treatment with both targeted therapy for the pulmonary hypertension, combined with immunosuppressive treatment may be effective [179,180].

**Pulmonary vasculitis**

Vascular inflammation is considered the primary event in the formation of rheumatoid nodules [181]. In nodule formation,
small-vessel vasculitis leads to fibrinoid necrosis that forms the core of the lesion, surrounded by fibroblastic proliferation. In contrast to this type of blood vessel inflammation, however, the term “rheumatoid vasculitis” refers specifically to a protean, destructive inflammatory process that is centered on the blood vessel wall itself and associated with substantial morbidity. Rheumatoid vasculitis may affect a wide range of blood vessel types, from medium-sized muscular arteries, to somewhat smaller arterioles, to post-capillary venules leading to necrosis, blood vessel occlusion, and tissue ischemia in a manner that resembles other forms of systemic vasculitis. It typically occurs in patients with long-standing, joint-destructive RA and is strongly positive for rheumatoid factor [182]. It is a multisystem disease and most commonly involves the skin, digits, peripheral nerves, eyes, and heart. However, primary vasculitic involvement of the lung is uncommon and must be distinguished from interstitial lung disease that is not vasculitic in nature. Although rheumatoid nodules occur in the lungs and pathologic evidence of vasculitis is an inherent feature of rheumatoid nodules wherever they are found, most patients with rheumatoid nodules in the lungs do not have evidence of systemic vasculitis [29,183].

**Thoracic cage immobility**

Abnormalities of thoracic cage mobility have been reported and suggested to be associated with pleurisy, myopathy, and thoracic rigidity. Restrictive patterns with reduced lung volumes with a low or normal DLCO and a high DLCO/VA have been reported [4].

**Infections**

Patients with RA have been shown to have an increased risk of infections compared with the general population, even after adjustment for age, sex, smoking status, leukopenia, corticosteroid use, and diabetes mellitus [44,184]. Several treatment modalities for RA may induce infections, including corticosteroids, disease-modifying agents (DMARDS), TNF antagonist, and new biotherapies. Opportunistic infections may also appear. Pneumonia is a major cause of mortality in patients with RA and is probably the most common respiratory cause of death [4]. The relative risk for pneumonia and lower respiratory tract infections is 1.68 and 1.88 respectively [44]. Wolfe et al. reported an incidence density of pneumonia of 17 per 1000 patient-years. They found a dose-related relationship between prednisone use and pneumonia risk in RA patients, and no increase in risk for anti-TNF therapy or methotrexate use [7]. Simon et al. reported the risk of hospitalized pneumonia following abatacept treatment was the same order of magnitude as that of patients on non-biologic DMARD therapy [185]. Treatment of RA and other autoimmune disorders with anti-TNF agents is associated with an increased risk of reactivation of latent *Mycobacterium tuberculosis* [174,181,186–191]. The rate of TB in patients with RA treated with anti-TNF therapy is three to four times higher in patients receiving infliximab and adalimumab than in those receiving etanercept [181,191]. Other granulomatous infections such as candidiasis, coccidioidomycosis, histoplasmosis, listeriosis, nocardiosis, and infections due to nontuberculous mycobacteria were reported with significantly greater frequency among infliximab-treated patients [181].

**Drug-related lung toxicity**

Drug-related pulmonary disease is an important consideration in the differential diagnosis of patients with RA who present with respiratory symptoms [192]. It is important to exclude undiagnosed pulmonary disease prior to initiating drug treatment in patients with RA.

**Methotrexate**

Methotrexate (MTX) is the most commonly used disease-modifying antirheumatic drug in patients with RA. Pulmonary disease may occur with the relatively low doses (< 20 mg per week) that are used in patients with RA. However, MTX may also exacerbate a preclinical pulmonary disease. Pulmonary complications are not associated with folate deficiency [193]. The incidence of MTX pneumonitis is 0.3 to 11.6% [193–195]. In Japan, the estimated incidence was 2.874 per 1000 cases [194]. Pneumonitis can begin early after the drug is started and most cases occur within two years of the initiation of therapy [196]. Risk factors for the development of an adverse drug reaction includes older age, rheumatoid pleuropulmonary involvement, hypoalbuminemia, diabetes mellitus, and previous use of disease-modifying antirheumatic drugs, particularly auranofin (oral gold), sulfasalazine, or penicillamine [195,197,198]. MTX lung injury is most often a subacute process, in which symptoms are present for several weeks before diagnosis. Approximately 50% of cases are diagnosed within 32 weeks of initiation of MTX treatment [199]. Predominant clinical features of MTX lung injury include shortness of breath, cough, and fever [199]. Hypoxemia and a restrictive pattern on pulmonary function testing are observed. Chest x-rays and CT demonstrate diffuse infiltrates. In 70% of cases, HRCT demonstrates diffuse homogeneous ground-glass opacity (GGO) with sharp demarcation by interlobular septa-type A GGO [200]. This picture may also be seen with *Pneumocystis jiroveci* rendering the distinction of these two disorders difficult [200]. The diagnosis in some cases can be made where there is evidence supporting methotrexate pneumonitis without a pathologic diagnosis. Bronchoalveolar lavage and transbronchial biopsy can be helpful in excluding other diagnosis such as infection. However, open lung biopsy is frequently required to establish a pathologic diagnosis [15]. Histologic examination shows an interstitial pneumonitis with granuloma formation, occasional
Infiltration of eosinophils, and bronchiolitis. Methotrexate should be temporarily stopped in any patient with RA on MTX therapy who complains on nonproductive cough and dyspnea, without evidence of upper respiratory infection. In patients with new evidence for interstitial lung disease, it should be stopped permanently. Earlier recognition and drug withdrawal may avoid the serious and sometimes fatal outcomes that have been observed [199]. Patients generally respond to withdrawal of methotrexate and the prognosis is usually good. Uncontrolled studies suggest that glucocorticoids can hasten recovery and may be important for severely ill patients. Rechallenge with methotrexate has been reported without recurrence of lung disease, and can be tried with caution.

**Leflunomide**

Leflunomide has been reported to induce interstitial lung disease and cases of new or accelerated pulmonary nodule formation, which stabilized after cessation of the drug [201–204]. Risk factors for the development of lung injury included pre-existing lung disease (the most significant risk factor), smoking, low body weight, and use of a loading dose [205,206]. In patients with known ILD, leflunomide treatment in RA patients with pulmonary involvement is not recommended due to the possibility of causing accelerating ILD in these patients.

**Anti-TNF-alpha and pneumonitis**

There is some evidence that anti-TNF therapy can induce lung disease characterized by granuloma formation (both noncaseating and necrotizing) without evidence of mycobacterial infection [205–209]. Lung disease improved over two to four weeks after withdrawal of etanercept and treatment with glucocorticoids [207–211]. Other studies reported severe worsening of interstitial lung disease related to initiation of infliximab or etanercept [205–209]. These data suggest that serious precautions should be taken before administering TNF-alpha blockers in patients with RA and pulmonary involvement, especially in combination with other drugs such as MTX.

**Gold salts**

Pneumonitis due to gold is well recognized but uncommon. The pneumonitis typically begins after the cumulative ingestion of about 500 mg of gold. Gold-induced pulmonary disease most often follows improvement in RA, presumably induced by the gold therapy. Patients commonly present with cough and dyspnea. There have been rare reports of acute respiratory failure requiring mechanical ventilation. Gold-induced lung disease can be distinguished from rheumatoid lung disease by the following features, including female predominance, presence of fever or skin rash, absence of subcutaneous nodules or finger clubbing, low titers of rheumatoid factor at onset of lung disease, lymphocytosis in bronchoalveolar lavage fluid (BALF), and alveolar opacities along the bronchovascular bundles on chest CT scan. It usually improves with cessation of therapy or treatment with corticosteroids [211–213].

**D-penicillamine**

Pulmonary complications related to D-penicillamine are rare, occurring in 1 to 3% of cases [199]. Original reports of obliterative bronchiolitis (OB) in patients with RA suggested that D-penicillamine was the causative agent, but OB in the setting of rheumatoid disease has also been associated with gold, sulfasalazine, and in RA patients with no drug therapy [195]. Patients usually complain on subacute onset of cough and dyspnea on exertion. Chest radiograph may be normal or reveals only hyperinflation. On chest CT scans, mosaic pattern of ground-glass opacification is noted. On pulmonary function tests, a progressive obstructive ventilatory defect without bronchodilator response is generally present. Definitive diagnosis requires a lung biopsy, which reveals typical findings of OB. The prognosis of OB associated with D-penicillamine is poor, with an estimated mortality of 50%. There is little evidence that systemic steroids are effective, although a trial of therapy is recommended [214,215].

**Monitoring for lung disease**

The role of surveillance for lung disease in patients with RA is not clear, since minor abnormalities of unknown clinical significance are common, the natural history and prognosis of the disorder are variable, and the role of therapy is uncertain. However, in specific circumstances that include life-threatening deterioration (such as upper airway obstruction due to cicatrytenoid disease), pulmonary-related drug reaction, or interstitial lung disease that may respond to steroid treatment, early diagnosis is important. Thus, a thorough history and examination for pulmonary symptoms and signs should be performed in all patients. When abnormalities are found, further investigations are likely to be required to define the process. Lung function tests, HRCT, bronchoscopy with bronchoalveolar lavage, and transbronchial or surgical lung biopsy, when indicated. Lung function tests, including DLCO should be used serially to monitor disease progression. The role of HRCT and bronchoalveolar lavage in asymptomatic ILD to guide early treatment is still controversial and further studies defining the natural history of abnormalities detected, as well as the effect of early treatment is needed. The discrepancy between the high prevalence of ILD in patients with RA and the less frequent symptomatology and mortality may be explained by the existence of different clinical phenotypes. In patients with RA-ILD, the pattern seen on surgical lung biopsy may be an important predictor of early mortality, with fibrotic disease as in usual interstitial pneumonia having a worse prognosis than that characterized by cellular disease, as in nonspecific interstitial pneumonia.
Several clinical measures may be used to define disease progression in patients with RA-ILD. These measures include among others, serial changes in vital capacity and DLCO on pulmonary function tests. Disease progression seen on HRCT is a stronger prognostic marker than baseline measures. In summary, the approach to patients with rheumatoid arthritis presenting with respiratory symptoms needs to take into account multiple possible causes, including interstitial lung disease, drug-related lung toxicity and infection secondary to immunosuppression. Careful history and physical examination, including a search for extrapulmonary signs of disease in concert with pulmonary function tests and HRCT may suggest the underlying diagnosis. Lung biopsy may be needed before treatment is administered.

Conflicts of interests: none

References


In summary, the approach to patients with rheumatoid arthritis presenting with respiratory symptoms needs to take into account multiple possible causes, including interstitial lung disease, drug-related lung toxicity and infection secondary to immunosuppression. Careful history and physical examination, including a search for extrapulmonary signs of disease in concert with pulmonary function tests and HRCT may suggest the underlying diagnosis. Lung biopsy may be needed before treatment is administered.

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References


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