REVIEW ARTICLE

Pulmonary manifestations of rheumatoid arthritis: a review

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Abstract

Background: Pulmonary involvement is a frequent and among the most severe extra-articular manifestations of rheumatoid arthritis. Rheumatoid arthritis can affect the lung parenchyma, airways and pleura. Pulmonary complications are directly responsible for 10-20% of all mortality in RA patients.
Objective: To highlight the common and important manifestations of rheumatoid lung disease and discuss the recent studies on each.
Data source: Articles on rheumatoid lung disease, reviews done in the American Thoracic Society and European Respiratory Society, Medscape and Upto date Version 19.3.
Data extraction: This was done over a period of 6 months from November 2011 to April 2012.
Conclusion: A thorough history and examination for pulmonary symptoms and signs should be performed in all RA patients. When abnormalities are found, further investigations are likely to be required to define the process. Lung function tests can be used as the baseline tests to detect those who will need more expensive and/or invasive investigations such as HRCT, bronchoscopy with bronchoalveolar lavage, and transbronchial or surgical lung biopsy, when indicated.

Key words: Rheumatoid arthritis, Lung diseases, Interstitial, Bronchiolitis

Introduction

Rheumatoid arthritis (RA) is the most commonly encountered connective tissue disease. It is a chronic inflammatory and systemic disease which mostly affects the synovial joints with a prevalence ranging from 0.5% to 2%[1]. It is a progressive autoimmune process characterized by symmetrical erosive synovitis. Although the central pathology of RA develops within the synovium of diarthrodial joints, many nonarticular organs become involved, particularly in patients with severe joint disease. The female to male ratio of RA is 2.5:1 most frequently seen in the 25-55 year age group.

The prevalence of widely disseminated lesions in other regions of the body has been highlighted with clinical observation and studies, thus pointing out the systemic nature of the disease. The strongest predictors of premature mortality appear to be the presence of RA-related complications and associated co morbidities, specifically, cardiovascular disease and pulmonary disease[2].

In recent cohort studies, nearly 40% of patients with RA suffered from some type of extra-articular manifestations [2-4]. Pulmonary involvement is a frequent and among the most severe extra-articular manifestation of RA[5]. It is a leading cause of excess death in patients with RA[6] and might be the second cause of death in this patient population[7]. RA pulmonary complications are directly responsible for 10 to 20% of all mortality [8-10]. When compared with control populations, patients with RA and with a respiratory disease have an estimated standardized mortality ratio that ranges from 2.5 to 5.0[6,9]. The majority of lung disease occurs within the first 5 years after the initial diagnosis, and may be a presenting manifestation in 9 to 20% of patients. The onset of respiratory manifestation may even precede the onset of symptoms of arthritis.

Lung disease directly associated with the underlying RA is more common, even though pulmonary infection and drug toxicity are frequent complications of RA. The lung is involved in rheumatoid disease because of the abundant vasculature and connective tissue which is involved in collagen vascular diseases. RA can affect the lung parenchyma, airways,

and the pleura, with variable amounts of pathological inflammation and fibrosis. 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. However, all studies concur in that a high prevalence of abnormality can be found. Furthermore, while the prevalence of other serious extra-articular manifestations is declining, RA-associated lung disease is increasing[10] both pulmonary infection and drug-induced lung disease included[11,12].

Pleuropulmonary manifestations of rheumatoid arthritis can be considered under seven categories:

1. Pleural disease
2. Parenchymal involvement
   - Interstitial lung disease
   - Rheumatoid nodules
   - Caplans syndrome (rheumatoid pneumoconiosis)
3. Pulmonary airway involvement
   - Cricoarytenoid arthritis
   - Bronchiolitis
   - Bronchiectasis
4. Infections
5. Drug induced disease
6. Thoracic cage abnormality
7. Vascular involvement

(1) ***Pleural disease:***

Pleural involvement is a common, subclinical entity in RA patients. The annual incidence of rheumatoid pleural effusion in the RA population is 0.34 % in women and 1.54 % in men[13]. The estimated prevalence is approximately 5%. Many pleural effusions are found incidentally on chest radiography. 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 [14,15].

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. A genetic predisposition to rheumatoid pleurisy has also been reported, with a high prevalence of HLA-B8 and Dw3 associated with rheumatoid pleural effusion[16].

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%[12]. 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[12].

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[17,18].

Thoracocentesis reveals pleural fluid which is exudative, nonodorous, and usually straw coloured. Glucose levels are typically low although in acute or recent rheumatoid pleurisy, glucose levels may be normal. PH levels are generally less than 7.3 and reflect ongoing inflammation in the pleural cavity. High LDH levels (above 700IU/L) are considered an indicator of the degree of pleural inflammation and may be useful in monitoring the effects of therapeutic intervention.

2. Parenchymal involvement

2.1 *Interstitial lung disease:* Interstitial lung disease (ILD) is a frequent manifestation of rheumatoid lung disease and a significant cause of morbidity and mortality in the RA patient population, often asymptomatic [6,19]. Estimates of the prevalence of interstitial lung disease (ILD) in RA range between 19% and 44% [19, 20]. The reported prevalence of ILD in patients with RA is highly variable and depends on the methods of detection e.g. high-resolution CT [HRCT] scan, chest radiograph, or pulmonary function testing and the population selected for study i.e. symptomatic or asymptomatic, autopsy series.

Through chest radiography, the diagnosis of rheumatoid lung disease is made in 1% - 5% of RA patients[10]. In most cases it may be normal albeit presence of disease. The estimated prevalence of RA-ILD using HRCT is 20–44%[20] and is a highly sensitive modality to use although expensive investigation in resource limited centres. It has been shown that 40% of patients may have restrictive abnormalities when pulmonary function tests (PFTS) - Spirometry and reduction in CO diffusion capacity (DLCO) when used as diagnostic measures[20]. Asymptomatic ILD often precedes the articular manifestations of RA by months or years. ILD typically becomes symptomatic late in its course when fibrosis is present. Presentation is more common at 50 to 60 years of age, in men, and in association with seropositive and erosive joint disease [21].

Pathogenesis: Clinical, genetic, and environmental factors have been used to predict the development of lung disease in RA. In contrast to most connective tissue diseases, RA-ILD is three times more common in males than in females, in individuals with late-onset disease, high titre rheumatoid factor and in smokers [22, 23]. High-titre rheumatoid factor (RF) has been associated with the presence of RA-ILD [24] and decreased diffusion capacity for carbon monoxide (DLCO)[25,26].

One hypothesis for the development of lung fibrosis in RA is that a cellular inflammatory process is required for and initiates a secondary fibro proliferative process, and that the fibro proliferative process may become progressive and independent of its initiating cause.

A similar paradigm has been hypothesized in patients with hypersensitivity pneumonitis. In these patients, reversible granulomatous inflammation is generally seen. However, once the fibro proliferative process begins, the clinical course and gene expression profile become similar to those of idiopathic interstitial fibrosis (IPF), the prototypical fibrosing lung disease, and the disease becomes unresponsive to immunosuppression[27,28].

Pathology: A wide variety of histopathology 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].

These disorders affect not only the interstitium (space between endothelial and epithelial basement membranes) but also the adjacent airspaces, the peripheral airways, and the vessels. Currently available data show that among RA-ILD patients, there is a higher proportion of a patient with usual interstitial pneumonia (UIP) pattern compared to patients with other connective tissue diseases. Lee *et al.*[31] found UIP to be the most common histopathology pattern in RA-ILD patients (56%). This was followed by non-specific interstitial pneumonia (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 diseases. 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].

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[34]. A careful exposure history (including occupational, environmental and pharmaceutical) should be conducted to evaluate potential alternative causes.

Pulmonary function tests frequently demonstrate reduced lung volumes and Diffusion Capacity of Carbon monoxide (DLCO) even in the absence of symptoms[20]. Reduced DLCO was suggested to be the most sensitive marker for interstitial pneumonia on HRCT[34]. Progressive dyspnea as measured by a standardized questionnaire is a strong predictor of shortened survival[35]. The declining size of the lung as measured by plain chest radiographic study[36] as well as the extent of disease seen on HRCT[37] are powerful predictors of disease. Serial changes in pulmonary physiology with declines in forced vital capacity [38 - 40] can be used both in detection, prediction and follow up tool of disease progression. These changes over time are stronger prognostic markers than baseline measures[41].

Treatment: 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[26,33, 42]. Other drugs reported to be beneficial include cyclophosphamide, azathioprine, hydroxychloroquine, D-penicillamine, and cyclosporine[44, 45]. Effective treatment of the joint disease should not be used as a surrogate for beneficial or even adequate treatment of the ILD. Just as clinically important diffuse lung disease can precede the development of active joint disease in RA, progressive ILD can occur despite the absence of synovitis[33]. This strongly argues for continued regular pulmonary follow-up of known lung disease in patients with even excellent control of their joint disease as well as early pulmonary referral when respiratory symptoms develop or progress in patients with RA, regardless of the activity of their joint disease.

Despite the absence of effective treatments for advanced respiratory disease it is possible that therapeutic intervention at an early stage may be beneficial. It has been suggested that early diagnosis and treatment with antifibrotic agents may alter the prognosis of pulmonary fibrosis [33].

2.2 Rheumatoid nodules

Rheumatoid nodulosis is considered a benign variant of rheumatoid arthritis and is the only pulmonary manifestation specific for the disease. They are more common in men than in women and are usually asymptomatic unless cavitated. They usually present more of a diagnostic than a therapeutic challenge because malignancy has to be ruled out through biopsy. Rheumatoid lung nodules are detected on chest radiograph in about 0.2% of unselected patients with RA[12] and more frequently on HRCT (4%)[45]. In chest radiographs they are usually multiple or solitary, well circumscribed masses ranging from a few millimeters to 7cm in diameter. They are located in sub pleural areas or in association with interlobular septa.

Histologically, the pulmonary nodules are similar to nodules at other sites, with central necrosis, palisading epithelioid cells, a mononuclear cell infiltrate, and associated vasculitis. The clinical course of pulmonary nodules is variable. The nodules may precede the clinical manifestation of RA or be concurrent. They may increase in size, resolve spontaneously, or appear at new sites as older nodules resolve[46]. Complications may include pleural effusion, pneumothorax, hemoptysis and infection.

2.3 Rheumatoid pneumoconiosis (Caplan's syndrome)

Caplan in 1953, defined rheumatoid pneumoconiosis as characterized by rounded, peripheral pulmonary radiological images, 0.5–5.0cm 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 [47]. Although the syndrome was originally described in coal miners, several cases have since been diagnosed in individuals exposed to free silica or asbestos.

Histologically, the findings are similar to those with simple rheumatoid nodules, except that the nodules in Caplan's syndrome are surrounded by pigmented cells. There is no effective treatment for Caplan's syndrome, but the prognosis is good.

3.0 Pulmonary airway involvement

Rheumatoid arthritis is known to cause both upper and lower airway disease. Cricoarytenoid arthritis and bronchiectasis are the major manifestations of large airways involvement. Major manifestations of small airway disease encompass bronchiolitis; follicular bronchiolitis, constrictive bronchiolitis/obliterative bronchiolitis, fibrosing alveolitis and panbrochiolitis.

3.1 Cricoarytenoid arthritis

The cricoarytenoid joints are small diarthrodial 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. Upper airway involvement is more common in women and in patients with long-standing RA. Jurik and Pedersen[48] found arthritis of the cricoarytenoid joints in 55% of 150 patients with RA. The incidence was higher in females (65%) than in males (20%). When HRCT and fiber optic laryngoscopy were used, cricoarytenoid abnormalities were seen in up to 75% of the patients although symptoms were reported in only about half this number [49].

3.2 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 2mm in diameter. These include bronchiolar diseases such as follicular bronchiolitis and constrictive bronchiolitis (also called bronchiolitis obliterans). These diseases are usually seen in patients with positive rheumatoid factor and active joint disease. The symptoms are characterized by dyspnea and nonproductive cough.

Although chest radiograph is generally normal, computed tomography may show areas of air trapping, small nodular opacities in centrilobular distribution (follicular bronchiolitis and bronchiolitis obliterans), patchy areas of low attenuation (bronchiolitis obliterans), and peribronchial thickening (follicular bronchiolitis and bronchiolitis obliterans). Pulmonary function tests reveals airflow obstruction with normal DLco.

Follicular bronchiolitis: In RA, follicular bronchiolitis represents lymphoid hyperplasia in response to an extrinsic immune stimulus or altered systemic immune response, situated in the walls of the bronchioles and, to some extent, in larger bronchi. Although in the past lymphocytic bronchiolitis was thought to be rare and there are only few series and case reports in the literature, Tansey *et al*[50] and Rangel-Moreno *et al*[51] showed that in biopsies from patients with RA, most patients had follicular bronchiolitis as the main pattern of pulmonary disease, or as a finding occurring with another form of RA-associated pulmonary disease .

Constrictive bronchiolitis or obliterative bronchiolitis: Constrictive bronchiolitis (CB) or obliterative bronchiolitis (OB) is a rare, usually fatal, condition characterized by progressive concentric narrowing of membranous bronchioles [52]. Although Geddes *et al*.[53] first reported CB with RA in 1977 only a few years later, it became clear that the disease was related to RA. Patients typically present with the rapid onset of dyspnea and dry cough. The rapidity of onset and severity of symptoms are out of keeping with most other forms of lung disease and should lead to suspicion of the diagnosis. The prognosis and response to therapy are poor. Although no therapy has proven consistently effective, a trial of high dose glucocorticoids (e.g., prednisolone 1–1.5mg/kg per day) is warranted.

The reported prevalence of obstructive dysfunction in small airways in RA patients, estimated on the basis of decreases in FEF 25-75 values, varies among studies, ranging from 8% to 65%. This variation may be explained by the different criteria used in different studies to assess small-airway disease as well as by variation in the patient populations examined. Shunsuke *et al*[54] in Japan obtained evidence suggesting that obstructive dysfunction of small airways is common among 155 RA patients, even among those without a diagnosis of interstitial pneumonia or bronchiolitis pattern on HRCT. Prevalence of obstructive small-airway disease in RA patients without the IP or bronchiolitis HRCT pattern was 30.3%. In Africa, a study done by Amir *et al* [55]on Egyptian patients with rheumatoid arthritis (non smokers) revealed that out of the 36 patients studied 23 (64%) demonstrated abnormalities in PFTs and 47% in HRCT. Mixed restrictive and obstructive pattern was the commonest and reported in nearly 31%. ILD was the commonest pulmonary affection detected by HRCT at 39%.

Pathogenesis: The reason for the high incidence of small-airway obstruction in RA patients remains unclear. One of the most attractive explanations is that the obstructive changes are due to frequent and recurrent infections in the small airways[53]. Colonization of the small airways by pathogenic microorganisms has been reported in patients with clinically stable bronchiectasis[55,56] the evidence indicates that RA patients may have an increased susceptibility to airway infections or a reduced ability to eradicate these infections.

Chronic colonization, secondary persistent inflammation, and progressive lung injury may contribute to the frequent development of airway obstruction during the disease course. As an alternative explanation, several stud-

ies have proposed that bronchi/bronchioles are one of the main targets of autoimmunity in RA patients. Bronchiolar inflammation may secondarily induce mucosal edema, which eventually leads to development of small-airway obstruction [57 58]. Such pulmonary lesions may create a favorable environment for persistent infections. It is uncertain whether microbial colonization may precede bronchiolar obstructive changes or not. Regardless of which came first, a vicious spiral of infections and obstructive changes in the small airways can develop in the lungs of RA patients.

Diagnosis: The diagnosis of RA-associated pulmonary disease should be supported by clinical features (signs, symptoms and laboratory tests), abnormal pulmonary function tests, and either a compatible computed tomography or a lung biopsy[59].

Pulmonary function testing (PFT) has proved valuable in detection of RA-associated lung disease. High resolution computed tomography (HRCT) has been widely used and is highly sensitive for detecting the presence of interstitial lung disease (ILD), with variable incidence of reported abnormalities may reach up to 80% of the patients in some studies[34].

The precise characterization of obstructive changes in small airways that is enabled by both PFT and HRCT appears to be helpful in evaluating not only their long-term significance as pulmonary complications of RA but also their implication in RA pathogenesis.

3.3 Brochiectasis

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[59].

Walker and Wright[12] has shown that patients with RA are more prone to respiratory tract infections than patients with osteoarthrosis, and bronchiectasis is also more common The prevalence of bronchiectasis in HRCT among RA patients is 16.6– 58% [60,61].

4.0 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 [62,63]. 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[9]. The relative risk for pneumonia and lower respiratory tract infections is 1.68 and 1.88 respectively [63]. Wolfe *et al* [64]. 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.

Treatment of RA and other autoimmune disorders with anti-TNF agents is associated with an increased risk of reactivation of latent *Mycobacterium tuberculosis* [65 66]. 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 [65].

Geddes *et al* [53] attributed the high prevalence of obstructive airway disease in RA patients may be due to frequent respiratory tract infections.

5.0 Drug-induced lung disease

Several of the medications used to treat RA can be associated with lung injury. The incidence of pulmonary toxicity in patients treated with methotrexate for RA is 1–5% [66]. There appears to be no relationship between the occurrence of pulmonary toxicity and cumulative dosage. Toxicity is rare with doses less than 20 mg per week, although more recent studies have reported that methotrexate pneumonitis occurs with a dose of 5 mg per week[67].

Methotrexate: 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 [68]. Predominant clinical features of MTX lung injury include shortness of breath, cough, and fever [68]. 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 [69].

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 [70]. 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.

Leflunomide: Interstitial pneumonia as an adverse reaction of leflunomide is rare. The incidence of such cases is reported to be 0.02% in Western countries[71]. In Japan in 2003, 16 cases (0.48%) of ILD, including five fatal cases (0.15%), were associated with leflunomide therapy among 3360 registered patients[72]. 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 [8].

6.0 Thoracic cage abnormality

Abnormalities of thoracic cage mobility can be present in RA and is 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 9.

7.0 Vascular involvement

Vascular inflammation is considered the primary event in the formation of rheumatoid nodules. During nodule formation, small-vessel vasculitis leads to fibrinoid necrosis that forms the core of the lesion, surrounded by fibroblastic proliferation. However, primary vasculitic involvement of the lung is uncommon and must be distinguished from interstitial lung disease that is not vasculitic in nature.

Conclusion

A thorough history and examination for pulmonary symptoms and signs should be performed in all RA patients. When abnormalities are found, further investigations are likely to be required to define the process. Lung function tests can be used as the baseline tests to detect those who will need more expensive and/or invasive investigations such as HRCT, bronchoscopy with bronchoalveolar lavage, and transbronchial or surgical lung biopsy, when indicated.

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