Chapter 6
Thoracic Imaging in Rheumatoid Arthritis

Simon Walsh

Interstitial Lung Disease

Epidemiology and Risk Factors

Interstitial lung disease (ILD) is the most common pulmonary manifestation of RA although there is some variability in the reported prevalence depending on the imaging modality used to detect the disease, the criteria used to define the disease and the population studied. Low rates have been reported based upon chest X-ray abnormalities, whereas much higher rates have been reported based upon abnormal physiology (41%) or HRCT (71%) [1–3]. In an Australian cohort of 36 patients with RA joint disease of fewer than 2-year duration, abnormalities consistent with interstitial lung disease were found on either CXR, HRCT, ^{99M}Tc-DPTA, physiologic evaluation of lung function or analysis of bronchoalveolar lavage fluid in 58% [4]. In a more recent study investigating the prevalence of ILD in 40 patients with RA of not more than 2-year duration, 10% of patients were found to have clinically significant ILD, 27% had interstitial abnormalities on HRCT and 32.5% had abnormal lung function tests [5]. It is estimated that approximately 30% of patients with RA have subclinical ILD on HRCT [6, 7].

Imaging

For evaluating ILD, the chest X-ray is of limited value. Even in the hands of experienced radiologists, the accuracy of chest X-ray for a histologically specific ILD diagnosis is no more than 50% [8]. Furthermore, approximately 10% of patients

S. Walsh, MD, FFRRCSI
King's College Hospital Foundation Trust, London, UK
e-mail: slfwalsh@gmail.com

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with ILD have undetectable disease radiographically [8]. The chest radiographic manifestations of RA-ILD are indistinguishable from those in patients with idiopathic interstitial pneumonia; however the presence of pleural effusions, pleural thickening (in 5–15% of cases) or pulmonary nodules may suggest that rheumatoid arthritis is the underlying cause for the ILD [9, 10].

HRCT is the imaging modality of choice for evaluating ILD. A variety of HRCT patterns may be seen in patients with RA-ILD. The most common is usual interstitial pneumonia (UIP), which occurs in 40–62% of cases. This is in distinction to other connective tissue disease in which non-specific interstitial pneumonitis (NSIP) is more frequently seen. HRCT criteria for a diagnosis of UIP require the presence of honeycombing in a basal and subpleural distribution without features considered incompatible with UIP (Figure) [11]. The HRCT features of honeycombing are clustered cystic airspaces usually of consistent diameter (3–10 mm, but occasionally larger), with characteristically thick, well-defined walls (Fig. 6.1). Traction bronchiectasis is invariably present (figure). Numerous studies have reported on the accuracy of a UIP pattern on HRCT for pathologic UIP demonstrating a positive predictive value for a pathologic diagnosis of UIP between 90 and 100%, and consequently, an HRCT pattern of UIP obviates the need for surgical lung biopsy to secure diagnosis [12–20].

Non-specific interstitial pneumonia (NSIP) is the second most prevalent HRCT pattern seen in patients with RA-ILD occurring in approximately 11–32% of patients [21]. Although no large analyses of the appearances of NSIP on chest X-ray have been performed, most commonly, NSIP presents radiographically as bilateral lower lobe predominant or patchy parenchymal and interstitial opacities [22–24]. On HRCT, ground-glass opacification is the predominant finding in the majority of cases and may be the sole manifestation of in a third of cases [23, 25, 26]. The ground-glass opacity is usually subpleural, bilaterally, and often symmetrical (Fig. 6.2). A fine band of subpleural sparing has also been described (Fig. 6.3) [27, 28]. Within the ground-glass opacification, fine reticular opacities may be seen in

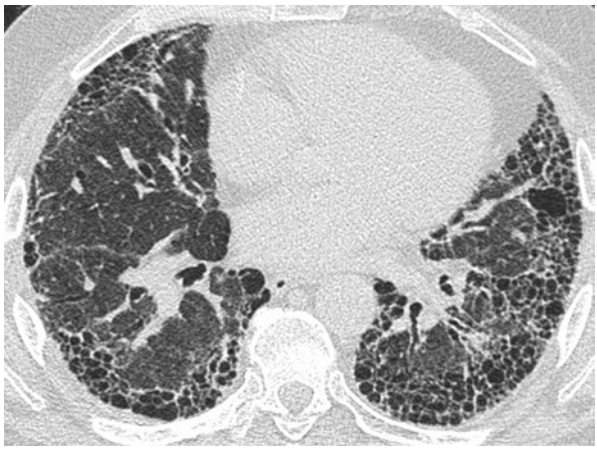

Fig. 6.1 Axial HRCT image of the lower lobes in a patient with rheumatoid arthritis-related usual interstitial pneumonia (UIP). The basal predominant, subpleural distribution of honeycombing is characteristic of this entity

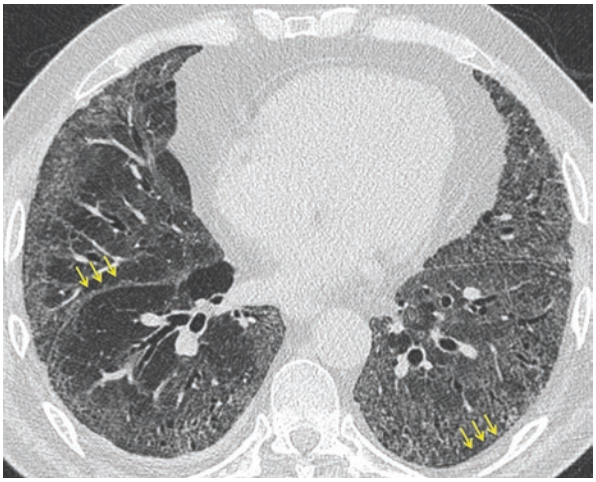

Fig. 6.2 Axial HRCT image of the lower lobes in a patient with rheumatoid arthritis-related nonspecific interstitial pneumonia (NSIP). In this patient, diffuse but predominantly subpleural textured ground-glass opacification is demonstrated containing areas of traction bronchiectasis particularly in the left lower lobe. Although honeycombing is absent, there is significant volume loss in the right lower lobe highlighted by the retraction of the right oblique fissure. A thin region of subpleural sparing is seen in the right lung at this level

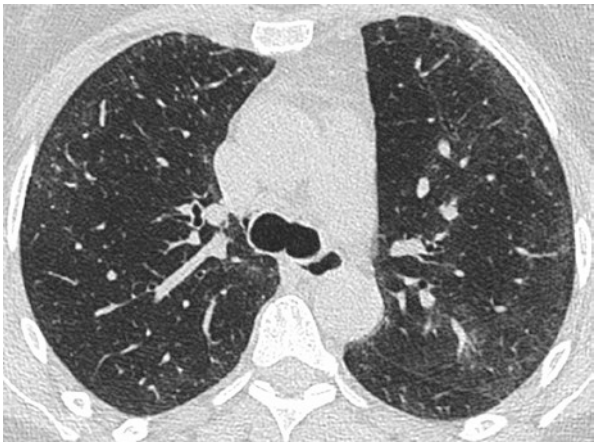

Fig. 6.3 Axial HRCT image of the upper lobes in a patient with rheumatoid arthritis-related NSIP. In the left upper lobe, the subpleural ground-glass opacification spares the juxtapleural lung

half of cases, which may or may not be associated with traction bronchiectasis (Fig. 6.4). Honeycombing is usually absent; however in fibrotic HRCT, limited honeycombing may be present. In these cases, distinguishing between fibrotic NSIP and UIP can usually only be made on histopathologic grounds [29].

Some other, less common HRCT patterns of interstitial pneumonia are seen in patients with rheumatoid arthritis. Organizing pneumonia, which is a non-specific inflammatory response to lung injury, may be present before the onset of

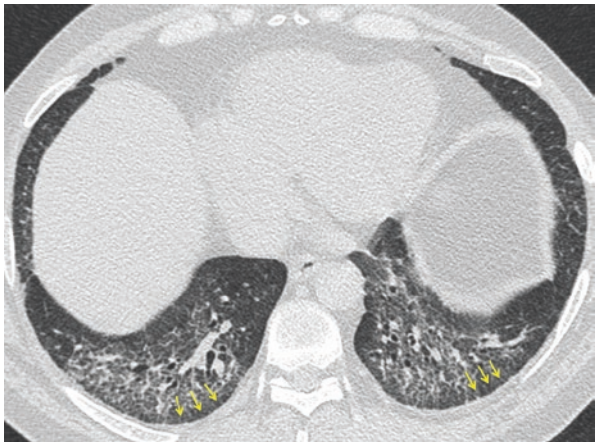

Fig. 6.4 Axial HRCT image of the lower lobes in a patient with rheumatoid arthritis-related NSIP. The lower lobe ground-glass opacification has admixed areas of reticulation and traction bronchiectasis but no honeycombing

articular disease and, at least in this author's experience, is unusual but may represent lung injury as the sole manifestation of RA [30, 31]. When this occurs, an alternative connective tissue disease may be considered. The HRCT patterns of organizing pneumonia in rheumatoid arthritis are identical to those seen in patients with cryptogenic organizing pneumonia, namely, diffuse airspace opacities, which are usually bronchocentric, with or without perilobular opacities or "reverse-halo" lesions (Figs. 6.5 and 6.6). Diffuse alveolar damage is a rare occurrence in patients with rheumatoid arthritis but may occur both in those with pre-existing ILD and as a de novo manifestation of rheumatoid arthritis. When this occurs, drug toxicity or infection should always be considered in the differential diagnosis. This will be discussed in more detail separately. Lymphocytic interstitial pneumonia (LIP) and desquamative interstitial pneumonia (DIP) have also been described in patients with RA-ILD but are rare. In one small series of 15 patients with LIP, only one patient had an established diagnosis of rheumatoid arthritis [32]. At the time of writing, only one case of DIP preceding the onset of rheumatoid arthritis has been reported [33]. As with other forms of RA-ILD, the HRCT appearances of LIP and DIP in patients with rheumatoid arthritis are like their idiopathic counterparts.

Imaging and Prognostication

The role of HRCT as a prognostic tool in the setting of fibrotic idiopathic interstitial pneumonia (fibrotic IIP), i.e., IPF/UIP and fibrotic NSIP, has been extensively studied. Since the most common patterns of ILD in patients with RA are UIP and NSIP, a brief discussion of outcome prediction using HRCT in the setting of idiopathic fibrotic lung disease is worthwhile.

At the most basic level, the radiologic presentation is of prognostic significance. In the setting of biopsy-proven IPF/UIP, Flaherty et al. demonstrated that a typical UIP pattern on HRCT, indicating radiologic-histopathologic concordance, was

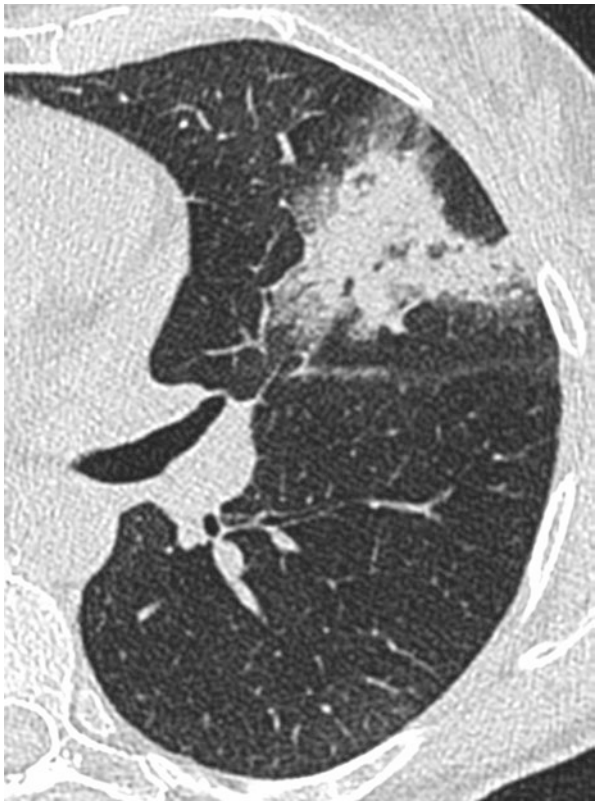

Fig. 6.5 Cropped HRCT image of the left upper lobe of a patient with rheumatoid arthritis. An area of bronchocentric consolidation with perilobular sparing is demonstrated consistent with organizing pneumonia

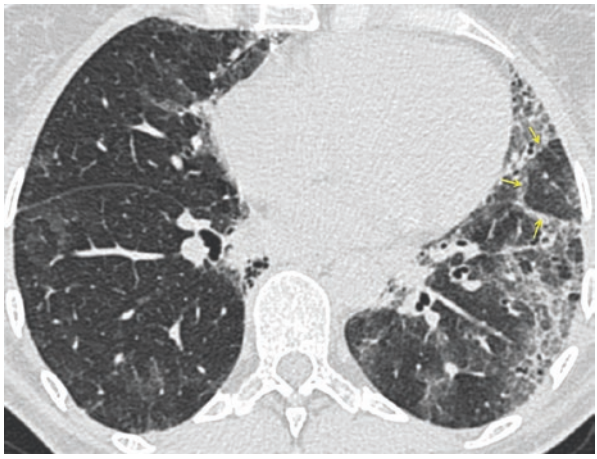

Fig. 6.6 Axial HRCT image of the lower lobes in a patient with rheumatoid arthritis-related NSIP characterized by subpleural reticulation, ground-glass opacification and traction bronchiectasis. In addition to the fibrotic lung disease, there is evidence of subpleural perilobular sparing indicating admixed organizing pneumonia

associated with increased mortality when compared to those patients with an atypical UIP or fibrotic NSIP pattern on HRCT [34]. More specifically, individual HRCT patterns may be predictive of mortality. The overall extent of fibrosis on HRCT, for example, expressed as a CT-fibrosis score and usually representing the combined

extents of honeycomb and reticular abnormalities on HRCT, has been shown to have prognostic significance in several studies. Gay et al. evaluated 38 patients with biopsy-proven IPF, according to diagnostic criteria at the time, to identify parameters predictive of response to treatment and mortality and reported that a CT-fibrosis score (representing the combined extent of reticulation and honeycombing on HRCT) was the only variable, which predicted outcome [35]. A similar study in 115 patients with a diagnosis of IPF/UIP based upon either a typical HRCT appearances or surgical lung biopsy reported that the CT-fibrosis score was a predictor of survival [36]. In a larger study involving 315 patients with IPF enrolled in a clinical trial of IFN-γ1b, Lynch et al. reported that overall extent of fibrosis, again, defined as extent of reticular and honeycomb abnormalities combined, was the strongest predictor of mortality [37]. Finally, Sumikawa et al. demonstrated that a fibrosis score (which included extent of ground-glass opacification) predicted outcome in 98 patients with histopathologic diagnosis of UIP and a clinical diagnosis of IPF [38]. More recently, emerging evidence indicates that severity of traction bronchiectasis may be an important predictor of outcome in fibrotic IIP [38, 39].

Despite the prognostic role of HRCT being extensively studied in fibrotic IIP, the number of studies reporting on the role of HRCT in predicting prognosis in RA-ILD is comparatively small [40–42]. Kim et al. evaluated the prognostic impact of a UIP pattern specifically in the setting of 82 patients with RA-ILD and demonstrated no significant survival differences between those patients with RA-UIP (n = 20) and patients with IPF/UIP (n = 51) [40]. These findings were corroborated in a more recent study comparing survival in fibrotic IIP and CTD-ILD [43]. Most recently, in a study of 168 patients with all-comers CTD-FLD (RA-ILD, n = 39), Walsh et al. sought to evaluate the prognostic impact of individual HRCT patterns [41]. On multivariate analysis, as has been shown in patients with fibrotic IIP, the extent of honeycombing and severity of traction bronchiectasis were independent predictors of survival. Although not published, these findings were maintained on subgroup analysis of the patients with RA-ILD. Two further observations from this study are worth highlighting. First, a simple binary determination of traction bronchiectasis being present or absent was highly predictive of mortality. Second, a subgroup analysis of overall presenting HRCT pattern (UIP versus fibrotic NSIP) in patients with biopsy-proven UIP showed that patients showing radiologic-histopathologic concordance (UIP on HRCT, UIP on biopsy) had a worse outcome than those with radiologic-histopathologic discordance (NSIP on HRCT, UIP on biopsy). These findings mirror those reported by Flaherty et al. in the setting of fibrotic IIP, discussed earlier [34].

Airway Disease

The use of HRCT for evaluating patients with rheumatoid arthritis presenting with respiratory symptoms has demonstrated that airway disease is a common pattern of abnormality in this group of patients. However, like RA-ILD, the

prevalence of airway disease in this setting is variable, depending on the patient population studied and how the disease is defined. An additional challenge when attempting to correlate airway disease with rheumatoid arthritis is the presence of confounding factors such as smoking or the presence of RA-ILD [44–46].

Obliterative Bronchiolitis

There is a well-recognized association between rheumatoid arthritis and obliterative bronchiolitis (OB, also known as constrictive bronchiolitis) in which predominately mural inflammation and fibrosis progressively narrows the lumens of the membranous and respiratory bronchioles [47–51]. Clinically, obliterative bronchiolitis presents with rapidly progressive dyspnoea, cough and bronchorrhea without systemic symptoms and evidence of irreversible airflow obstruction. The chest radiograph may be normal or show signs of hyperinflation and oligaemia. The characteristic HRCT finding is of mosaic perfusion with air trapping (Fig. 6.7) and may be associated with mild cylindrical bronchiectasis.

Follicular Bronchiolitis

Follicular bronchiolitis is histologically characterized by the presence of hyperplastic lymphoid follicles with reactive germinal centres distributed along the bronchioles and bronchi [52, 53]. It is defined as lymphoid hyperplasia of the bronchus-associated lymphoid tissue and may be seen in a variety of connective tissue disorders including rheumatoid arthritis. In 1 study of 12 patients with

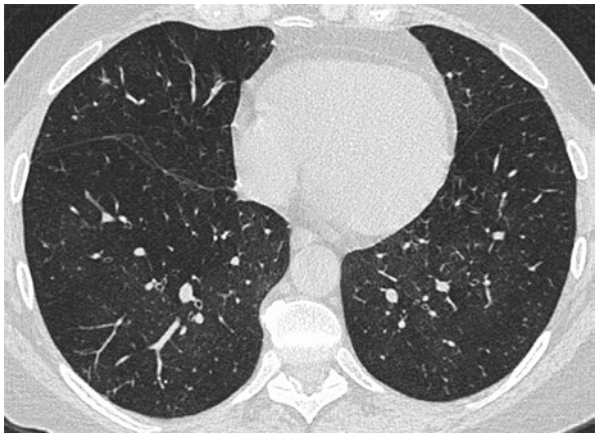

Fig. 6.7 Axial HRCT image of the lower lobes in a patient with rheumatoid arthritis demonstrating subtly the mosaic pattern of obliterative bronchiolitis, characterized by areas of normal lung interspersed with areas of low attenuation (dark lung)

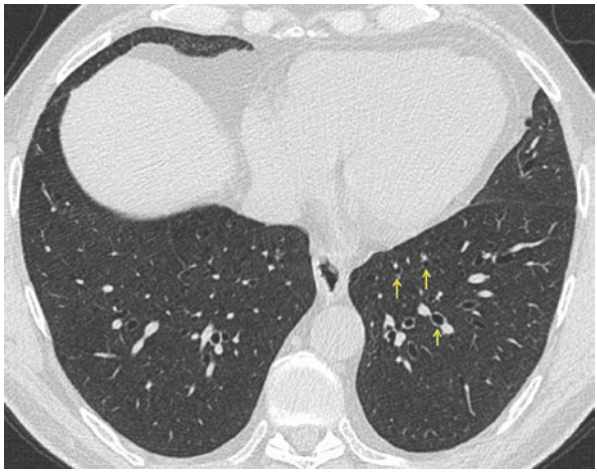

Fig. 6.8 Axial HRCT image of the lower lobes in a patient with rheumatoid arthritis demonstrating mild cylindrical bronchiectasis involving the segmental and subsegmental airways of both lower lobes. The affected bronchi are larger in cross-sectional diameter than the accompanying pulmonary artery, a diagnostic feature of bronchiectasis

histopathologically confirmed follicular bronchiolitis, the cardinal HRCT features were small (<3 mm) centrilobular nodules variably associated with peribronchial nodules and areas of ground-glass opacification [54].

Bronchiectasis

The association between rheumatoid arthritis and bronchiectasis has been recognized since the 1960s. In CT-based studies, the overall frequency is about 20% with a range of 6–41% [4, 55–60]. Rheumatoid arthritis usually precedes the onset of bronchiectasis by 11.5–24.7 years, and the presence of bronchiectasis does not appear to reflect rheumatoid arthritis severity [61, 62]. Various hypotheses have been suggested to explain the link between rheumatoid arthritis and bronchiectasis, which have included genetic predisposition, susceptibility to chronic suppurative infections leading to airway damage or as a manifestation of drug-related pulmonary toxicity [56, 63]. On HRCT, bronchiectasis seen in patients with rheumatoid arthritis is usually cylindrical and may be associated with physiologic evidence of small airway disease (Fig. 6.8) [44].

Pleural Disease

Pleural changes are common in patients with rheumatoid arthritis, occurring in up to 50% of cases at postmortem examination [64]. Although 20% of patients with rheumatoid arthritis experience pleurisy at some stage in their disease, pleural effusion is significantly less common—in one study of 516 patients with

rheumatoid arthritis, only 17 (3.3%) had pleural effusions [65]. Pleural effusion in rheumatoid arthritis is more common in males than females [65]. Other associations include middle age (usually the sixth decade), high rheumatoid factor titres, long-standing active articular disease and rheumatoid nodules [10, 66]. Most pleural effusions are unilateral although bilateral pleural effusions do occur in approximately 20% of cases, and unlike in other connective tissues, pleural effusion in rheumatoid arthritis may be asymptomatic [10, 67, 68]. In approximately one-third of patients with rheumatoid arthritis and pleural effusion, other rheumatoid-related pulmonary abnormalities will be present including interstitial lung disease or pulmonary nodules [10]. Although effusions may resolve within weeks, some may persist for months or years, often becoming loculated [10]. Persistent, symptomatic pleural effusion requires thoracocentesis [68]. Occasionally effusions may be associated with pneumothorax. Following resolution of pleural effusion, residual pleural thickening, fibrothorax, or rounded atelectasis may be seen [10, 64, 69] (Fig. 6.9). Diagnosis is established by examination of the pleural fluid or possibly pleural biopsy (which may demonstrate pleural rheumatoid nodules). High cellular content, low glucose (<60 mg/L), low pH (<7.3) and raised lactate dehydrogenase (may be >700 IU/L) are characteristics [67, 70]. It is likely because of the high cellular content that rheumatoid-related pleural effusion may be intensely FDG-avid on PET [71]. In many cases, pleural effusion can be diagnosed on erect chest radiography. Diagnostic pleural aspiration is aided by ultrasound, and CT will demonstrate comorbid rheumatoid-related parenchymal pathology. In particular, CT allows the identification of cavitating pulmonary nodules, which can rupture resulting pneumothorax or sterile "empyematous" effusions and subsequent bronchopleural fistula [68] (Fig. 6.10a, b).

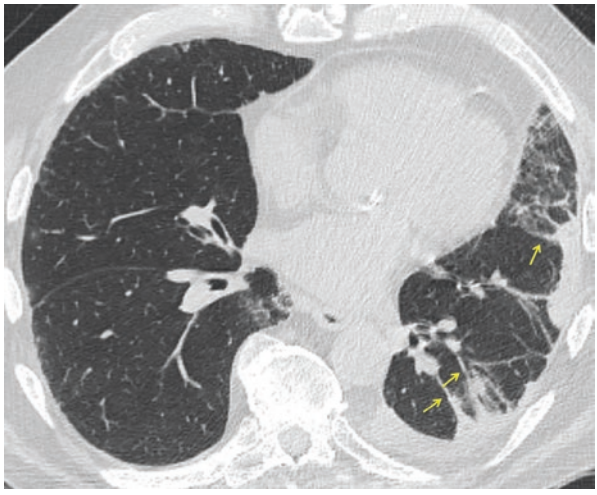

Fig. 6.9 Axial HRCT image of the lower lobes in a patient with rheumatoid arthritis demonstrating a shallow left-sided pleural effusion with overlying regions of rounded atelectasis. Each region of rounded atelectasis has bands of linear atelectasis arising from it, extending into the lung parenchyma—the "comet-tail" sign

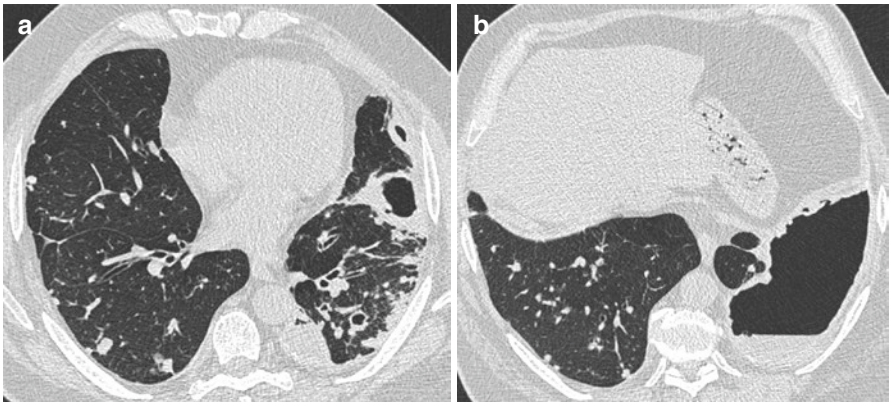

Fig. 6.10 (**a**) Multiple solid and cavitating pulmonary nodules are demonstrated throughout both lungs in a patient with rheumatoid arthritis. Areas of pleural thickening and subpleural round atelectasis are demonstrated in the left lower lobe. A nodule has cavitated into the left pleural space (**a**) and resulted in formation of a bronchopleural fistula and large loculated hydropneumothorax inferiorly (**b**)

Necrobiotic Nodules

Necrobiotic nodules in the lung are identical pathologically to subcutaneous rheumatoid nodules consisting of a necrotic centre engulfed by palisading histiocytes and surrounded by plasma cells and lymphocytes. Necrobiotic nodules may occur in patients with established arthritis or before the onset of arthritis [72]. Almost 90% of patients with necrobiotic nodules are rheumatoid factor positive, and about 80% also have subcutaneous nodules [10, 72, 73].

Necrobiotic nodules are an unusual finding on the chest radiograph: in 2 series of 955 patients, no examples were found [57, 74], and only 2 cases were identified in a second series or 516 patients [10]. CT is more sensitive for detecting necrobiotic nodules than radiography and in various CT studies; the prevalence has been reported as ranging from 0 to 37% [4, 58, 75–78]. Necrobiotic nodules are usually round or lobulated on CT, may cavitate, have a mid-/upper zone predilection and are often subpleural [73, 79] (Fig. 6.11). Although necrobiotic nodules are usually asymptomatic, erosion and cavitation of subpleural nodules into the pleural space may occur resulting in a pneumothorax, hydropneumothorax or bronchopleural fistula (Fig. 6.10a, b) [73]. They may be single but are more commonly multiple and may produce a miliary pattern [73]. They range in size from several millimetres to 7 cm. Small rheumatoid nodules have also been reported along the pleura and in the trachea [80]. Necrobiotic nodules may be stable for years, increase in size and number or resolve spontaneously [81, 82]. There is some limited evidence to suggest that necrobiotic nodules may occasionally paradoxically enlarge with methotrexate treatment [83]. Necrobiotic nodules may calcify [84, 85]. As they are indistinguishable from primary lung neoplasms, close

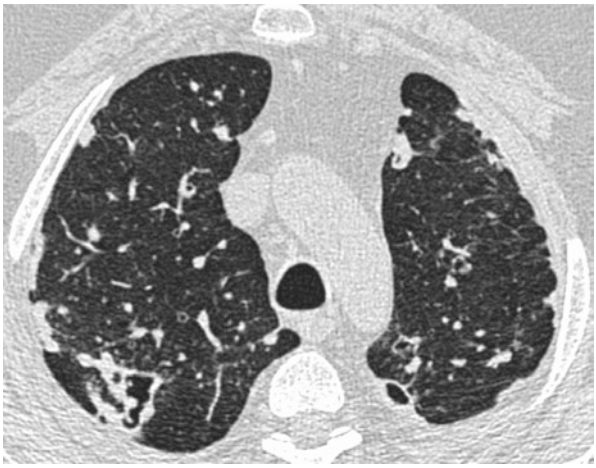

Fig. 6.11 Axial HRCT image of the upper lobes in a patient with rheumatoid arthritis demonstrating multiple irregular-shaped pulmonary nodules, some of which are cavitating. Nodules located along the pleura may cavitate into the pleural space resulting in bronchopleural fistula (Fig. 6.10a, b)

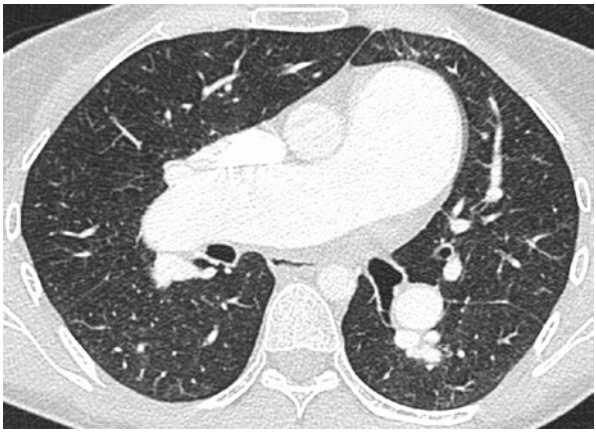

Fig. 6.12 Axial HRCT image in a patient with rheumatoid arthritis and confirmed pulmonary artery hypertension on right heart catheterisation studies. There is gross enlargement of the main pulmonary artery

follow-up or histologic confirmation may be required [86]. On PET-CT, necrobiotic nodules may [87] or may not be FDG-avid [71] (Fig. 6.12).

Caplan's syndrome is the occurrence of multiple variable-sized (0.5–5.0 cm) pulmonary nodules on the chest radiographs of coal miners with rheumatoid arthritis [88]. This syndrome may also occur in rheumatoid arthritis patients with occupational exposures to silica or asbestos [89]. The characteristic imaging finding in patients with Caplan's syndrome is solitary or multiple pulmonary nodules often 1–2 cm in diameter but may be as large as 5 cm [90]. Reports suggest that the nodules of Caplan's syndrome have a predilection for the junction of the outer and middle third of the lung on chest radiograph. Caplan's nodules may cavitate or calcify [90]. They may heal with scarring, remain stable or grow slowly over years. Nodules are usually asymptomatic but become symptomatic if they cavitate and become infected or rupture into the pleural space. Small Caplan's nodules may be indistinguishable from those seen in silicosis [90].

Imaging of Drug-Related Pulmonary Toxicity

Drug-induced pulmonary toxicity is an important consideration in the differential diagnosis of patients with rheumatoid arthritis presenting with new respiratory symptoms. Although chest radiography as a preliminary investigation is sufficient to demonstrate new parenchymal disease, HRCT is the modality of choice for depicting histologically distinct patterns of disease.

Methotrexate-induced lung toxicity may manifest as acute/subacute hypersensitivity pneumonitis or less commonly as chronic pneumonitis. Chest radiographs may be normal in the early stages of the disease. HRCT findings may be those of hypersensitivity pneumonitis, namely, diffuse ground-glass opacities which are nodular in the upper lobes, combined with lobular areas of low attenuation representing air trapping due to airway disease (Fig. 6.13). The diagnosis of methotrexate-induced lung toxicity is usually made by a combination of clinical, imaging and BAL findings. Chronic progressive pulmonary fibrosis because of methotrexate treatment in patients with rheumatoid arthritis has been described and presents on HRCT as a non-specific diffuse interstitial fibrosis, although whether this is directly related to methotrexate is unclear [91–93].

Perez-Alvarez et al. reported on 122 cases of new onset or exacerbated ILD following TNF inhibitor (TNFi) administration, 108 of whom had rheumatoid arthritis. In this study, TNFi-associated pulmonary toxicity was diagnosed by HRCT in 50 cases. The most common HRCT pattern (36/50) was diffuse ground-glass opacification representing diffuse alveolar damage (DAD) (Fig. 6.14a, b). Pulmonary fibrosis was seen less frequently.

Although there is one case report of rituximab-induced organizing pneumonia in a patient with rheumatoid arthritis, the evidence supporting a link between rituximab and ILD specifically in patients with rheumatoid arthritis is not compelling [94]. Figure 6.15a demonstrates diffuse ground-glass opacities representing DAD, in a patient with RA following rituximab treatment followed 15 days later by DAD with areas of incorporated organizing pneumonia (Fig. 6.15b). Note in this example the ground-glass opacities unmask emphysema which appears to mimic honey-

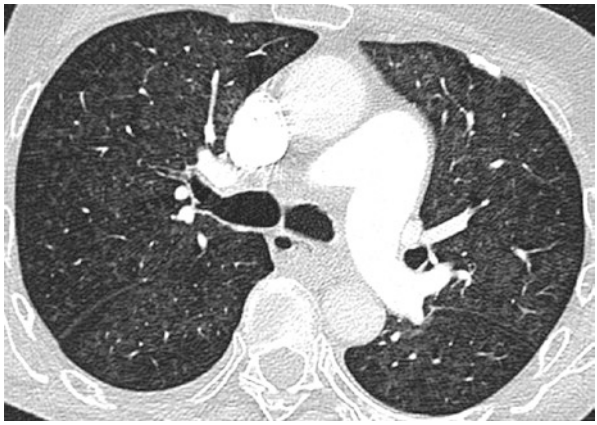

Fig. 6.13 Methotrexate toxicity in a patient with rheumatoid arthritis. There are subtle nodular regions of ground-glass opacification in the upper lobes, also seen in patients with hypersensitivity pneumonitis

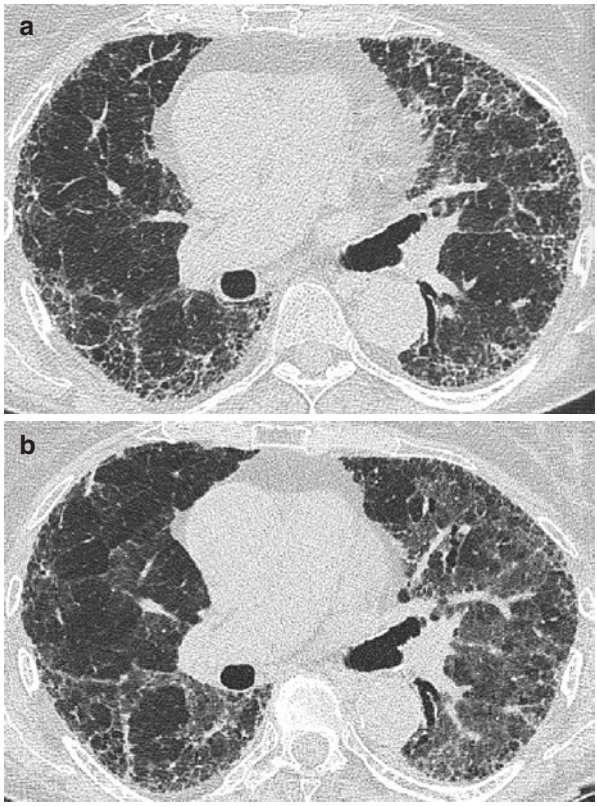

Fig. 6.14 TNF inhibitor pulmonary toxicity in a patient with rheumatoid arthritis and pre-existing interstitial lung disease. (**a**) Before treatment there are subpleural reticular abnormalities with traction bronchiectasis consistent with fibrotic lung disease. (**b**) Following treatment with TNF inhibitor, progressive dyspnoea prompted further HRCT evaluation which demonstrated new homogeneous ground-glass opacities throughout both lungs consistent with diffuse alveolar damage. An important differential diagnosis not to overlook in this setting is opportunistic infection (see text)

combing. Nearly 1 month following the initial HRCT, consolidation with a perilobular distribution consistent with organizing pneumonia remained (Fig. 6.15c).

Occasionally in RA patients presenting with acute dyspnoea, imaging patterns on HRCT may point to a specific drug, and together with the timing of treatment, a relatively confident diagnosis of drug-related pulmonary toxicity can be made. More often, however, the HRCT findings are those of relatively non-specific ground-glass opacification and consolidation. In this setting, it is important not to overlook the possibility of opportunistic infection, which may have similar HRCT appearances and more likely in RA patients receiving immunosuppressive therapy. A variety of severe infections have been reported with the use of TNFi and rituximab. In one study, the most common infection was bacterial pneumonia which may present on HRCT as focal or multifocal consolidation. In addition to reactivation of tuberculosis (TB), increased susceptibility to nontuberculous mycobacterial infection (NTM) also occurs in RA patients receiving TNFi therapy. NTM infection usually presents on HRCT as a combination of cavitating nodules, tree-in-bud opacification and focal areas of fibrotic scarring causing localized traction bronchiectasis (Fig. 6.16a, b). Numerous fungal infections have also been reported in association with TNFi therapy, including *Pneumocystis jirovecii*, histoplasmosis, coccidioidomycosis, *Cryptococcus* and *Aspergillus*.

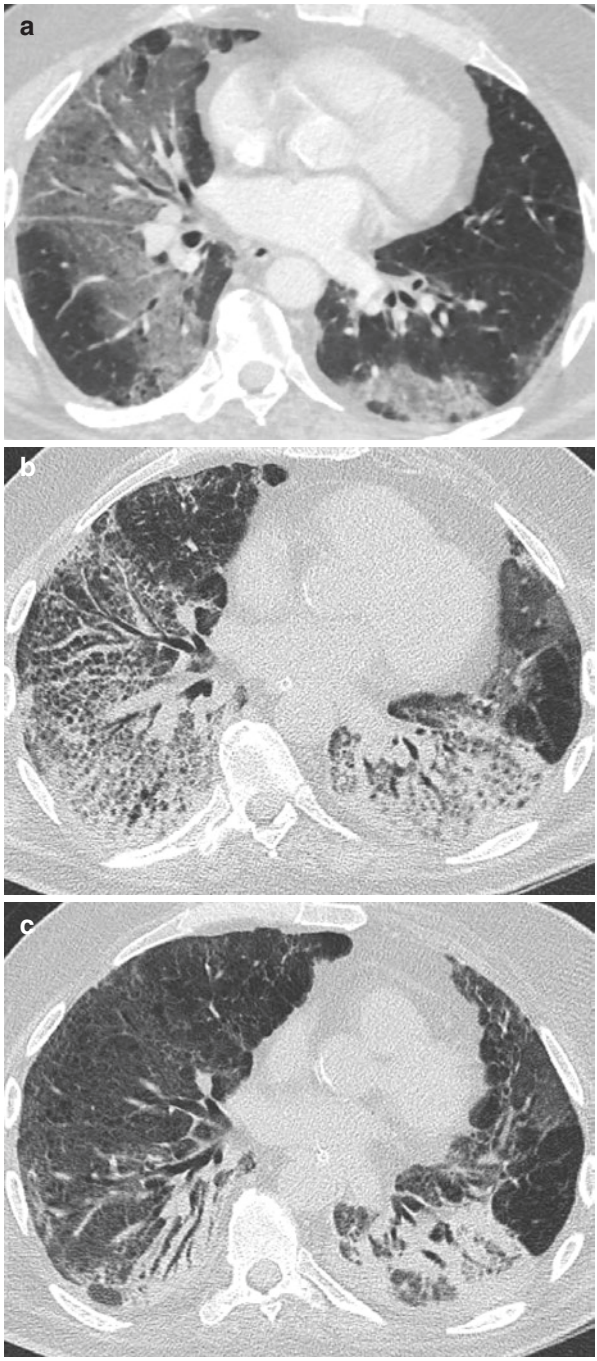

Fig. 6.15 Series of HRCT images of a RA patient receiving rituximab therapy. Soon after commencing therapy, the patient presented with acute dyspnoea. The HRCT (**a**) demonstrated diffuse ground-glass opacities representing DAD. Fifteen days later, a repeat HRCT showed (**b**) DAD with areas of incorporated organizing pneumonia. Note in this example the ground-glass opacities unmask emphysema which appears to mimic honeycombing. Nearly 1 month following the initial HRCT, consolidation with a perilobular distribution consistent with organizing pneumonia remained (**c**)

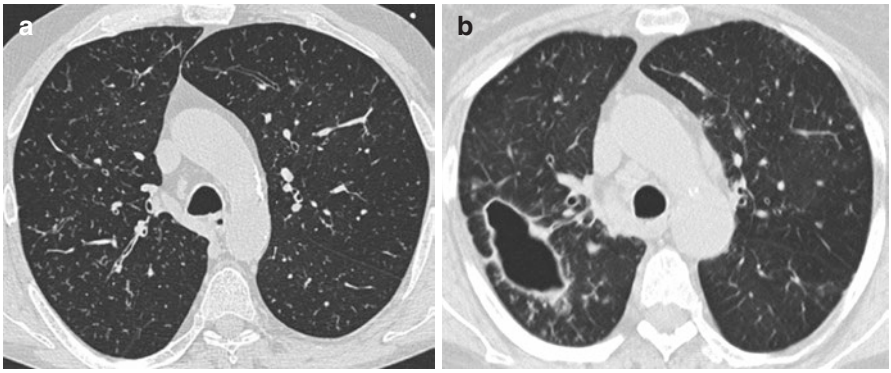

Fig. 6.16 Nontuberculous mycobacterial infection in two patients being treated with TNFi therapy. (**a**) Axial HRCT image in a RA patient demonstrating tree-in-bud-type opacities throughout both lungs consistent with exudative bronchiolitis seen in nontuberculous mycobacterial infection. (**b**) Axial HRCT image in a RA patient with a large cavitation lesion with surrounding demonstrating tree-in-bud-type opacities indicating the presence of exudative bronchiolitis. Nodules with cavitation and tree-in-bud opacification are HRCT features of nontuberculous mycobacterial infection

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