Rheumatoid Arthritis

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Introduction

Rheumatoid arthritis (RA) is the most common autoimmune-mediated joint disease affecting especially small and medium size joints leading to inflammation of the synovium with destruction of cartilage and bone [1]. It is also a systemic disorder, and the effects of systemic inflammation, and patients who have severe extraarticular rheumatoid arthritis disease manifestations have increased morbidity and are at higher risk of premature death [2, 3].

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Epidemiology

Rheumatoid arthritis affects approximately 1 % of the US population and is more common in persons of European and Asian ancestry. Approximately 75 % of patients with RA are women. Rheumatoid arthritis can affect persons at any age, with the mean age of onset of about 55 years of age [1, 4]. Extraarticular disease manifestations occur in more than 40 % of patients during the disease course and include keratoconjunctivitis sicca and rheumatoid nodules [4, 5]. Severe extraarticular manifestations such as vasculitis, Felty's syndrome, glomerulonephritis, pericarditis, pleuritis, scleritis, and interstitial lung disease (ILD) develop in approximately 15 % of patients during the course of the disease [4, 5].

Etiology and Pathogenesis

Rheumatoid arthritis is an autoimmune disease, which is due fundamentally to a loss of self-immunological tolerance [6]. The causes of the loss of immunological tolerance are not known; however, several factors are important in the disease pathogenesis. Genetic predisposition, including the presence of HLA-DR4, CTLA5, PTPN22, and environmental factors, the best studied of which is smoking, increase the risk of development of RA [1, 6]. The immune response is characterized by the development of specific autoantibodies including rheumatoid factor and anti-citrullinated protein antibodies (ACPA) [7, 8].

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The immune dysfunction in RA is mediated by antigen-specific T-cell activation as well as B-cell and TH17-cell co-stimulation. The result is joint inflammation and ultimately osteoclastogenesis with bone and cartilage degradation, and pannus formation leading to the typical pattern of joint destruction and erosive disease seen on joint radiographs [1].

Patients who smoke are at higher risk of developing extraarticular manifestations including lung disease [5, 9–11]. In particular, patients who have HLA-DR4, HLA-B40, HLA-DQB1, and HLA-B54 and possibly alpha-1 proteinase inhibitor appear to have an increased likelihood of lung disease, particularly in the setting of smoking [6, 9, 12]. ACPAs, which are thought to be pathogenetic in RA, may be found in the lung in patients with RA, and there is evidence of increased levels of CD4, CD8, and CD54 T-cells as well as macrophages and CD20-positive B-cells in the lung tissue from patients with RA as well [13–15]. Low levels of interferon gamma and TGF-beta 2 are associated with the presence of fibrosis [16]. It has been speculated that TNF-alpha and interleukin-6 production by macrophages is increased in patients with RA-related ILD, and the presence of high proliferative potential colony forming cells in the peripheral blood has been associated with RA-related ILD [17, 18].

Clinical and Radiologic Features

Joint involvement in patients with RA is characterized by symmetrical swelling of appendicular joints, especially the interphalangeal joints, the metacarpophalangeal joints, the metatarsophalangeal joints, and often medium and large joints. In approximately one-quarter of patients, however, the disease onset is oligoarticular, often beginning in the knee.

Extraarticular disease manifestations can occur at any point during the disease and even occasionally may precede the development of joint disease [1, 4]. Signs of systemic inflammation include constitutional symptoms of fatigue, low-grade fever, weight loss, and elevated levels of inflammatory biomarkers including the C-reactive protein and erythrocyte sedimentation rate. Rheumatoid nodules develop in approximately 30 % of all patients with RA sometime during the disease course, typically over pressure areas such as the elbow [5]. Active RA is associated with anemia of chronic disease. Chronic neutropenia with splenomegaly in the absence of lymphoma occurs in patients with Felty's syndrome, typically occurring in patients with longstanding, seropositive, nodular, deforming RA. Systemic vasculitis may present with involvement of small- and medium-sized vessels of the skin and progressive sensorimotor neuropathy with mononeuritis multiplex and vasculitis of the lower extremities, nailfold infarcts, leg ulcers, purpura, and digital gangrene [1, 4, 5].

Pulmonary involvement in RA is frequent, although not always clinically recognized, and is one of the leading causes of death in patients with RA [19, 20]. The most common forms of lung disease include ILD, constrictive (obliterative) bronchiolitis, and pleuritis. Pericarditis is the most frequent cardiac manifestation of rheumatoid arthritis, which can present as acute chest pain and dyspnea with tamponade, and lead to chronic constrictive pericarditis. Scleritis and peripheral ulcerative scleritis are severe complications of RA and typically occur with longstanding joint disease, which may or may not be active when the scleritis occurs. Patients with RA may also develop milder eye manifestations such as episcleritis, often in the setting of active disease, or keratoconjunctivitis sicca in the setting of secondary Sjögren's syndrome associated with xerostomia. As well, patients with RA, and especially those with severe extraarticular RA are at approximately a twofold increased risk of developing cardiovascular disease and severe infections as well as osteoporosis [21–24].

Rheumatoid factor is present in approximately 80 % of patients with RA, although the specificity is low. ACPA occur in approximately 40–50 % of patients with RA and have a specificity of 90–95 % for the disease [8]. Conventional radiographic examination reveals erosions in patients with established disease. Erosions and findings of synovitis may also be detected on magnetic resonance imaging and ultrasonography.

Diagnosis

The diagnosis of RA is based on the presence of characteristic joint swelling and presence of autoantibodies such as rheumatoid factor and ACPA. The key diagnostic features of RA include morning stiffness of greater than 1 h, arthritis of three or more joint areas, arthritis of the hands, symmetric arthritis, presence of rheumatoid nodules, presence of autoantibodies, and typical radiographic changes in the small joints of the hands and feet [1].

In an effort to facilitate the early diagnosis of RA, a new classification system has been developed, which focuses on features at earlier stages of the disease that are associated with persistent and erosive disease rather than defining the disease by its late-stage features such as erosive disease on radiographs. In the absence of other competing diagnoses, patients can be classified as having definite RA based on the confirmed presence of synovitis in at least one joint, absence of an alternative diagnosis that better explains the synovitis, and achievement of a total score of 6 or greater (of a possible 10) from individual scores in four domains: number and site of involved joints (score range, 0–5), serologic abnormality (score range, 0–3), elevated acute-phase response (score range, 0–1), and symptom duration (2 levels; 0 = symptom duration of less than 6 weeks; 1 = duration of symptom of greater than 6 weeks) [25].

Treatment

The treatment of RA is directed toward the underlying autoimmune disease pathology and guided by the severity of symptoms and signs [26]. Several quantitative measures of disease activity which are based on patient and physician global assessment, presence of joint pain, joint swelling, a patient reported measure of physical disability, and acute-phase reactants are used in the formal assessment of patients with RA. These measures are summarized as the disease activity score 28 (DAS-28), which includes 28 joint count, as well as other measures, such as the simplified disease activity index (SDAI), the clinical disease activity index (CDAI), and others. These summary measures are useful in assessment of disease severity and in management in practice [26].

In the past decade, important advances in the understanding of RA and its management and treatment, including the new classification criteria and better definitions of disease outcome and remission and the introduction of biologic response modifying drugs to inhibit the inflammatory process have greatly altered the approach to managing RA [26, 27]. Early diagnosis and more aggressive management of disease early and throughout the course of disease using standard disease assessment tools have resulted in improvement in function, quality of life, reduction in co-morbidities, and improved survival.

The goals of therapy for RA are to control the underlying inflammatory disease, to alleviate pain, restore quality of life, and preserve independence and the ability of patients to function in their activities of daily living. Prevention of joint destruction and co-morbidities of disease, including heart and lung disease are essential to these treatment goals.

The primary target of therapy in RA is remission, which is defined as the absence of signs or symptoms of inflammatory disease activity. The initial treatment approach in patients with RA is directed toward reduction of inflammatory symptoms and signs and includes the use of disease modifying anti-rheumatic drugs (DMARDs), usually methotrexate, with or without glucocorticosteroids, supplemented by nonsteroidal anti-inflammatory agents where helpful. Combinations of conventional DMARDs including hydroxychloroquine, sulfasalazine, and methotrexate are often used, with early assessment of response and intensification of therapy in the first 12 weeks following initiation of therapy as needed.

Treatment is intensified in patients who have high disease activity scores by the DAS-28 or CDAI or other. For patients on monotherapy, treatment can be escalated to triple DMARD therapy with the addition of sulfasalazine and hydroxychloroquine or the addition of biologic response modifiers including TNF inhibition, anti-cytokine therapy, T-cell co-stimulatory blockade, or kinase inhibition. For patients already taking combined

methotrexate and a TNF inhibitor, an alternative biologic response modifier can be used for persistent active disease [1, 27, 28]. Currently approved biologic response modifiers for RA include anti TNF agents (infliximab, adalimumab, etanercept, certolizumab, golimumab), T-cell costimulatory factor inhibitor (abatacept), anti-IL1 blocker (anakinra), anti-IL6 receptor monoclonal antibody (tocilizumab), Janus kinase inhibitor (tofacitinib) and anti-CD20-directed therapy (rituximab).

Modern treatment of RA also includes attention to physical therapy, occupational therapy, and disease education for both the patient and their families. It is important to address the prevention of disease and treatment-related side effects including osteoporosis and cardiovascular disease, and pursue age-appropriate immunizations to reduce the likelihood of infections [26]. Treatment of extraarticular disease is directed at the specific extraarticular disease manifestations and can include, for example, topical therapies for dry eyes and dry mouth, and systemic immunosuppression with azathioprine, mycophenolate mofetil, and/or cyclophosphamide for more severe disease manifestations including vasculitis, scleritis, and lung disease.

Prognosis

Rheumatoid arthritis is associated with significant disability [1]. More than 75 % of patients with RA are partially disabled, and about 15 % of patients are completely disabled after a decade of disease. The disability begins early, with up to 20–30 % of patients disabled within the first 2–3 years of disease. Life expectancy is shortened by up to 3–7 years, especially in patients with extraarticular disease; infections and serious treatment-related side effects including tumors and gastrointestinal toxic effects from drugs used to treat RA further contribute disease morbidity and premature mortality [2, 4].

Patients who have RA are at 50 % higher risk of heart attack and more than twofold risk for heart failure with attendant decreased survivorship. Patients with RA-related ILD are at more than twofold increased risk of premature death [1, 2, 4].

Pulmonary Manifestations of Rheumatoid Arthritis

Introduction

A broad spectrum of pulmonary manifestations may be encountered in patients with RA and can involve any of the intrathoracic compartments including the lung parenchyma, pleura, airways, and the pulmonary vasculature (Table 3.1). Parenchymal lung disease consists of ILD and rheumatoid lung nodules. Rheumatoid lung nodules can be confused for malignancy. Airway diseases include cricoarytenoiditis, bronchiectasis, and small airways disease including constrictive bronchiolitis which can cause progressive airflow obstruction. Other forms of intrathoracic involvement include pleuritis, pleural effusion, and pulmonary vasculitis. In addition, drug-induced

Table 3.1 Spectrum of pulmonary manifestations in rheumatoid arthritis

Parenchymal
Usual interstitial pneumonia (UIP)
Nonspecific interstitial pneumonia (NSIP)
Organizing pneumonia (OP)
Lymphoid interstitial pneumonia (LIP)
Diffuse alveolar damage (DAD)
Desquamative interstitial pneumonia (DIP)
Eosinophilic pneumonia (EP)
Overlapping patterns of interstitial pneumonias
Rheumatoid lung nodule
Caplan's syndrome
Airways
Bronchiectasis
Constrictive bronchiolitis
Follicular bronchiolitis
Cricoarytenoiditis (upper airway obstruction)
Pleural
Pleuritis
Pleural effusion
Empyema
Pulmonary vascular
Vasculitis
Pulmonary hypertension
Others
Drug-induced lung disease
Infections

lung disease and pulmonary infections are relatively common in this patient population.

Pulmonary manifestation can be the presenting feature of RA, preceding articular manifestations in 10–20 % of RA patients [16, 29]. Clinical presentation of pulmonary disease may range from subclinical abnormalities identified by radiologic imaging or pulmonary function testing in the absence of accompanying symptoms to acute respiratory failure.

Interstitial Lung Disease

ILD is likely the most common pulmonary manifestations in RA and has been detected in 7–58 % of patients using chest imaging and pulmonary function testing [20, 30–34]. The wide range of this estimate is, in part, due to differing survey methods, e.g., chest radiography versus high-resolution computed tomography (HRCT) scan, but also on the criteria used to define the disease and the study population (e.g., stage of RA). Rheumatoid arthritis-related ILD is more commonly encountered in men who are middle-aged [34, 35]. High rheumatoid factor level, active joint disease, and smoking are risk factors for RA-related LD [5, 30, 36–38].

Various underlying histopathologic patterns may be seen in patients with RA-related ILD. Most common patterns are usual interstitial pneumonia (UIP) and nonspecific interstitial pneumonia (NSIP) but other patterns including diffuse alveolar damage (DAD), organizing pneumonia (OP), lymphocytic interstitial pneumonia (LIP), desquamative interstitial pneumonia (DIP), and eosinophilic pneumonia may also be encountered [29, 38–41]. Distinguishing these histopathologic patterns generally requires larger lung specimens as obtained via surgical lung biopsy rather than bronchoscopic biopsy. Underlying histopathologic patterns appear to have prognostic implications. For example, patients with UIP or DAD have shorter survival compared to those with NSIP or OP pattern [29, 39]. However, overlapping histopathologic patterns may be seen on lung biopsy, e.g., UIP with OP, in patients with RA-related ILD.

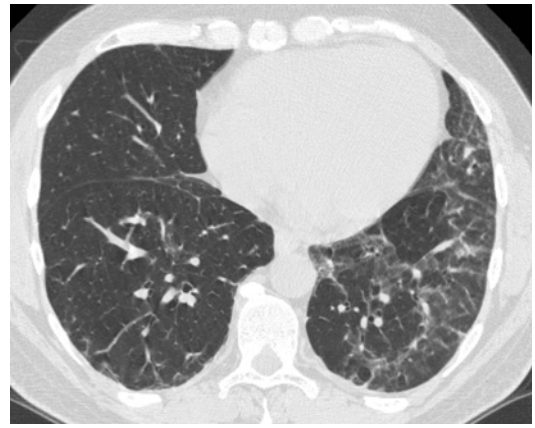

Fig. 3.1 High-resolution computed tomography (HRCT) scan of a 51-year-old man, ex-smoker, with rheumatoid arthritis and exertional dyspnea. Asymmetric parenchymal infiltrates are seen characterized by ground-glass opacities located peripherally, mainly in the left lung. Bronchoscopic biopsy showed organizing pneumonia

In some patients HRCT findings may suggest the dominant histologic pattern obviating the need for a lung biopsy [42].

Clinical features associated with ILD are nonspecific and usually include progressive exertional dyspnea and non-productive cough [16, 43]. In the early stages of ILD, patients may not experience any respiratory symptoms [16, 30, 43]. Sometimes, RA-related ILD may present in an acute manner, resembling acute respiratory distress syndrome. In such situations, lung biopsy, if performed, usually reveals DAD [44–46].

Lung auscultation usually reveals inspiratory crackles over the lung bases [16, 33, 43]. Digital clubbing is uncommon. With advanced ILD, signs of respiratory distress and pulmonary hypertension may be present.

Chest radiography typically reveals bilateral interstitial infiltrates (reticular or reticulonodular opacities), more prominent in the lower lobes [16, 33, 43]. Sometimes the infiltrates may be patchy and homogeneous (ground-glass or consolidative opacities), especially when the underlying histopathologic pattern is OP (Fig. 3.1). High-resolution CT of the chest will provide a more detailed depiction of parenchymal opacities which will mostly consist of reticular and ground-glass opacities, with or without subpleural

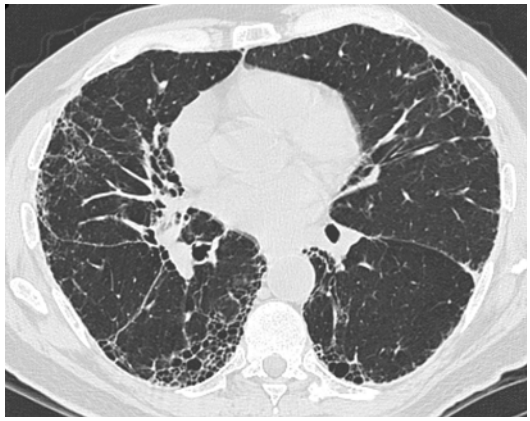

Fig. 3.2 HRCT scan of a 67-year-old man, nonsmoker, with a 6-year history of rheumatoid arthritis and slowly progressive exertional dyspnea over the preceding 2 years. Subpleural honeycombing is seen in both lungs, characteristic of usual interstitial pneumonia (UIP) pattern

honeycombing (seen in UIP pattern) (Fig. 3.2) [39, 47–49]. Radiologic findings on HRCT may suggest the predominant histopathologic pattern of underlying ILD but at other times present nonspecific results.

Pulmonary function testing will yield restrictive abnormalities similar to other ILDs with reduced lung volumes and diffusing capacity [16, 33, 43]. A mixed pattern of abnormalities, e.g., combined pattern of obstructive and restrictive changes, may be seen in patients with preexisting obstructive lung diseases such as chronic obstructive pulmonary disease or coexisting bronchiolar disease related to RA [50, 51]. Oxygen desaturation with exercise may be seen but hypoxemia at rest suggests advanced ILD.

In the majority of patients with RA and evidence of ILD, lung biopsy is not needed for diagnosis and management [16, 43, 52]. Bronchoscopy or surgical lung biopsy may be needed if there are atypical clinical or radiologic features that suggest a disorder other than that directly related to RA, e.g., infection, lymphoproliferative disease, etc.

The decision of whether treat RA-related ILD or not hinges on multiple factors including the severity of lung disease and symptoms, evidence of progression, comorbidities, likelihood of treatment response, potential side effects, and patient preferences [16, 43]. Most of the treatment data in RA-related ILD consists of case series and other uncontrolled studies [16, 43, 52, 53].

For patients with progressive RA-related ILD, pharmacologic therapy usually involves corticosteroids which produce variable subjective and objective improvement [16, 33, 43, 54]. Typically, oral prednisone is used at a dose of 0.5–1.0 mg/kg/day. Other immunosuppressive agents that have been reported to be useful include azathioprine, cyclophosphamide, hydroxychloroquine, cyclosporine, mycophenolate mofetil, and tumor necrosis factor-α (TNF-α) inhibitors [16, 43, 54–56]. However, TNF-α inhibitors have also been reported to cause acute progression of RA-related ILD [57–60]. Rituximab has also been used in the management of RA-related ILD, with uncertain benefits; like TNF-inhibitors, it has also been reported to cause pulmonary decompensation in patients treated with it for cancer [61, 62]. It cannot be assumed that effective treatment for articular disease in RA will necessarily be effective in treating extraarticular manifestations including RA-related ILD. Methodical studies investigating the use of pharmacologic therapy in the treatment of RA-related ILD is needed including the use of novel biologic response modifiers. Lung transplantation is an option for patients with advanced RA-related ILD in the absence of contraindications.

In most patients with RA-related ILD, the lung disease slowly progresses over a number of years. The risk of death approximately three times higher in patients with RA-related ILD compared to RA patients without ILD [20]. Additionally, acute worsening ("acute exacerbation") of RA-related ILD has been reported and is commonly fatal (Fig. 3.3) [44–46].

Rheumatoid Lung Nodules and Caplan's Syndrome

Rheumatoid lung nodules are detected by chest radiography in 1 % of patients with RA whereas HRCT can detect lung nodules in up to 22 % [31, 63, 64]. The nodules are usually multiple and well-circumscribed, ranging in size from few millimeters to several centimeters (Fig. 3.4).

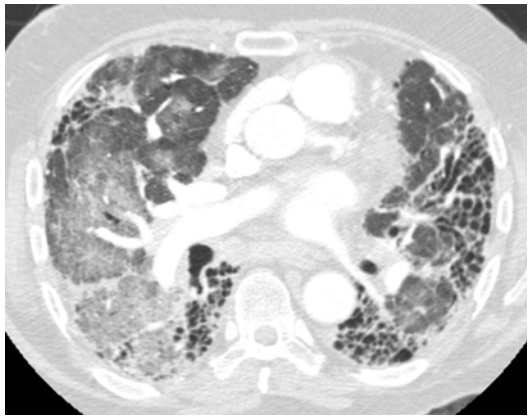

Fig. 3.3 HRCT scan of a 72-year-old man, ex-smoker, with a long history of rheumatoid arthritis and interstitial lung disease (ILD) presenting with acutely worsening dyspnea over the preceding few days. New ground-glass opacities are seen superimposed on preexisting ILD characterized by subpleural honeycombing bilaterally likely representing diffuse alveolar damage superimposed on UIP pattern. Two weeks later, the patient died of progressive respiratory failure

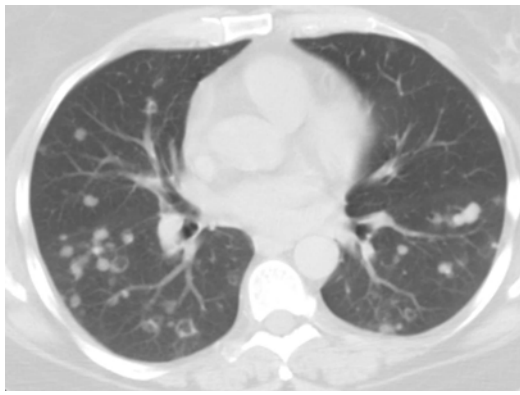

Fig. 3.4 HRCT scan of a 51-year-old woman, nonsmoker, with a long history of rheumatoid arthritis and bilateral lung nodules. Numerous nodules, some cavitated, are seen in both lungs. Transthoracic needle aspiration biopsy confirmed the diagnosis of rheumatoid lung nodules

Pathologically, rheumatoid lung nodules appear granulomatous with collections of macrophages, lymphocytes, plasma cells, and palisading epithelioid cells around a necrotic core [38, 40, 41]. Rheumatoid lung nodules are pathologically identical to subcutaneous nodules and are the only pulmonary manifestation that is specific for RA [40].

Rheumatoid pulmonary nodules are detected radiologically and are usually not associated with symptoms. Rheumatoid lung nodules need to be distinguished from malignant and infectious nodules. In this regard, it should be noted that rheumatoid lung nodules can demonstrate mild fluorodeoxyglucose (FDG) uptake on positron emission tomography (PET) scanning. Transthoracic needle biopsy or bronchoscopic biopsy and sometimes surgical lung biopsy may be needed to confirm the diagnosis in cases where evolution of the lung lesion(s) causes suspicion regarding the underlying nature.

Rheumatoid lung nodules generally have a benign course. However, these lung nodules that are commonly subpleural in location can cavitate and cause pneumothorax and sometimes a bronchopleural fistula or empyema [38, 63, 65–67].

Caplan's syndrome refers to multiple lung nodules seen in patients with both RA and pneumoconiosis as originally described by Caplan in 1953 [68–72]. It has sometimes been called "rheumatoid pneumoconiosis" [68, 70]. Pneumoconiosis may be related to coal, silica, asbestos, or other inorganic dust exposure. Histopathologically, findings of necrobiotic nodule are seen with the additional presence of inorganic dust particles [40, 68, 73]. In this setting, these nodules can appear relatively rapidly over a course of weeks to a few months and often cavitate, resembling tuberculomas [68, 69]. Most patients with Caplan's syndrome are asymptomatic.

Airway Disease

Rheumatoid arthritis can cause several forms of airway disease including upper airway obstruction (cricoarytenoiditis), bronchiectasis, and small airways disease (bronchiolitis) [31, 33, 40, 43]. HRCT can detect signs of airway abnormalities such as bronchiectasis, air trapping, and bronchial wall thickening in the majority of patients with RA [63, 74, 75].

Upper airway obstruction resulting from cricoarytenoiditis can be life-threatening [76, 77]. Cricoarytenoiditis results from synovitis of the cricoarytenoid joint and generally occurs in

patients with long-standing RA and severe articular disease [33]. Cricoarytenoid abnormalities can be seen by laryngoscopy and CT in up to 75 % of patients with RA but is not associated with symptoms in most of these subjects. When cricoarytenoiditis is bilateral and severe causing fixed airflow obstruction, flattening (plateau) is seen in the inspiratory and expiratory limbs of the flow-volume loop on pulmonary function testing [78]. Management of cricoarytenoiditis may require surgical intervention with mobilization of the cricoarytenoid joints. In those patients presenting with acute stridor emergency, tracheostomy may be needed [79].

Bronchiectasis (permanently dilated bronchi) has been reported in up to 30 % in patients with RA [63, 74, 75]. In most of these patients, relevant respiratory symptoms are absent and bronchiectasis does not appear to be clinically significant.

Bronchiolar disease seen in patients with RA is varied. Perhaps the most serious form of bronchiolar disease in this population is constrictive bronchiolitis (also called obliterative bronchiolitis or bronchiolitis obliterans). Although uncommon, constrictive bronchiolitis can gradually progress resulting in worsening airflow obstruction and eventually respiratory failure [51, 78, 80–83]. These patients usually present with persistent exertional dyspnea and cough. Lungs will typically sound clear to auscultation with no crackles or wheezes [51, 81]. Pulmonary function testing reveals evidence of airflow obstruction with air-trapping and hyperinflation. Airflow obstruction is irreversible with no response to inhaled bronchodilator. Diffusing capacity measurement is normal or only mildly reduced. High-resolution CT scan of the chest typically demonstrates a mosaic pattern with patchy areas of air-trapping (areas of hypoattenuation) which becomes more pronounced on expiratory CT imaging (Fig. 3.5) [81, 84]. Management of constrictive bronchiolitis in patients with RA remains difficult because it generally does not respond to currently available therapies including, corticosteroids, immunomodulators, macrolides, etc. [80, 81, 85].

Follicular bronchiolitis is another form of bronchiolar disease that can be seen in patients with RA [51, 86, 87]. Follicular bronchiolitis is associated with small nodular opacities in the lung on HRCT and variable abnormalities on pulmonary function testing [86–88]. In contrast to constrictive bronchiolitis, prognosis is relatively good for patients with follicular bronchiolitis [86–88].

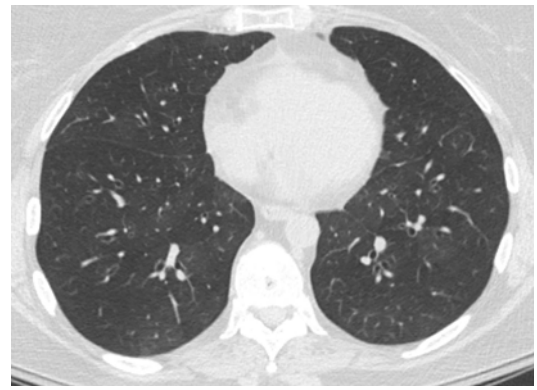

Fig. 3.5 HRCT scan of a 35-year-old woman, non-smoker, with a long history of rheumatoid arthritis and progressive exertional dyspnea over the preceding several months. Mosaic pattern in seen in both lungs due to patchy air trapping. Her FEV1 was 1.84 L (53 % predicted) with an FEV1/FVC ratio of 57.9 %. Six years later, she underwent a double lung transplant for progressive obstructive lung disease. Explant confirmed the diagnosis of constrictive bronchiolitis

Pulmonary Vascular Disease

Systemic vasculitis can rarely be seen in patients with RA and involve the pulmonary vasculature [40, 89]. This vascular involvement can result in alveolar hemorrhage [90]. Pulmonary hypertension in patients with RA is usually associated with advanced ILD but can sometimes be seen with pulmonary vasculitis in the absence of parenchymal fibrosis [33, 91, 92].

Pleural Disease

Pleural disease is common in patients with RA although it is frequently subclinical. On autopsy, pleural abnormalities can be identified in 38–73 % of patients [33, 40, 93, 94]. The spectrum of pleural involvement in RA includes pleuritis, pleural effusion, empyema, pneumothorax and bronchopleural fistula.

Pleural effusion is more commonly seen in men with longstanding joint disease and subcutaneous nodules [32, 33, 95]. Most rheumatoid pleural effusions are small, unilateral, and asymptomatic [32, 33, 95, 96]. The pleural fluid will typically be exudative by biochemical parameters with a low glucose level (usually <30 mg/dL) and a high rheumatoid factor titer [33, 95, 96]. For persistently symptomatic pleural effusions, treatment with corticosteroids (e.g., prednisone 10–20 mg/day), other immunosuppressive therapies, as well as nonsteroidal anti-inflammatory agents has been reported to be effective [33, 96, 97]. Pleurodesis is rarely needed in patients with rheumatoid pleural effusion [66, 96].

Sometimes, the rheumatoid pleural effusion may display characteristics of pseudochylothorax (also called chyliform, pseudochylous or cholesterol pleural effusion) and appear turbid or milky white with a high cholesterol level (typically >200 mg/dL) [95, 96, 98]. This is seen in the setting of a chronic pleural effusion associated with thickened pleura.

More severe forms of pleural disease are rare and include spontaneous pneumothorax, empyema, fibrothorax, and broncho-pleural fistula [33, 66, 95, 96]. Not uncommonly, management of these complications involves surgical maneuvers.

Conclusions

Rheumatoid arthritis can cause a wide spectrum of intrathoracic manifestations, some of which can lead to progressive respiratory embarrassment and occasionally death. Appropriate management of these disease features depends on establishing their relationship to the underlying RA, since similar presentations can be seen with drug-induced diseases and infectious complications. In addition, management must be tailored to the individual patient context including severity of the pulmonary manifestation and comorbidities. These situations can be complex and require a judicious clinical approach.

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