Chapter 7
Lung Histopathology in Rheumatoid Arthritis

Kirk D. Jones

Introduction

In 1948, Ellman and Ball published a series of three cases of pulmonary disease in patients with rheumatoid arthritis [1]. Two of the cases were shown on post-mortem histological examination to have alveolar septal fibrosis with chronic inflammation. Since the joint symptoms closely preceded the pulmonary symptoms, the authors stated that "one might not unreasonably assume, without wishing to appear in any way dogmatic, that the joint and lung lesions are manifestations of one and the same pathological process." They continued to express that the disease process should be referred to as "rheumatoid disease" rather than "rheumatoid arthritis" in order to reflect the multiple systemic manifestations of the disease. This notion that rheumatoid arthritis was a systemic disease met some resistance, with other physicians believing these cases represented undiagnosed tuberculosis or sarcoidosis [2]. However, over the next several decades, pulmonary disease in rheumatoid arthritis became more widely recognized. Pathologic changes with similar morphology in the lung as the joints, such as rheumatoid nodules and pleurisy, were accepted fairly quickly, while diseases with non-specific morphology, such as interstitial inflammation and fibrosis, were accepted more slowly. Currently, pulmonary disease is recognized as a major source of morbidity and mortality in patients with rheumatoid arthritis, accounting for approximately 10% of deaths [3].

Despite this acknowledged frequent pulmonary involvement, diagnosis of rheumatoid arthritis-associated pulmonary disease is hindered by the fact that the lung has a limited number of reaction patterns to injury. This results in the histologic conundrum that the changes in rheumatoid arthritis may closely

K.D. Jones, MD
University of California, San Francisco, CA, USA
e-mail: Kirk.Jones@ucsf.edu

A. Fischer, J.S. Lee (eds.), *Lung Disease in Rheumatoid Arthritis*, Respiratory Medicine, https://doi.org/10.1007/978-3-319-68888-6_7

Table 7.1 Histologic changes in surgical lung biopsies in rheumatoid arthritis

Interstitial fibrotic or inflammatory disease
Usual interstitial pneumonia
Non-specific interstitial pneumonia
Bronchiolocentric fibrosis
Organizing pneumonia
Diffuse alveolar damage
Rheumatoid nodules
Other (lymphoid interstitial pneumonia, desquamative interstitial pneumonia)
Airway disease
Follicular bronchiolitis
Cellular bronchiolitis
Obliterative bronchiolitis
Pleural disease
Pleural effusion
Pleuritis
Vascular disease
Pulmonary angiitis
Pulmonary hypertension
Drug reaction
Antirheumatic agents: Cellular interstitial pneumonia, diffuse alveolar damage
Biologics: Infections, diffuse alveolar damage, organizing pneumonia
NSAIDs: Eosinophilic pneumonia
Infection
Bacterial pneumonia
Fungal pneumonia (including *Pneumocystis*)
Mycobacterial pneumonia
Other

resemble those in both drug reactions and infections. This chapter will explore the more frequent patterns of disease encountered in rheumatoid arthritis, including drug reactions and infectious disease (Table 7.1).

Patterns of Interstitial Inflammation and Fibrosis

The patterns of interstitial fibrosis and inflammation are categorized using the classifications of the American Thoracic Society and European Respiratory Society [4, 5]. This system divides different histopathologic patterns based on quality and distribution of inflammation and fibrosis. Histologic differentiation of rheumatoid arthritis-interstitial lung disease from idiopathic disease is supported by the presence of additional findings including lymphoid hyperplasia,

pleuritis, angiitis, and a paucity of fibroblast foci, as described in the section below on histologic features of rheumatoid arthritis.

Usual Interstitial Pneumonia

Usual interstitial pneumonia (UIP) is the most common pattern encountered in pathologic examination of lungs in rheumatoid arthritis [6–10]. This pattern is characterized by interstitial fibrosis with both spatial and temporal heterogeneity (Fig. 7.1). Spatial heterogeneity is identified by more severe fibrosis occurring in a peripheral and basilar distribution. In these cases, the disease shows accentuation of fibrosis in the subpleural and paraseptal regions and is more advanced at the inferior portions of the lobes of the lung. Temporal heterogeneity is manifested as fibrosis of differing apparent ages occurring within the pulmonary tissue, often within a single lobule. The subpleural tissue shows advanced fibrosis with microscopic honeycombing, characterized by irregular airspaces lined by bronchiolar epithelium and surrounded by dense scarring. The alveoli in the central lung surrounding the bronchovascular bundle show thin normal-appearing septa. At the interface between the fibrotic and less involved portions of the lobule, one often observes fibroblast foci. These foci are characterized by a proliferation of fibroblasts within a myxoid stroma, arranged roughly parallel to the airspace surface, often with a reactive-appearing cuboidal epithelial cap.

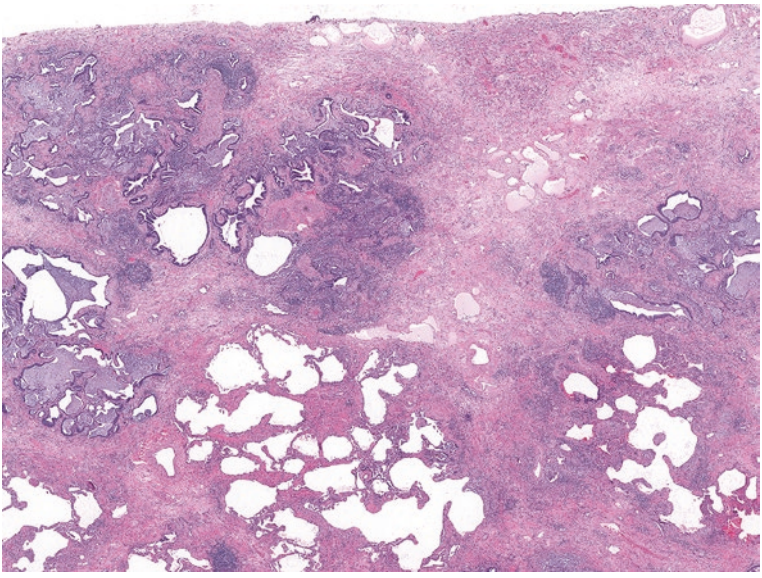

Fig. 7.1 Usual interstitial pneumonia. Low magnification view shows subpleural fibrosis with microscopic honeycombing (*top*) which transitions into less fibrotic alveolar septa (*mid-lower*)

Non-Specific Interstitial Pneumonia

Non-specific interstitial pneumonia (NSIP) is frequently observed in lung biopsies of patients with rheumatoid arthritis and is the most common pattern observed in some series [11]. Non-specific interstitial pneumonia is characterized by diffuse alveolar septal thickening within the pulmonary lobule (Fig. 7.2). While some cases may show nearly perfect uniformity, a more important criterion is that there are similar degrees of inflammation or fibrosis in the subpleural, peribronchiolar, and intermediate portions of the lobule, without significant architectural destruction.

Bronchiolocentric Fibrosis

Bronchiolocentric fibrosis, or bronchiolocentric interstitial pneumonia, is occasionally observed as a primary pattern in RA patients but is also commonly observed as a secondary pattern [6, 11]. It is characterized by fibrous thickening of the alveolar septa adjacent to the terminal bronchioles and alveolar ducts (Fig. 7.3). This fibrosis normally does not cause architectural distortion. The thickened alveolar septa often show peribronchiolar metaplasia, where the bronchiolar epithelium extends onto the alveolar surface, replacing the normal type 1 pneumocytes [12].

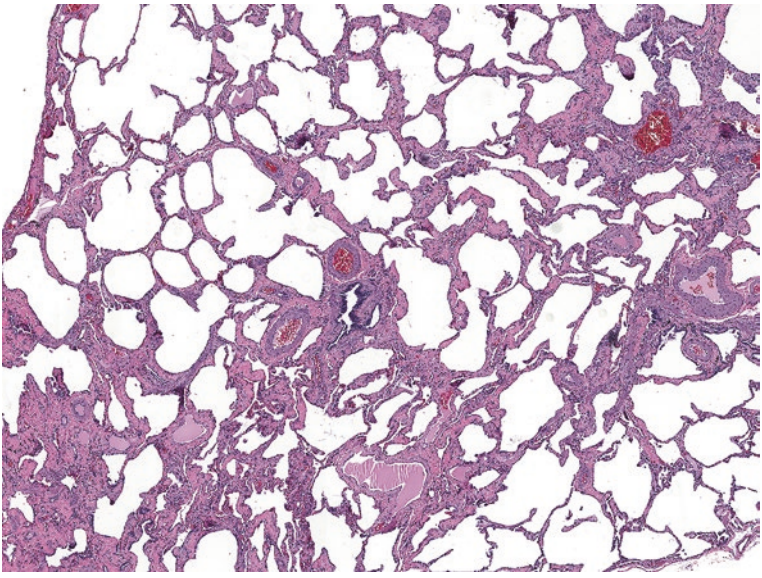

Fig. 7.2 Non-specific interstitial pneumonia. Low magnification view shows uniform alveolar septal thickening by fibrosis

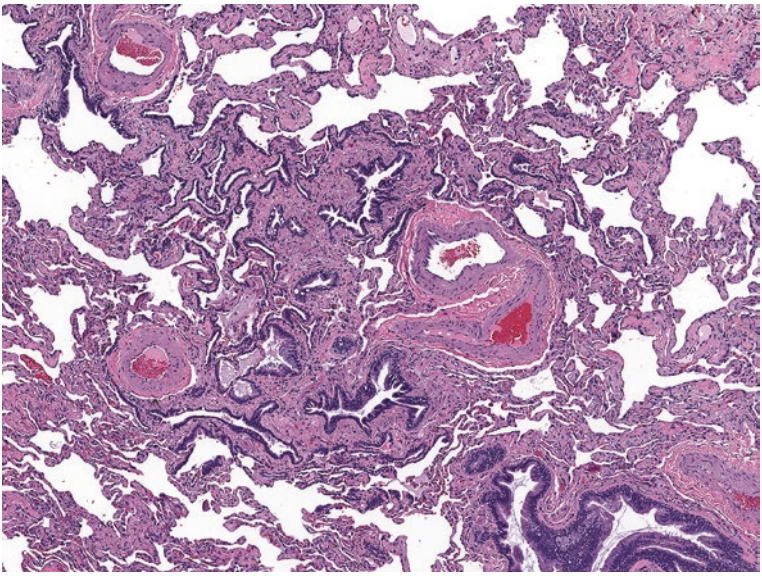

Fig. 7.3 Bronchiolocentric fibrosis. Low magnification view shows fibrosis of the peribronchiolar alveolar septa with bronchiolar-type epithelial metaplasia lining the thickened walls

Organizing Pneumonia

Organizing pneumonia (OP) is traditionally classified as an interstitial disease; however, it is characterized by alveolar filling rather than interstitial fibrosis or inflammation. Organizing pneumonia is occasionally observed as a primary pattern in RA patients but is very common as a secondary or associated finding [6, 8, 9, 11]. The airspaces in organizing pneumonia show consolidation by polypoid-rounded branching plugs of granulation tissue (Fig. 7.4). These cases will often show airspace accumulation of macrophages with foamy cytoplasm.

Rheumatoid Nodule

Pulmonary rheumatoid nodules are an uncommon finding in rheumatoid arthritis. They are frequently asymptomatic but may present with pleural effusions. These lesions are more common in men and smokers, and are often accompanied by similar cutaneous rheumatoid nodules [13, 14]. They are frequently located in the periphery of the lung, often straddling the pleural parenchymal or interlobular interface. Rheumatoid nodules have a stereotypical histologic appearance with central fibrinoid necrosis, surrounding by a palisading layer of epithelioid histiocytes, with an outer layer of chronic inflammation composed of lymphocytes and plasma cells with occasional hyperchromatic multinucleate histiocytes (Fig. 7.5).

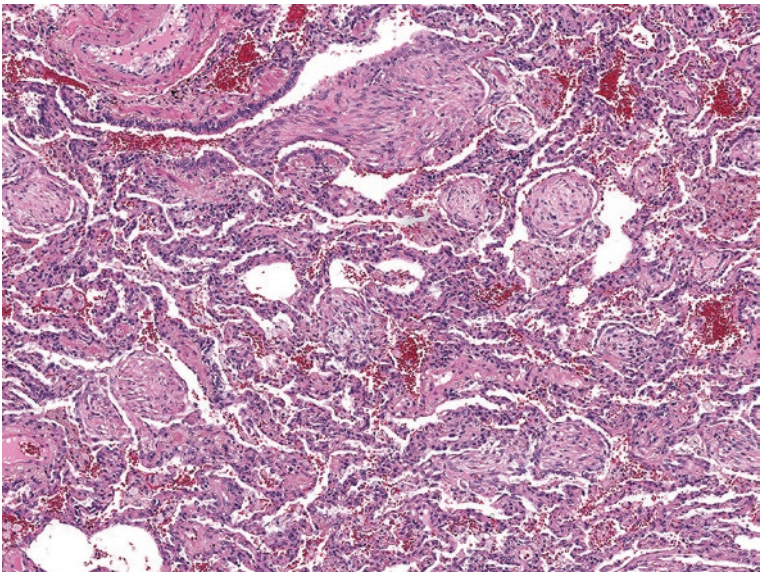

Fig. 7.4 Organizing pneumonia. Low magnification view shows alveolar spaces with patchy consolidation by rounded elongate plugs of granulation tissue-like fibrosis

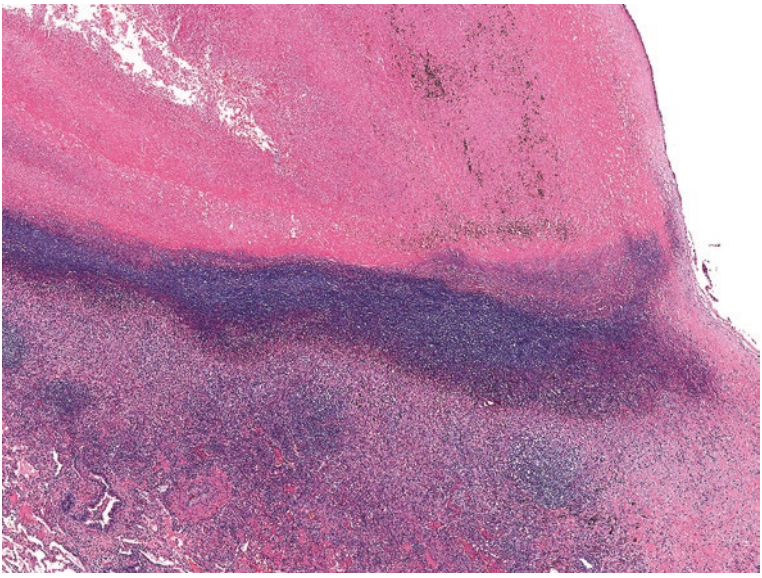

Fig. 7.5 Rheumatoid nodule. Low magnification view shows a large pleural-based nodule. There is eosinophilic acellular necrosis (*top*) and basophilic necrosis with adjacent palisading histiocytes (*bottom*). A small amount of the normal lung is present (*lower left*)

Diffuse Alveolar Damage

Diffuse alveolar damage is the pathologic appearance of severe acute lung injury. DAD is an uncommon manifestation of rheumatoid arthritis [6, 9]. It is characterized by alveolar septal thickening by edema, sparse inflammation, and the formation of hyaline membranes in close apposition to the alveolar walls. The alveolar spaces show filling by edematous proteinaceous fluid. The term diffuse in these cases refers to diffuse involvement of the alveolar unit with both the endothelial alveolar capillary as well as the epithelial pneumocyte damage.

Other Less Common Patterns of Inflammation or Fibrosis

Desquamative interstitial pneumonia is characterized by accumulation of macrophages within the alveolar spaces. This pattern of inflammation is most commonly associated with smoking but has been described in some case reports in rheumatoid arthritis [15].

Lymphoid interstitial pneumonia is characterized by lymphoid hyperplasia that expands the alveolar interstitium. This pattern is more commonly limited to the peribronchiolar tissues in rheumatoid arthritis and is classified as follicular bronchiolitis. Although LIP is an uncommon primary pattern of disease in rheumatoid arthritis, the finding of scattered lymphoid follicles in other patterns of RA-ILD (e.g., UIP or NSIP) is relatively common [6, 11, 16, 17].

Airway Disease

Follicular Bronchiolitis

Follicular bronchiolitis is a chronic inflammatory disease characterized by the presence of lymphoid nodules, often with germinal center formation, surrounding bronchioles (Fig. 7.6). When the inflammatory infiltrate is less marked, the term cellular interstitial pneumonia or lymphoid hyperplasia may be used, and if the inflammation extends prominently into the interstitium, the term lymphoid interstitial pneumonia may be used. Follicular bronchiolitis is a common secondary pattern in rheumatoid arthritis and is often observed in association with varying degrees of interstitial fibrosis and inflammation [6, 18].

Obliterative Bronchiolitis

Obliterative bronchiolitis (OB) is a scarring disease of the small airways that results in concentric narrowing of the bronchiolar lumen by fibrosis (Fig. 7.7). The terms constrictive bronchiolitis or cicatrical bronchiolitis are synonymous. The disease is

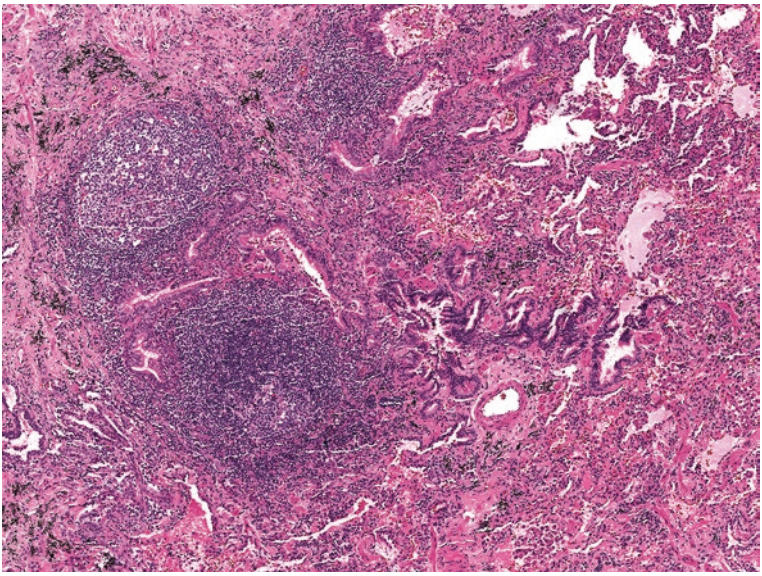

Fig. 7.6 Follicular bronchiolitis. Low magnification view shows lymphoid follicles with germinal centers that surround a bronchiole

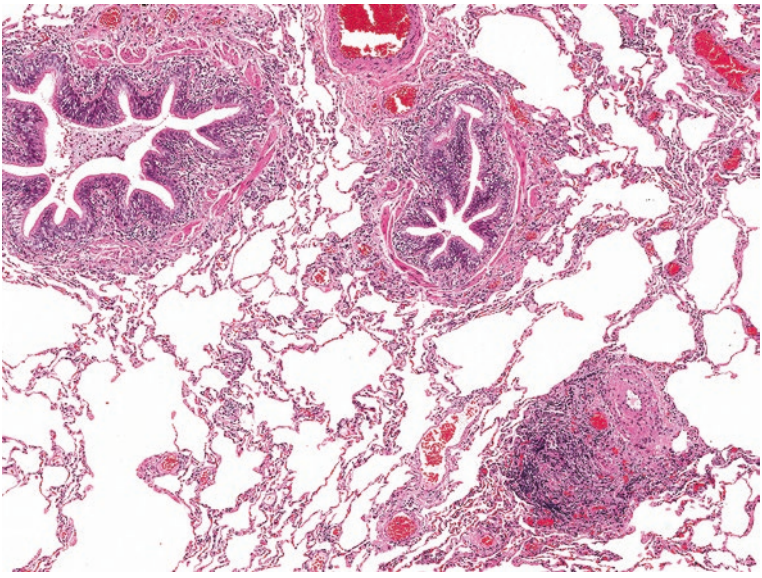

Fig. 7.7 Obliterative bronchiolitis. Low magnification view shows two bronchioles (*upper left*) with subepithelial chronic inflammation and fibrosis and a bronchiole with fibrous obliteration (*lower right*, identified by its proximity to a paired pulmonary artery)

commonly accompanied by accumulation of foamy macrophages in the airway and airspaces both proximal to and distal to the region of stenosis, occasionally with cholesterol granuloma formation. In chronic cases, proximal bronchiolectasis and bronchiectasis may occur. The length of stenosis is short in comparison with the length of the uninvolved airway; therefore, multiple sections of the tissue blocks and elastic tissue stains may be required for recognition of OB. Obliterative bronchiolitis is an uncommon finding in rheumatoid arthritis [19]. It has also been observed in some patients undergoing treatment with penicillamine [20].

Pleural Disease

Symptomatic pleural disease occurs in approximately 2–3% of patients in patients with rheumatoid arthritis [21]. Pleural effusion may precede joint disease and be the presenting finding in rheumatoid arthritis. It is important to highlight that it is essential to exclude infectious or malignant causes for pleural effusions in patients with rheumatoid arthritis. A rheumatoid effusion is exudative, and cytologic evaluation of the pleural fluid often shows findings that parallel those in rheumatoid nodules, including elongate histiocytes, multinucleate histiocytes, and granular debris. The pleura tends to undergo fibrosis in patients with chronic effusions. The presence of a visceral acute or chronic pleuritis can be a histologic clue in surgical lung biopsies and can help distinguish idiopathic interstitial pneumonia from rheumatoid arthritis-associated interstitial lung disease [22]. Rare drug reactions (e.g., sulfasalazine or TNF inhibitors) may result in a lupus-like syndrome with a pleuritis [23, 24].

Vascular Disease

It is relatively common to see myointimal thickening of the pulmonary arteries in cases with advanced pulmonary fibrosis or smoking-related changes. These changes are frequently observed in pulmonary hypertension but are not pathognomonic and may be seen in patients with normal pulmonary arterial pressures.

Inflammatory changes of pulmonary vessels may be observed as a secondary pattern of lung injury. Angiitis was identified in 12.5% of the surgical biopsies obtained in the series from Yousem et al. In their cases, the pulmonary arteries and veins showed mural widening by chronic lymphocytic inflammation without fibrinoid necrosis [6].

Diffuse alveolar hemorrhage is rarely observed in rheumatoid arthritis. This disorder is manifested by the consolidation and expansion of alveolar spaces by red blood cells and hemosiderin-filled macrophages. In their series of 34 cases of diffuse alveolar hemorrhage, Travis et al. had a single case of rheumatoid arthritis. This patient had focal alveolar capillaritis and angiitis [25]. There is some overlap in these cases with polyangiitis with granulomatosis, so serologic and clinical evaluation is suggested to differentiate between these two disorders [26].

Histologic Findings in Rheumatoid Arthritis

The classical patterns of pulmonary interstitial, airway, pleural, and vascular disease often occur in pure forms when they are idiopathic. One of the difficulties in trying to classify rheumatoid arthritis and other connective tissue diseases into these specific categories is that they often show overlapping histologies with secondary patterns of disease or involvement of multiple pulmonary compartments (alveolar spaces, alveolar interstitium, small airways, vessels, and pleura). This was first highlighted in the series from Yousem et al. that showed that classical patterns of UIP, OP, and rheumatoid nodules were often accompanied by less common secondary patterns including tissue eosinophilia and angiitis [6]. This observation was supported by the series from Tansey et al. that showed frequent involvement of both interstitial and airway compartments of the lung [11]. In their series of connective tissue disease patients, Cipriani et al. showed that RA patients with a UIP pattern inevitably also showed foci with NSIP pattern fibrosis [17]. That is, the regions of temporal heterogeneity in UIP that are normal-appearing in idiopathic pulmonary fibrosis showed uniform alveolar septal thickening in cases with RA-ILD. Several series have demonstrated that UIP and NSIP patterns in RA differ from their idiopathic counterparts by increased numbers and size of lymphoid aggregates (Fig. 7.8). These rounded lymphoid nodules often form secondary follicles with germinal centers. In some studies, the cases of rheumatoid arthritis with a UIP pattern also differ from idiopathic pulmonary fibrosis by having fewer fibroblast foci [17].

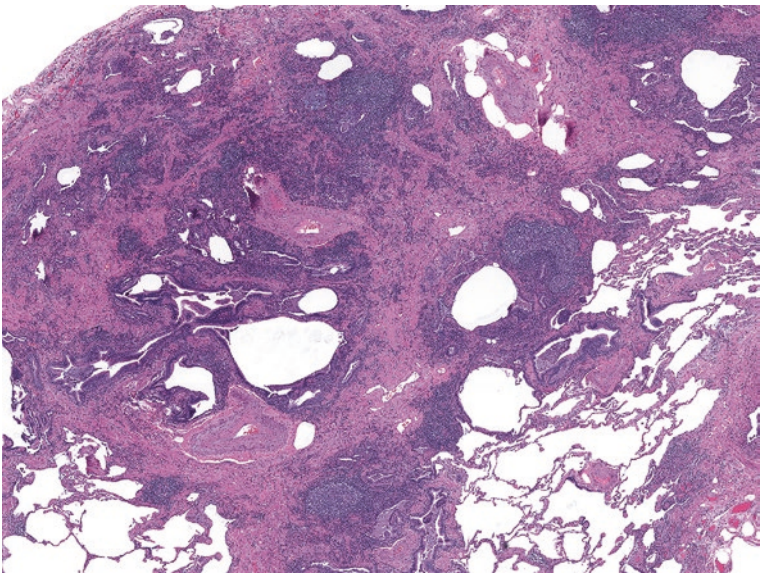

Fig. 7.8 Usual interstitial pneumonia with lymphoid hyperplasia. Low magnification view showing marked interstitial fibrosis with microscopic honeycombing (*upper left*) and the nearly normal lung (*lower right*). There are several lymphoid aggregates around bronchioles consistent with follicular bronchiolitis

Drug Reaction

Nearly any pattern of lung injury can be elicited secondary to a drug reaction, and it might seem that differentiation from the various patterns observed in rheumatoid arthritis would be difficult. However, in practice, the most common patterns of drug reactions include eosinophilic pneumonia, pulmonary edema, and diffuse alveolar damage (Table 7.2). These are unusual manifestations of rheumatoid

Table 7.2 Common drugs used in the treatment of RA and their most typical reactions

Class or name of drug	Pathologic reaction
Disease-modifying antirheumatic drugs	
Methotrexate	CIP with granulomas Diffuse alveolar damage Infection (esp. *Pneumocystis*) Lymphomatoid granulomatosis
Hydroxychloroquine	Eosinophilia (rare)
Leflunomide	Exacerbation of existing ILD Diffuse alveolar damage (rare)
Sulfasalazine	Eosinophilic pneumonia Lupus-like syndrome
Biologics	
Tumor necrosis factor inhibitor Etanercept Adalimumab Infliximab Certolizumab Golimumab	Infection: Tuberculosis, non-tuberculous mycobacteria, fungi Lupus-like syndrome
Interleukin-6 receptor antibody Tocilizumab	Infection Organizing pneumonia (rare) Sarcoidosis (rare)
T-cell immunomodulator (CD80/CD86 antagonist) Abatacept	Diffuse alveolar damage (rare)
CD20 antagonist Rituximab	Infection (especially *Pneumocystis*) Diffuse alveolar damage Organizing pneumonia
NSAIDs	
Celecoxib Naproxen Diclofenac Meloxicam	Eosinophilic pneumonia Pulmonary edema
Aspirin	Asthma Eosinophilic pneumonia Diffuse alveolar damage Pulmonary edema
Ibuprofen	Eosinophilc pneumonia (rare)
Others	
Opiates Hydrocodone	Aspiration pneumonia
Acetaminophen	Eosinophilia (rare)
Corticosteroids	Infection (especially *Pneumocystis*, fungi)

arthritis-interstitial lung disease. Some pathologist's advocate treating drug reactions in RA as a diagnosis of exclusion [22]. This sensible approach is based on the relatively low incidence of drug reactions compared to RA-related complications and infections and the aforementioned lack of significant overlap between the most common patterns of drug-related and RA-related lung disease.

Methotrexate toxicity is one of the more common drug reactions observed in RA, with an incidence of approximately 2 cases per 192 patient-years [27, 28]. The most common manifestation is as a cellular interstitial pneumonia with alveolar septal thickening by lymphocytes and small non-necrotizing granulomas (Fig. 7.9) [29]. This pattern most closely resembles chronic hypersensitivity pneumonia (extrinsic allergic alveolitis). Discontinuation of the drug may be suggested if the histological changes are consistent with the diagnosis and other clinical and radiological data support a drug reaction. While less common, methotrexate has also been shown to cause acute respiratory distress syndrome [30] and the EBV-related B-cell lymphoproliferative disorder lymphomatoid granulomatosis [31–33].

Nonsteroidal anti-inflammatory drugs most commonly present with an allergic-type reaction, showing either eosinophilic pneumonia, tissue eosinophilia, or pulmonary edema. While tissue eosinophilia is occasionally observed as secondary pattern in rheumatoid arthritis, the presence of numerous eosinophils filling alveolar spaces in a biopsy should suggest either a drug reaction, a reaction to cigarette smoking, or an infection.

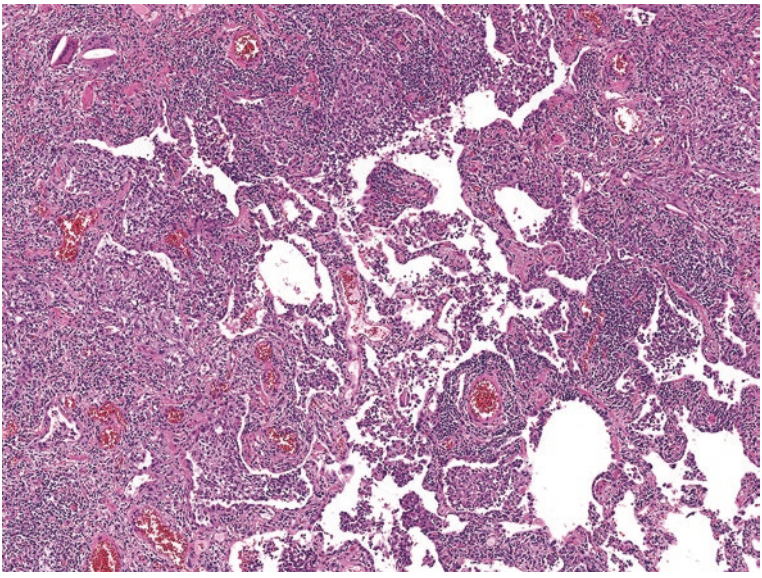

Fig. 7.9 Methotrexate toxicity. There is diffuse alveolar septal thickening by lymphocytic interstitial inflammation. A poorly formed granuloma is present (*upper left*) composed of two multinucleate histiocytes with cytoplasmic cholesterol clefts

The biologic agents, by virtue of their interactions with normal inflammatory reactions, increase susceptibility to infection. These agents include inhibitors of tumor necrosis factor-α (TNF-α), B-cell CD20-binding agents, T-cell inhibitors, and IL-6 receptor inhibitors [34]. Other reactions observed in patients treated with biologic agents include sarcoidosis-like reactions [35–37], acute lung injury [38], and lupus-like syndrome [24].

Infection in Rheumatoid Arthritis

Patients with rheumatoid arthritis have an increased risk of infection even in the absence of immunomodulatory therapy. Corticosteroids, some disease-modifying antirheumatic drugs, and the biologics have been shown to predispose rheumatoid arthritis patients to serious infection [39, 40]. The most common culprits are *Pneumocystis jirovecii*; other fungi, including *Aspergillus* species, *Cryptococcus*, and the zygomycetes; tuberculosis; non-tuberculous mycobacteria; and bacteria [39–45]. The histologic patterns observed in infectious pneumonias are multiple and varied. Acute bronchopneumonia is most commonly observed in bacterial infection and shows increased neutrophils filling alveolar spaces and small airways (Fig. 7.10). Nodular regions of necrosis or fibrin-rich debris are frequently observed in fungal infections and Nocardia infection (Fig. 7.11). Necrotizing granulomas are often observed in fungal infections and tuberculosis and are characterized by

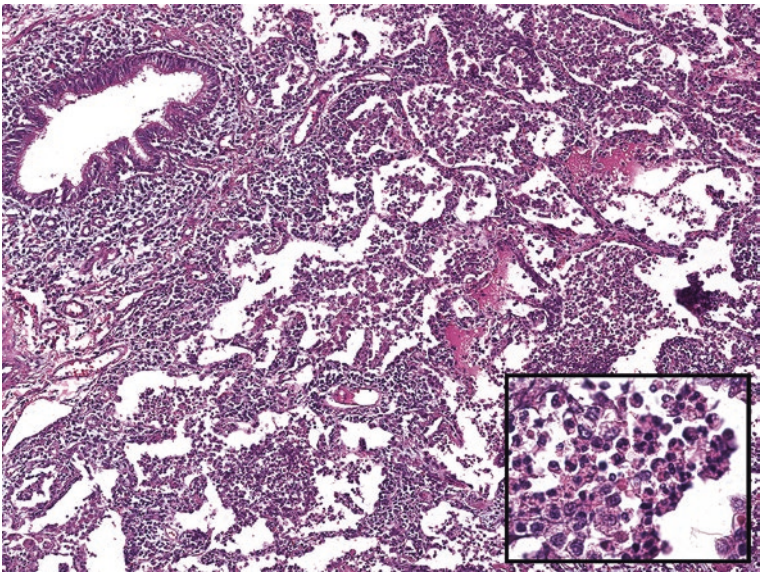

Fig. 7.10 Acute bronchopneumonia. Low magnification view shows alveolar filling with neutrophils and fibrin (inset shows high magnification of alveolar space)

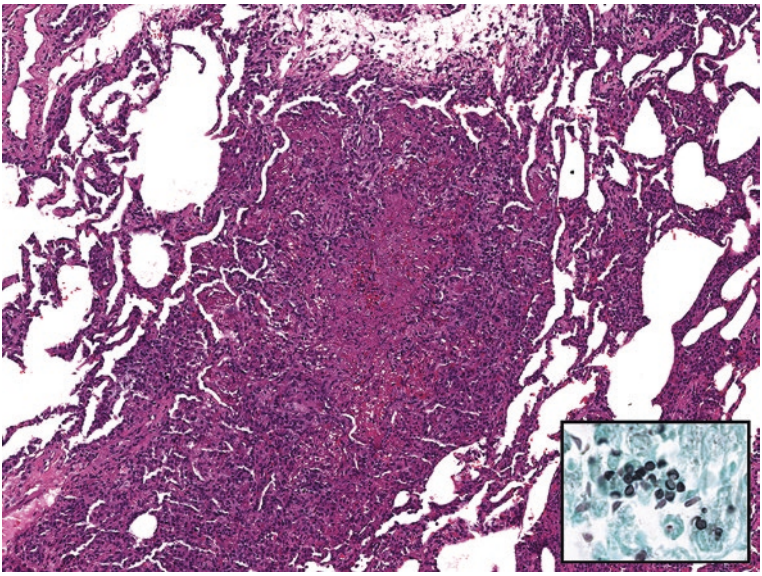

Fig. 7.11 *Pneumocystis* pneumonia. Low magnification view shows a nodular region of fibrin-rich necrosis with surrounding mixed lymphohistiocytic inflammation. High magnification (inset, GMS stain) shows typical irregular spherical structures of *Pneumocystis*

rounded regions of necrosis, surrounded by epithelioid histiocytes with multinucleate giant cells and chronic inflammation. There are often smaller satellite sarcoidal non-necrotizing granulomas surrounding the larger dominant granuloma. These necrotizing granulomas should be evaluated with histochemical stains or immunohistochemical stains for fungi (Grocott methenamine silver (GMS)) and acid-fast bacilli (Fite, Kinyoun, or other). Both neutrophilic acute bronchopneumonia and necrotizing granulomatous pneumonia are rarely observed as a pattern of lung injury in rheumatoid arthritis, and, when present, should trigger a search for an infectious cause. Aspiration pneumonia may also show similar findings and should be considered if foreign material is observed histologically or if the patient is on opiates [46].

Conclusion

Rheumatoid arthritis can show a wide spectrum of pathologic changes, most commonly manifesting as interstitial fibrosis and inflammation. While classification of these changes is classically attempted using the same criteria as for idiopathic interstitial pneumonias, rheumatoid arthritis often fails to fit neatly into a pathologic pigeonhole but rather shows multiple overlapping patterns. In fact, it is this involvement of multiple compartments of the lung that is frequently used as a clue that a

patient has connective tissue disease. Common patterns of drug toxicity often do not show significant overlap with rheumatoid arthritis, and infections will often manifest as acute or granulomatous diseases, making separation from the patient's primary disease possible.

References

1. Ellman P, Ball RE. Rheumatoid disease with joint and pulmonary manifestations. Br Med J. 1948;2(4583):816–20.
2. Hart FD. Rheumatoid arthritis: extra-articular manifestations. Br Med J. 1969;3(5663):131–6.
3. Bongartz T, et al. Incidence and mortality of interstitial lung disease in rheumatoid arthritis: a population-based study. Arthritis Rheum. 2010;62(6):1583–91.
4. Travis WD, et al. An official American Thoracic Society/European Respiratory Society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med. 2013;188(6):733–48.
5. Sverzellati N, et al. American Thoracic Society-European Respiratory Society classification of the idiopathic interstitial pneumonias: advances in knowledge since 2002. Radiographics. 2015;35(7):1849–71.
6. Yousem SA, Colby TV, Carrington CB. Lung biopsy in rheumatoid arthritis. Am Rev Respir Dis. 1985;131(5):770–7.
7. Tanaka N, et al. Rheumatoid arthritis-related lung diseases: CT findings. Radiology. 2004;232(1):81–91.
8. Lee HK, et al. Histopathologic pattern and clinical features of rheumatoid arthritis-associated interstitial lung disease. Chest. 2005;127(6):2019–27.
9. Yoshinouchi T, et al. Nonspecific interstitial pneumonia pattern as pulmonary involvement of rheumatoid arthritis. Rheumatol Int. 2005;26(2):121–5.
10. Assayag D, et al. Rheumatoid arthritis-associated interstitial lung disease: radiologic identification of usual interstitial pneumonia pattern. Radiology. 2014;270(2):583–8.
11. Tansey D, et al. Variations in histological patterns of interstitial pneumonia between connective tissue disorders and their relationship to prognosis. Histopathology. 2004;44(6):585–96.
12. Fukuoka J, et al. Peribronchiolar metaplasia: a common histologic lesion in diffuse lung disease and a rare cause of interstitial lung disease: clinicopathologic features of 15 cases. Am J Surg Pathol. 2005;29(7):948–54.
13. Kitamura A, et al. Rheumatoid arthritis with diffuse pulmonary rheumatoid nodules. Pathol Int. 2004;54(10):798–802.
14. Tilstra JS, Lienesch DW. Rheumatoid nodules. Dermatol Clin. 2015;33(3):361–71.
15. Ishii H, et al. Desquamative interstitial pneumonia (DIP) in a patient with rheumatoid arthritis: is DIP associated with autoimmune disorders? Intern Med. 2009;48(10):827–30.
16. Cha SI, et al. Lymphoid interstitial pneumonia: clinical features, associations and prognosis. Eur Respir J. 2006;28(2):364–9.
17. Cipriani NA, et al. Pathologic quantification of connective tissue disease-associated versus idiopathic usual interstitial pneumonia. Arch Pathol Lab Med. 2012;136(10):1253–8.
18. Howling SJ, et al. Follicular bronchiolitis: thin-section CT and histologic findings. Radiology. 1999;212(3):637–42.
19. Schlesinger C, et al. Constrictive (obliterative) bronchiolitis: diagnosis, etiology, and a critical review of the literature. Ann Diagn Pathol. 1998;2(5):321–34.
20. Schlesinger C, Veeraraghavan S, Koss MN. Constrictive (obliterative) bronchiolitis. Curr Opin Pulm Med. 1998;4(5):288–93.
21. Chou CW, Chang SC. Pleuritis as a presenting manifestation of rheumatoid arthritis: diagnostic clues in pleural fluid cytology. Am J Med Sci. 2002;323(3):158–61.

22. Schneider F, et al. Pleuropulmonary pathology in patients with rheumatic disease. Arch Pathol Lab Med. 2012;136(10):1242–52.
23. Caulier M, et al. Sulfasalazine induced lupus in rheumatoid arthritis. J Rheumatol. 1994;21(4):750–1.
24. De Bandt M, et al. Systemic lupus erythematosus induced by anti-tumour necrosis factor alpha therapy: a French national survey. Arthritis Res Ther. 2005;7(3):R545–51.
25. Travis WD, et al. A clinicopathologic study of 34 cases of diffuse pulmonary hemorrhage with lung biopsy confirmation. Am J Surg Pathol. 1990;14(12):1112–25.
26. Torralbo A, et al. Alveolar hemorrhage associated with antineutrophil cytoplasmic antibodies in rheumatoid arthritis. Chest. 1994;105(5):1590–2.
27. Alarcon GS, et al. Risk factors for methotrexate-induced lung injury in patients with rheumatoid arthritis. A multicenter, case-control study. Methotrexate-Lung Study Group. Ann Intern Med. 1997;127(5):356–64.
28. Sathi N, et al. How common is methotrexate pneumonitis? A large prospective study investigates. Clin Rheumatol. 2012;31(1):79–83.
29. Imokawa S, et al. Methotrexate pneumonitis: review of the literature and histopathological findings in nine patients. Eur Respir J. 2000;15(2):373–81.
30. Hargreaves MR, Mowat AG, Benson MK. Acute pneumonitis associated with low dose methotrexate treatment for rheumatoid arthritis: report of five cases and review of published reports. Thorax. 1992;47(8):628–33.
31. Kameda H, et al. Lymphomatoid granulomatosis and diffuse alveolar damage associated with methotrexate therapy in a patient with rheumatoid arthritis. Clin Rheumatol. 2007;26(9):1585–9.
32. Blanchart K, et al. Fatal pulmonary lymphomatoid granulomatosis in a patient taking methotrexate for rheumatoid arthritis. Minerva Anestesiol. 2014;80(1):119–20.
33. Oiwa H, et al. Grade 3 lymphomatoid granulomatosis in a patient receiving methotrexate therapy for rheumatoid arthritis. Intern Med. 2014;53(16):1873–5.
34. Keyser FD. Choice of biologic therapy for patients with rheumatoid arthritis: the infection perspective. Curr Rheumatol Rev. 2011;7(1):77–87.
35. Kudrin A, et al. Sarcoid-like granulomatous disease following etanercept treatment for RA. J Rheumatol. 2007;34(3):648–9.
36. Toussirot E, et al. Sarcoidosis occuring during anti-TNF-alpha treatment for inflammatory rheumatic diseases: report of two cases. Clin Exp Rheumatol. 2008;26(3):471–5.
37. Gifre L, et al. Lung sarcoidosis induced by TNF antagonists in rheumatoid arthritis: a case presentation and a literature review. Arch Bronconeumol. 2011;47(4):208–12.
38. Roubille C, Haraoui B. Interstitial lung diseases induced or exacerbated by DMARDS and biologic agents in rheumatoid arthritis: a systematic literature review. Semin Arthritis Rheum. 2014;43(5):613–26.
39. Patkar NM, et al. Association of infections and tuberculosis with antitumor necrosis factor alpha therapy. Curr Opin Rheumatol. 2008;20(3):320–6.
40. Furst DE. The risk of infections with biologic therapies for rheumatoid arthritis. Semin Arthritis Rheum. 2010;39(5):327–46.
41. O'Reilly S, et al. Invasive pulmonary aspergillosis associated with low dose methotrexate therapy for rheumatoid arthritis: a case report of treatment with itraconazole. Tuber Lung Dis. 1994;75(2):153–5.
42. Ohosone Y, et al. Clinical characteristics of patients with rheumatoid arthritis and methotrexate induced pneumonitis. J Rheumatol. 1997;24(12):2299–303.
43. Mayordomo L, et al. Pulmonary miliary tuberculosis in a patient with anti-TNF-alpha treatment. Scand J Rheumatol. 2002;31(1):44–5.
44. Woyciechowsky TG, et al. Paracoccidioidomycosis induced by immunosuppressive drugs in a patient with rheumatoid arthritis and bone sarcoma: case report and review of the literature. Mycopathologia. 2011;172(1):77–81.
45. Liao TL, et al. Risk factors and outcomes of nontuberculous mycobacterial disease among rheumatoid arthritis patients: a case-control study in a TB endemic area. Sci Rep. 2016;6:29443.
46. Dublin S, et al. Use of opioids or benzodiazepines and risk of pneumonia in older adults: a population-based case-control study. J Am Geriatr Soc. 2011;59(10):1899–907.