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Lung Disease in Rheumatoid Arthritis

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Preface

Rheumatoid arthritis (RA) affects ~1% of the adult population, and although characterized by symmetric polyarthritis, a variety of extra-articular manifestations are also associated with the disease. In particular, there is a growing appreciation that lung disease is common in patients with RA, and every compartment of the lungs is potentially at risk. Despite the remarkable advances over the past decades in managing the articular aspects of the disease, RA-associated lung disease continues to be associated with significant morbidity and is a leading cause of mortality in patients with RA. Although some risk factors have been identified (such as smoking), we still have major gaps in our understanding of why some RA patients are more likely to develop lung disease, and there is much to learn about the natural history and treatment of lung involvement in these patients.

The clinical care and research of lung disease in RA is of particular interest to practitioners in primary care, rheumatology, pulmonary medicine, radiology, and pathology. However, this topic is often approached from one specialty alone—rather than in an interdisciplinary, synergistic model. This textbook on *Lung Disease in Rheumatoid Arthritis* aims to serve as a unique resource for clinicians. It is a comprehensive, interdisciplinary compilation that encompasses the spectrum of lung disease encountered in patients with RA. This textbook aims to provide a single, practical, and clinically oriented resource for this complex disease state with hopes of optimizing approaches to the evaluation and management of RA-associated lung disease. This compilation also goes beyond the bedside to provide insights into disease etiology and pathogenesis, highlight areas of uncertainty, and lay the groundwork for future research and discovery.

This textbook begins with a thorough overview of the clinical aspects of RA followed by state-of-the-art reviews of the current understanding of pathophysiology and etiopathogenesis of the disease. Within these sections, the hypothesis that the lungs may be central to the development of RA is explored. The next two chapters focus on what is known about the epidemiology of lung disease in RA, followed by a review of risk factors and biomarkers associated with this complex disease state. A practical overview of the radiologist's approach to lung disease in RA patients is followed by a comprehensive review of the pulmonary histopathologic patterns

identified in these cohorts. The subsequent chapters provide practical approaches to the comprehensive evaluation and management of interstitial lung disease (ILD) in RA, followed by a final chapter that reviews the non-ILD pulmonary manifestations associated with RA.

We recognize the outstanding combined efforts of the authors of this textbook on "*Lung Disease in Rheumatoid Arthritis*" and hope this volume serves to further your understanding of the complex intersection of lung disease in RA and proves to be a useful resource that enhances your care and research of these patients.

Aurora, CO — Joyce S. Lee
Aurora, CO — Aryeh Fischer

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Chapter 1
Clinical Overview of Rheumatoid Arthritis

Sterling West

Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory disease characteristically manifested by a persistent symmetric polyarthritis involving the small joints of the hands, wrists, and feet [1]. The primary site of pathology is the synovium of diarthrodial joints. Most but not all patients have rheumatoid factor (RF) and/or anti-citrullinated protein antibodies (ACPAs) in their serum. Extra-articular manifestations may occur and most commonly involve the skin, lungs, heart, eye, and hematologic system. If untreated joint destruction with deformity and significant organ dysfunction leading to disability and death can occur. The etiology is unknown, but an environmental exposure inciting an autoimmune response in a genetically predisposed individual has been proposed. Over the past 20 years, there have been several major advancements in the diagnosis and management of this disease.

Etiology

The cause of RA is unknown but is thought to result from an intricate interplay between genetics and environment [2, 3]. Notably, autoantibodies (RF, ACPAs) can be found in a patient's sera years before the development of clinical symptoms. This suggests that initiating events trigger a complex interaction between the innate and adaptive immune systems which breaks tolerance and leads to autoreactivity. Over time and with exposure to perpetuating factors, a critical immune threshold is breached resulting in inflammation, clinical symptoms, and tissue damage.

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Genetic Factors

Twin studies show that genetic factors account for 60% of an individual's susceptibility to rheumatoid arthritis. There are now over 100 genetic loci that have been associated with RA. The major histocompatibility complex (MHC) on chromosome 6 that contains the human leukocyte antigen (HLA) class II region encoding certain HLA-DRB1 molecules is the most important and accounts for 30–40% of this genetic risk. The susceptibility to RA is mainly associated with the third hypervariable region of the DRβ chain from amino acids 70–74 (QKRAA, QRRAA, or RRRAA). This susceptibility/shared epitope (SE) is found on HLA-DRB1 alleles *0401,*0404, and *0101 in individuals of European ancestry and *0405 in individuals of Asian ancestry and is associated with a threefold to fivefold increased risk of developing ACPA+ RA. Less common HLA-DRB1 alleles containing the SE and associated with RA are *0102, *0104, *0408, *0901, *1001, and *1402. Single amino acids at positions 9, 11, and 13 which lie outside the classical SE region of DRB1 chain but within the peptide-binding groove also contribute to RA susceptibility. However, the association of the SE with RA susceptibility is not as strong in all ethnic groups (e.g., African-Americans, Hispanic-Americans) or in seronegative RA patients. Outside the MHC, PTPN22 that encodes for lymphoid tyrosine phosphatase which is a regulator of signal transduction from the T cell receptor has the largest genetic association (OR 1.6). Genome-wide association studies (GWAS) have identified multiple other non-MHC gene loci (CTLA-4, STAT4, TRAF1/C5, PADI4, others) each conferring a small risk (OR 1.2–1.4) for developing RA, and these can differ among ethnicities. Epigenetic factors (e.g., histone modification, DNA methylation) are also likely to be important.

Environmental Factors

Several environmental risk factors have been implicated in the development of RA. Smoking is the strongest factor conferring a 1.8-fold risk (>20 pack-years) for developing seropositive (RF+, ACPA+) RA. The individual risk increases with intensity (packs/day) and duration. The risk persists for 10–20 years after a person quits but does decrease during that time. Bacteria in the mouth, lungs, and gut may also be contributory. Smoking can alter microbiomes in the mouth and lung, whereas diet and antibiotics can alter gut flora. *Porphyromonas gingivalis* in patients with chronic periodontitis can express peptidylarginine deiminase (PAD) enzymes that can citrullinate proteins through the posttranslational modification of arginine to citrulline. *Aggregatibacter actinomycetemcomitans* is another candidate bacterium that can induce protein hypercitrullination. A similar process occurs with upregulation of myeloperoxidase that carbamylates proteins through modification of lysine to homocitrulline. Smoking is known to enhance the citrullination and carbamylation of proteins. Citrullinated and carbamylated proteins are neoantigens that cause a heightened immune response when presented to the immune system by

HLA-DR molecules containing the shared epitope. ACPAs and anticarbamylated protein antibodies generated during the immune response could potentially bind citrullinated and carbamylated proteins locally or form immune complexes that can deposit in tissues inciting an inflammatory response. Other environmental factors reported as RA risk factors include diet, coffee consumption, other infections (EBV, parvovirus, mycoplasma, others), low socioeconomic status, and exposure to urban and industrial environments have been proposed but not confirmed. Alcohol intake and use of HMG-CoA reductase inhibitors (statins) may decrease RA risk. It is unlikely that a single environmental factor is the only trigger for RA.

Host Factors

RA is more common in premenopausal females suggesting hormonal and reproductive factors may contribute to RA risk. Nulliparity, timing of pregnancy, lack of breastfeeding, obesity, and use of oral contraceptives have all been reported as risk factors but with varying and conflicting results.

Pathogenesis

The mechanism for the initiation of clinical synovitis is unknown. One hypothesis is that environmental factors influence the microbiome of a genetically predisposed host causing subsequent alterations in mucosal immunity. Immune complexes (ACPAs, RF) generated at these mucosal sites could circulate and deposit in synovial postcapillary venules inciting a vasculitis or tissue inflammation through complement activation [4]. Tissue inflammation can increase vascular permeability with the influx of more inflammatory cells. Inflammation can upregulate PAD enzymes and myeloperoxidase causing citrullination and carbamylation of synovial proteins and cartilage proteins. Inflammation can lead to cartilage damage with release of degraded collagen and proteoglycan neoepitopes. These modified proteins in the synovium and neoepitopes from cartilage can be taken up by an influx of dendritic cells into the synovium. These dendritic cells from an individual who is genetically predisposed to develop RA can present the neoantigens to T lymphocytes in both the synovial tissue and draining lymph nodes. Epitope spreading may occur with a break in tolerance and an immune response to native antigens. T cells (CD4+), macrophages, synovial fibroblasts, and B cells in the synovium are activated in different combinations to produce proinflammatory cytokines (TNFα, IL-1, IL-6, IL-8, others), chemokines, and inflammatory mediators that play a key role in the perpetuation of chronic synovitis, pannus formation, and tissue destruction. Neutrophils that traverse the synovium to enter the synovial fluid release degradative enzymes that contribute to cartilage damage, while local osteoclasts near sites of pannus formation are stimulated to cause bony erosions.

Epidemiology

Rheumatoid arthritis is the most common disease causing a chronic inflammatory polyarthritis. The estimated prevalence worldwide ranges between 0.4 and 1.1% of the adult population [1]. The prevalence varies geographically and among ethnicities (3–4% in certain Native American groups, rare in Afro-Caribbeans). In the United States, the prevalence of RA is 1.1%, increasing with age and peaking between ages 40 and 60 years old. Females are affected two to three times more than males. Twin studies show that the disease concordance is 12–20% in monozygotic twins and 2–4% in fraternal twins. First-degree relatives of individuals with RA are two to three times more likely to develop the disease.

Clinical Presentation: Early Arthritis and Periarthritis

The clinical hallmark of rheumatoid arthritis is a persistent symmetric polyarthritis involving the small joints of the hands, wrists, and feet [1]. The most common joints involved are the metacarpophalangeals (MCPs), proximal interphalangeals (PIPs), and metatarsophalangeals (MTPs). Larger joints (ankles, knees, elbows, shoulders) generally become symptomatic after the small joints. Temporomandibular, sternal, and cervical spine joints are less commonly involved (Table 1.1). The sacroiliac, thoracolumbar, and distal interphalangeal joints are spared.

The onset of systemic and articular symptoms is usually slow and insidious (70–85%). Patients typically report fatigue and arthritic symptoms of pain, swelling, warmth, and morning stiffness (>1 h), with the number of joints increasing over weeks to months. Up to 10% of patients can have an acute presentation characterized by the explosive onset of polyarthritis frequently associated with profound fatigue, low-grade fever, and weight loss. Another 1–5% of patients will present with transient self-limited painful episodes of mono- or oligo-arthritis (palindromic/episodic onset) lasting from one to several days before spontaneously resolving only to recur again after a variable asymptomatic period.

Table 1.1 Joint involvement in rheumatoid arthritis

MCP	90–95%	Ankle/subtalar	50–60%
PIP	75–90%	Cervical spine	40–50%
Wrist	75–80%	Elbow	40–50%
Knee	60–80%	Hip	20–40%
Shoulder	50–70%	TMJ	10–30%
MTP	50–60%		

MCP metacarpophalangeal joints, *PIP* proximal interphalangeal joints, *MTP* metatarsophalangeal joints, *TMJ* temporomandibular joints

Physical examination in early RA will show swelling, tenderness, mild warmth, and limitation of motion of the involved joints. Relative symmetry (bilateral) of joint involvement is most characteristic (85% of cases). Up to 25% of early RA patients initially present with only hand and wrist involvement. The PIP joints followed by the MCPs and wrists are the easiest joints to find early synovitis. Palpation of the swollen joints reveals a tender and spongy synovitis which must be separated from joint enlargement due to the hard bony hypertrophy from osteophytes. Extensor and flexor tenosynovitis of the digits and wrist as well as swelling of the extensor carpi ulnaris tendon sheath are commonly observed. Examination of the MTPs shows tenderness to metatarsal squeeze and individual joint palpation. A puffy forefoot, splaying of the toes, and difficulty fitting feet into shoes are also signs of synovitis. Up to 10–15% of early RA patients will develop MTP synovitis as the first manifestation of their disease before any hand/wrist involvement. Pain in the balls of their feet upon arising from bed is a common complaint.

Examination of the shoulder and hip in early RA may be difficult since these joints are deep and difficult to palpate. Patients will have limitation of motion and joint pain especially at night that interferes with sleep. Rotator cuff tendonitis and subacromial bursitis commonly occur in association with shoulder synovitis. Knee involvement in RA is frequent and associated with effusions. Posterior herniation of a large effusion can cause a popliteal (Baker's) cyst. This cyst can rupture into the calf causing pain, swelling, and edema mimicking a deep venous thrombosis. Elbow synovitis causes loss of full elbow extension. Synovitis can be palpated between the lateral epicondyle and olecranon. Some patients develop an olecranon bursitis. Ankle swelling may be due to tibiotalar and/or subtalar joint involvement. Tibiotalar synovitis restricts flexion and extension of the ankle, while subtalar disease diminishes inversion and eversion. Pain and swelling from tenosynovitis of the toe extensors and the peroneal and tibialis posterior tendons can also be seen.

The cervical spine, particularly the upper portion at C1–C2, is the only part of the spine involved in RA. This causes neck pain and restricted range of motion in all planes. The temporomandibular, sternoclavicular, and manubriosternal joints can be affected manifesting with pain, swelling, and tenderness. The thoracic spine, lumbosacral spine, sacroiliac, and finger distal interphalangeal (DIP) joints are not involved in RA. If these joints are involved, a diagnosis other than RA such as a spondyloarthropathy should be considered.

Clinical Manifestations: Late Articular and Periarticular Sequelae

Late manifestations of persistent synovitis that is inadequately treated leading to joint damage include joint deformity, decreased range of motion, malalignment, dislocation, and tendon ruptures [1]. This leads to loss of function and disability. Late joint sequelae in the hands include MCP joint subluxation, swan neck and

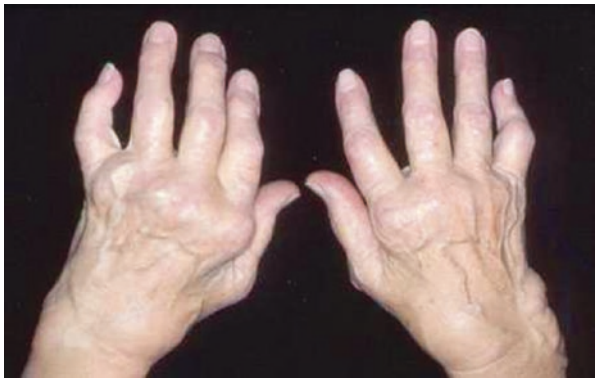

Fig. 1.1 Rheumatoid arthritis involving the hands and wrists

boutonniere deformities of the fingers, and Z-thumb deformity (Fig. 1.1). Wrist involvement causes radial drift of the carpal bones, volar subluxation of the carpus, and dorsal prominence of the ulnar styloid. As radial deviation of the carpus progresses, ulnar deviation of the phalanges worsens. Tendon rupture especially of the fourth and fifth extensor tendons of the fingers results from tenosynovitis and deformity of the dorsal wrist. MTP inflammation can cause the MTP joints to sublux causing the digital flexor tendons to become displaced leading to toe deformities including hallux valgus, bunion formation, fibular deviation of the toes, and claw toe deformities. Abnormal pressure points when walking results in calluses and at times ulcerations under the subluxed metatarsal heads or over the cocked-up toes.

Chronic shoulder synovitis and subacromial bursitis can lead to rotator cuff tears and superior subluxation of the humeral head limiting the ability to lift the arm. Hip and knee synovitis can cause flexion contractures, leg length discrepancy, and an abnormal gait. Ankle and foot deformities can alter a person's gait. Subtalar and midfoot involvement and rupture of the tibialis posterior tendon can cause collapse of the longitudinal arch of the foot causing a rigid flat foot and hindfoot valgus deformity.

Cervical spine damage from uncontrolled synovitis is a poor prognostic sign and can lead to neurologic manifestations from spinal cord compromise or vertebrobasilar insufficiency. All patients with long-standing RA should have a radiograph of the cervical spine before a surgical procedure. The most common abnormality is anterior atlantoaxial subluxation (C1–C2) caused by pannus eroding the odontoid and/or supporting ligaments. An atlanto-dens interval greater than 8–9 mm or atlantoaxial subluxation coupled with basilar invagination correlates with spinal cord compression. Involvement of lower levels of the cervical spine (C3–C7) by pannus destruction of the facet joints, ligaments, and discovertebral junctions can lead to subaxial subluxations. Cord compression is likely with subluxation of one vertebrae on another of 3.5 mm or more or if the space available for the spinal cord is 14 mm or less. An MRI can define the site and degree of spinal cord compression better than plain radiographs.

Extra-Articular Manifestations

Rheumatoid arthritis is a systemic inflammatory disease. Although all patients have joint manifestations, up to 50% will develop one or more extra-articular manifestations (EAM) (Table 1.2) with 15% having a severe manifestation [1]. Rarely a patient may present with an EAM before the onset of arthritis. Risk factors associated with developing these manifestations include smoking, high-titer RF and/or ACPAs, and having two copies of the HLA-DRB1*04 shared epitope alleles. It is critical for clinicians to rule out other potential causes (e.g., infection, malignancy, medications) for an EAM before ascribing it to RA, especially in a patient who is RF and ACPA negative.

The most common EAM occurring in up to 35% of RA patients is secondary Sjögren's syndrome manifested by dry eyes and dry mouth. Although most are RF and ANA positive, anti-SS-A and anti-SS-B antibodies, which are commonly seen in primary Sjögren's syndrome, are rarely seen in RA patients with secondary Sjögren's. Rheumatoid nodules are also a frequent EAM occurring in 25–30% of RA patients at some time during their disease although present in less than 10% at disease onset. Rheumatoid nodules are subcutaneous and develop most commonly on extensor surfaces and at pressure areas such as the elbow olecranon process, fingers, occipital scalp, Achilles tendon, and ischial tuberosities. They can rarely occur in internal organs such as the heart, lung, and meninges. Rheumatoid nodules have a characteristic histology of a central area of focal fibrinoid necrosis surrounded by a zone of palisading histiocytes and a peripheral layer of cellular connective tissue.

Table 1.2 Extra-articular manifestations in rheumatoid arthritis

General	Cardiac
– Fever	– Pericarditis
– Lymphadenopathy	– Myocarditis
– Weight loss	– Coronary vasculitis
– Fatigue	– Nodules
Dermatologic	Neuromuscular
– Palmar erythema	– Entrapment neuropathy
– Subcutaneous nodules	– Peripheral neuropathy
– Small vessel vasculitis	– Mononeuritis multiplex
Ocular	Hematologic
– Episcleritis/scleritis	– Felty's syndrome
– Keratitis	– Large granular lymphocyte syndrome
– Choroid and retinal nodules	– Lymphoma
Pulmonary	Other
– Pleuritis	– Sjögren's syndrome
– Nodules	– Amyloidosis
– Interstitial pulmonary fibrosis	– Osteoporosis
– Cryptogenic organizing pneumonia	– Atherosclerosis
– Constrictive bronchiolitis	– Medium vessel vasculitis

Pulmonary involvement is common but may be clinically silent. Lung manifestations include pleuritis and pleural effusions, pulmonary nodules, interstitial lung disease, and obliterative bronchiolitis. These manifestations are covered extensively in other chapters in this textbook. Cardiac involvement is also relatively common. Pericarditis is the most frequent manifestation with up to 30% having an asymptomatic pericardial effusion on echocardiography. Pain from pericarditis occurs in only 1–10% of RA patients. Chronic constrictive pericarditis and pericardial tamponade from a large pericardial effusion are both unusual but usually require surgical treatment when they occur. Rarely myocarditis causing congestive heart failure and endomyocardial nodules leading to conduction disturbances or valvular insufficiency have been reported.

Vasculitis is uncommon and usually occurs in RA patients with seropositive, nodular, erosive disease which is long-standing and inadequately treated. Small vessel vasculitis presents as palpable purpura of the lower extremities resulting from inflammation of postcapillary venules. Small arteriolar vasculitis can cause skin ulcers or digital pulp/nailfold infarcts which can rarely lead to digital gangrene and a sensory neuropathy. Medium vessel vasculitis is rare but can cause severe organ-threatening manifestations including livedo reticularis with skin ulceration, peripheral neuropathy including mononeuritis multiplex, and visceral involvement from vasculitis involving the mesenteric, coronary, and/or cerebral arteries.

Common hematologic manifestations in active RA patients include anemia and thrombocytosis. The anemia is usually due to inflammation-associated anemia of chronic disease, and the increased platelet count is a reactive thrombocytosis. Iron deficiency must be excluded. RA patients who develop leukopenia must have Felty's syndrome, large granular lymphocyte (LGL) syndrome, and medication effects excluded. Felty's syndrome is defined as the triad of RA, splenomegaly, and leukopenia. It is found in less than 1% of RA patients who typically have severe, long-standing, and seropositive disease. The leukopenia is generally a neutropenia (<2000/mm [3]) and may be associated with hepatomegaly and thrombocytopenia. The LGL syndrome is a subset of Felty's patients who have an expansion of large granular lymphocytes (CD2,3,8,16,57 phenotype) on peripheral smear in addition to splenomegaly and leukopenia. RA patients with either Felty's or LGL syndrome are prone (20-fold increase) to bacterial infections.

Entrapment neuropathies are relatively common in RA patients. The synovitis can compress peripheral nerves. The median nerve (carpal tunnel), posterior tibial nerve (tarsal tunnel), ulnar nerve (cubital tunnel), and posterior interosseous branch of the radial nerve are most commonly involved. In addition to keratoconjunctivitis sicca, there are other ophthalmologic manifestations that can occur in RA patients including episcleritis, nodular scleritis, and rarely ulcerative keratitis. Episcleritis is relatively asymptomatic, whereas scleritis and ulcerative keratitis are severely painful and can lead to permanent visual loss. Choroidal and retinal nodules can also occur.

Fever and lymphadenopathy can rarely be present in patients with an acute onset of RA. However, infection and lymphoma must always be ruled out first in these

patients. Amyloidosis due to deposition of amyloid A (AA) typically presents as nephrotic syndrome in patients with long-standing RA that has been inadequately treated. Cricoarytenoid arthritis can cause laryngeal pain, dysphagia, hoarseness, and rarely stridor. Arthritis involving the ossicles of the ear can cause tinnitus and decreased hearing.

Laboratory Findings

Routine laboratory tests in untreated RA reflect ongoing inflammation. Complete blood count may show a normocytic, normochromic anemia due to the anemia of chronic disease and a reactive thrombocytosis. Leukocyte count is normal in number and differential. Serum electrolytes, creatinine, and liver-associated enzymes are usually normal. A low serum albumin from depressed hepatic synthesis due to systemic inflammation is common. A polyclonal gammopathy can be present causing a slight elevation of total protein. Urinalysis is normal. The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are usually elevated. Both can be in the normal range in patients with limited disease. ESR can be elevated due to the hepatic synthesis of acute phase reactants caused by inflammation or due to hypergammaglobulinemia. CRP is not influenced by hypergammaglobulinemia and may be a better test to monitor disease activity.

One or more autoantibodies are present in the peripheral blood in the majority of patients with RA [5]. Some of these are present years before the clinical onset of disease. Rheumatoid factors (RF) are autoantibodies (IgM, IgG, IgA) directed against antigenic determinants on the Fc portion of IgG. Only the IgM-RF is routinely measured by one of several laboratory methods (agglutination, laser nephelometry, or ELISA). In early RA (<6 months), 50–60% will have a positive IgM-RF. By 2 years of disease, up to 80% will be positive for IgM-RF. The specificity of IgM-RF for RA is 85% if high titer (≥ 50 IU/mL) although hepatitis C/cryoglobulinemia, systemic lupus erythematosus (SLE), and Sjögren's syndrome can present with a polyarthritis and high-titer RF. Other isotypes (IgG, IgA) of RF may have diagnostic and prognostic importance but are not routinely investigated. RA patients tend to have multiple RF isotypes and patients with high-titer IgM-RF and IgA-RF have more severe and erosive disease. Notably 5–10% of healthy individuals, especially those over 60 years old, can have a low-titer IgM-RF which is clinically insignificant.

Anti-citrullinated protein antibodies (ACPAs) are found in 60–70% of RA patients with a specificity of 95%. Most patients are also RF positive, but 10–15% of RF-negative RA patients can be ACPA positive. ACPAs are directed against proteins [filaggrin, vimentin, fibrin(ogen), collagen II, α-enolase, others] that have been citrullinated by the posttranslational modification of the amino acid arginine by peptidylarginine deaminases (PADs) to become citrulline. The CCP2 and CCP3 assays that measure serum ACPAs use artificial peptides that mimic these citrullinated protein epitopes. Another member of the ACPA family is an autoantibody

against mutated citrullinated vimentin (MCV). Overall it has a sensitivity of 53–85% and specificity of 80–88% for RA and may be positive in RA patients who are negative for other autoantibodies.

Antinuclear antibodies (ANAs) can be positive in up to 30% of RA patients. The ANA is not directed against any specific nuclear antigen which helps separate it from the ANAs found in SLE patients. ANA is frequently positive in patients with seronegative (RF-, ACPA-) RA, especially middle-aged females. Seropositive RA patients who are also ANA positive are more likely to have secondary Sjögren's syndrome and develop extra-articular manifestations. RA patients should have normal complement (C3 and C4) levels. If low, a disease other than RA should be considered.

Synovial fluid analysis is important in the evaluation of a patient suspected to have RA. The synovial fluid will be inflammatory with a total white blood cell count above 2000 cells/mm^3 and usually higher (5000–50,000 cells/mm^3). Synovial fluid white blood cell counts higher than 50,000–100,000 cells/mm^3 can be seen but infection must always be excluded. There is typically a neutrophil predominance. Crystal examination, gram stain, and cultures are always negative.

Radiographic Imaging

Plain radiographs are important both diagnostically and for following disease progression [6]. Radiographs of the hands, wrists, and feet are most useful for early diagnosis and should be obtained at baseline. The earliest radiographic change is periarticular osteopenia. Within months juxta-articular bony erosions and symmetrical joint space narrowing can occur (Fig. 1.2). The MCPs, PIPs, and MTPs develop the earliest radiographic abnormalities. Radiographic changes can occur in the hands before the feet (33% of cases), feet before the hands (33%), or simultaneously in both hands and feet (33%). The appearance of erosions within 12 months of disease onset is a poor prognostic sign. Repeating radiographs periodically can assess disease progression and effectiveness of therapy. Late radiographic changes can include finger and toe subluxations and joint deformities characteristic of RA. Radiographic changes including osteopenia and erosions take longer to occur in large joints (hip, knees, shoulders, elbows, ankles) and therefore are not routinely obtained to follow disease progression. Advanced changes in large joints show degenerative signs with osteophytes and uniform joint space narrowing.

Advanced imaging techniques including ultrasonography and magnetic resonance imaging (MRI) are more sensitive than plain radiographs for detecting soft tissue changes (synovitis, tenosynovitis), tendon integrity (rupture), effusions, early erosions, and cartilage volume. Ultrasonography is particularly useful in detecting popliteal cysts, while MRI is the imaging modality that provides the most accurate assessment of RA involvement of the cervical spine.

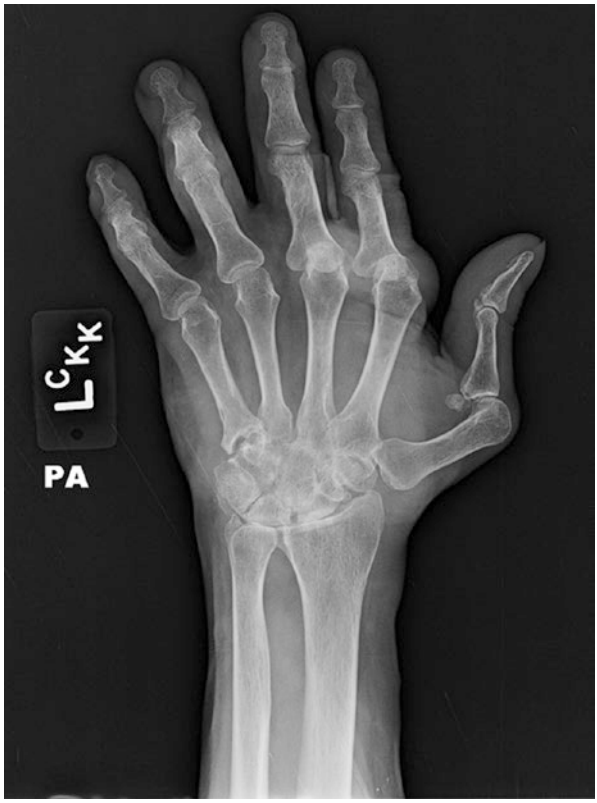

Fig. 1.2 Hand radiographs of a rheumatoid arthritis patient showing swelling, erosions, and joint space narrowing of the second and third metacarpophalangeal joints and wrist

Diagnosis, Classification Criteria, and Differential Diagnosis

The diagnosis of RA is made based on physical examination, laboratory, and imaging findings. Any patient with a symmetrical inflammatory polyarthritis involving the MCPs, PIPs, wrists, and MTPs associated with a positive IgM-RF, anti-CCP, and erosions on radiographs most definitely has RA. However, many patients with early disease are seronegative and do not have radiographic abnormalities. It is important to diagnose RA early in the disease course since these patients respond best to the available treatments. Consequently, the 2010 ACR/EULAR classification criteria for RA were developed to identify patients with an unexplained inflammatory arthritis of short duration who would benefit from early therapeutic intervention (Table 1.3) [7]. A patient with a score of 6/10 or higher can be classified as definite RA. Although these criteria were not created to diagnose RA, they are used to identify patients who are likely to benefit from early therapy. Pooled analysis shows these criteria have a sensitivity of 82% and specificity of 61% for diagnosing early RA.

Table 1.3 The 2010 ACR/EULAR classification criteria for rheumatoid arthritis[a]

1. Joint involvement	(0 to 5 points max)
– One medium to large joint	– 0
– 2–10 medium to large joints	– 1
– 1–3 small joints	– 2
– 4–10 small joints (with or without large joints)	– 3
– > 10 joints (at least one small joint involved)	– 5
2. Serology	(0 to 3 points max)
– Negative RF and negative ACPA	– 0
– Low positive RF or ACPA (<3× upper limit normal)	– 2
– High positive RF or ACPA (>3× upper limit normal)	– 3
3. Acute phase reactants	(0 to 1 point max)
– Normal CRP and ESR	– 0
– Abnormal CRP or ESR	– 1
4. Duration of symptoms	(0 to 1 point max)
– <6 weeks	– 0
– ≥6 weeks	– 1

Joint involvement defined as swollen or tender joint on examination or synovitis on ultrasound/MRI; medium/large joints include shoulders, elbows, hips, knees, ankles; small joints include MCPs, PIPs, 2–5 MTPs, wrists; *RF* rheumatoid factor, *ACPA* anti-citrullinated protein antibodies, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate

[a]Total score ≥ 6/10 meets classification criteria for rheumatoid arthritis

There are several diseases which can resemble early RA and therefore must be excluded by history, physical examination, and laboratory/radiographic tests:

Common diseases: Seronegative spondyloarthropathies (psoriatic arthritis, reactive arthritis, inflammatory bowel disease arthritis), calcium pyrophosphate deposition disease, systemic lupus erythematosus, systemic sclerosis, Sjögren's syndrome, polymyositis, mixed connective tissue disease, polymyalgia rheumatica, osteoarthritis, polyarticular gout, fibromyalgia, viral infection (EBV, HIV, hepatitis B, parvovirus B19, rubella, hepatitis C).

Uncommon diseases: Hypothyroidism, relapsing polychondritis, subacute bacterial endocarditis, rheumatic fever, hemochromatosis, sarcoidosis, hypertrophic osteoarthropathy, Lyme disease, amyloid arthropathy, paraneoplastic syndrome, myelodysplastic syndrome, hemoglobinopathies (sickle cell disease), hyperlipoproteinemias (types II, IV), Behçet's disease, disseminated gonorrhea.

Rare diseases: Whipple's disease, multicentric reticulohistiocytosis, angioimmunoblastic lymphadenopathy, familial Mediterranean fever.

Clinical Variants

The majority of patients with rheumatoid arthritis have a classical presentation with a seropositive symmetrical inflammatory polyarthritis involving the small joints of the hands, wrists, and feet. Other clinical subsets of RA have been described:

Seronegative rheumatoid arthritis: Approximately 20–25% of patients who meet criteria for RA are negative for both IgM-RF and anti-CCP [8]. Notably, some of these "seronegative" RA patients have a positive ANA or antibodies against mutated citrullinated vimentin or carbamylated proteins. Compared to seropositive RA, genetic factors contribute somewhat less to the risk of developing seronegative RA. The shared epitope alleles at the HLA-DRβ1 locus are much less important. Recently, a non-HLA gene variant of the *ankyrin repeat domain-55 (ANKRD55)* locus on chromosome 5 has shown a genetic association with seronegative RA. This gene is highly expressed in CD4+ T cells but has an unknown function. Notably this gene locus is near the gp130-encoding IL-6ST transcriptional start site which may play a role in the pathogenesis of RA. The initial polyarticular presentation of seronegative RA can be indistinguishable from the classical presentation of seropositive RA. Joint damage can be severe. However, in general, seronegative RA patients have a better prognosis, fewer EAM, and better survival. Seronegative RA patients are treated similar to seropositive RA patients but are less likely to respond to abatacept or rituximab treatment.

Late onset rheumatoid arthritis (LORA): Some patients with RA presenting after age 60 have an acute, explosive onset with systemic symptoms and polyarthritis. These patients have predominantly large joint involvement, especially the shoulders, and extremely elevated ESR/CRP. Some of these patients are seropositive, but many of them are seronegative making it difficult to separate their presentation from polymyalgia rheumatica. Many patients at presentation or later in their course develop small joint polyarthritis which can cause bony erosions especially in those who are seropositive.

Rheumatoid nodulosis: This variant of RA is more common in males. They present with mild arthritis, subcutaneous rheumatoid nodules, positive IgM-RF, subchondral bone cysts on radiographs, minimal systemic symptoms, and a benign clinical course. The course of the arthritis is typically episodic and rarely progresses to chronic erosive polyarthritis.

Remitting seronegative symmetrical synovitis with pitting edema (RS3PE syndrome): Patients present with the acute severe onset of symmetrical synovitis of the small joints of the fingers, wrists, and flexor tendon sheaths accompanied by pitting edema of the dorsum of the hand ("boxing-glove" hand). The feet and ankles can be involved. Other joints are rarely affected. Males are affected more than females. Patients are seronegative and do not develop bony erosions. The disease responds well to corticosteroids and is typically self-limited with a duration of 3–18 months and a good prognosis. Although initially considered a variant of RA, this syndrome's association with an elevated serum vascular endothelial growth factor, other connective tissue diseases, and malignancy suggests it is a distinct syndrome and not a subset of RA.

Early undifferentiated inflammatory arthritis: This is more an early clinical presentation than a clinical variant/subset of RA. These patients present with an inflammatory arthritis that is nonclassical in that it may involve few joints (<5), be asymmetric, or only involve large joints. The following are predictors of developing RA over time: (1) higher number of swollen joints, (2) persistence of arthritis longer than 6–12 weeks, and (3) serologic evidence (IgM-RF > 50 IU/mL and/or ACPAs).

Disease Activity and Disability Measures

There are several validated measurements for disease activity which are used clinically to assess how well the patient's RA is controlled on therapy [9]. They are:

Patient-driven composite tool:

PAS and PASII (Patient Activity Scale) (0–10)—measure health assessment questionnaire (HAQ or HAQII) (0–3) + patient pain visual analog scale (VAS) (0–10) + patient global assessment VAS (0–10). Total score adjusted to a 0–10 scale.

RAPID-3 (Routine Assessment of Patient Index Data with three measures) (0–10)—measures multidimensional health assessment questionnaire (MDHAQ) (0–3) + patient pain VAS (0–10) + patient global assessment VAS (0–10). Total score adjusted to a 0–10 scale.

Patient and provider composite tool: CDAI (Clinical Disease Activity Index) (0–76)—measures tender joint count (0–28) + swollen joint count (0–28) + patient global assessment VAS (0–10) + physician global assessment VAS (0–10).

Patient, provider, and laboratory composite tool:

DAS-28 (Disease Activity Score-28 joints) (ESR or CRP) scale (0–9.4): Calculates a score using the DAS calculator which applies a formula (www.das-score.nl). Components in the score are total joint count, swollen joint count, ESR or CRP, and patient global assessment.

SDAI (Simplified Disease Activity Index) (0–86): Measures tender joint count (0–28) + swollen joint count (0–28) + patient global assessment VAS (0–10) + physician global assessment VAS (0–10) + CRP (mg/dL) (0–10).

The values of these disease activity measurements that correlate with remission, low, moderate, and severe disease activity are shown in Table 1.4.

The measurement most commonly used to assess disability is one of the variants of the health assessment questionnaire (HAQ, HAQII, MDHAQ). This asks eight to ten questions that assess the patient's ability to perform activities of daily living that involve upper and lower extremity function. The score ranges from 0 to 3. A score ≥ 0.5 indicates some disability is present.

Table 1.4 Measurements of disease activity

Instrument (score range)	Remission	Low disease activity	Moderate disease activity	Severe disease activity
PAS/PASII (0–10)	≤0.25	≤3.7	<8	≥8
RAPID-3 (0–10)	≤1.0	≤2.0	≤4	>4
CDAI (0–76)	≤2.8	≤10	≤22	>22
DAS-28 (0–9.4)	≤2.6	≤3.2	≤5.1	>5.1
SDAI (0–86)	≤3.3	≤11	≤26	>26

Treatment

The most important goals for RA treatment are (1) to begin therapy early since the best results are seen when RA patients are started on treatment within 3 to 6 months of disease onset and (2) to treat to a target of low disease activity or remission [10–12]. All patients should receive education about their disease, joint protection, therapeutic exercise/rest, assistive devices, splints, foot orthotics, and when appropriate referred for physical and occupational therapy. Symptomatic therapy may include nonsteroidal anti-inflammatory medications, intraarticular corticosteroids, and/or low dose prednisone (≤5 mg/day). Higher doses of prednisone are used in patients with organ-threatening EAM. Patients should also be assessed for poor prognostic indicators which identify patients who need to be treated more aggressively (Table 1.5). Patients should be monitored every 3 months on therapy and treatment adjusted if there is an inadequate response by 6 months on a particular drug regimen.

Several synthetic disease-modifying antirheumatic drugs (sDMARDs) are available to treat rheumatoid arthritis (Table 1.6). Methotrexate has been the most effective drug used and can induce low disease activity as monotherapy in 30% of RA patients [13]. Patients who fail to achieve low disease activity can benefit from the addition of other synthetic DMARDs. The combination of methotrexate, sulfasalazine, and hydroxychloroquine can enable 50% of RA patients to achieve low disease activity in patients who did not respond adequately to monotherapy. RA patients who are intolerant to or have contraindications to using methotrexate can have leflunomide or, less commonly, azathioprine substituted.

Patients who fail to respond to methotrexate alone or in combination with other sDMARDs and/or RA patients with poor prognostic factors should receive one of the available biologic agents (Table 1.7) [14]. Prior to starting a biologic agent all patients are screened for prior exposure to tuberculosis and hepatitis B. Tofacitinib is

Table 1.5 Poor prognostic factors in rheumatoid arthritis

Generalized polyarthritis involving both small and large joints (>13–20 joints)
Rheumatoid factor and ACPA positive (usually have shared genetic epitope)
Poor functional status at baseline (MDHAQ > 1)
Extra-articular manifestations, especially nodules, vasculitis, major organ involvement
Persistently elevated ESR and/or CRP
Radiographic erosions within 2 years of disease onset
ANA positivity (if also RF positive)
Manual labor job contributing to joint damage

RF rheumatoid factor, *ACPA* anti-citrullinated protein antibodies, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *MDHAQ* multidimensional health assessment questionnaire (range 0–3), *ANA* anti-nuclear antibody

Table 1.6 Synthetic disease-modifying antirheumatic drugs (DMARD) for RA treatment

DMARD	Dose	Side effects	Precautions/monitoring
Methotrexate	10–25 mg/week oral or sc	Nausea, stomatitis, alopecia, pneumonitis, myelosuppression, ↑ LAEs	Viral hepatitis B and C screening; do not use if GFR < 50 cc/min. Teratogenic CBC, Cr, LAEs q8–12 weeks
Leflunomide	20 mg qd	Nausea, diarrhea, rash, alopecia, ↑ LAEs	Viral hepatitis B and C; teratogenic CBC, Cr, LAEs q8–12 weeks
Hydroxychloroquine	5 mg/kg/day (max 400 mg qd)	Nausea, rash, skin hyperpigmentation, retinopathy	Ophthalmologic exam at baseline, at year 5, then yearly if low risk
Sulfasalazine	1000–1500 mg BID	Nausea, abdominal bloating, rash, ↓ WBCs, ↑ LAEs	CBC, LAEs q12 weeks
Azathioprine	1–2 mg/kg/day	Nausea, rash, alopecia, myelosuppression, ↑ LAEs	TPMT screen, CBC, LAEs q12 weeks

LAEs liver-associated enzymes, *GFR* glomerular filtration rate, *CBC* complete blood count, *Cr* creatinine, *WBC* white blood cells, *sc* subcutaneously, *TPMT* thiopurine methyltransferase

an oral biologic agent which can be used alone or in combination with a sDMARD. All the other biologics are parenteral (subcutaneous or intravenous) and are usually used in combination with methotrexate. Patients on their first biologic agent can achieve low disease activity in 40–50% of cases. RA patients who fail to respond to an initial biologic within 3–6 months are typically switched to another biologic with a different mode of action. Unfortunately, only 30% of RA patients who have failed methotrexate and a first biologic will achieve low disease activity by switching to another biologic. Although the order of using biologics is not dictated, most RA patients are treated first with a tumor necrosis factor inhibitor unless they have a contraindication. Abatacept is as effective as TNF inhibitors and may cause less infections. Tocilizumab can be maximally effective with or without methotrexate. Rituximab is typically reserved for seropositive RA patients who have failed one or more biologic agents including at least one tumor necrosis factor inhibitor. RA patients who obtain remission on sDMARDs and/or biologic agents may be able taper their therapy but rarely if ever can discontinue all immunosuppressive medications.

Due to the high risk for disease- or treatment-associated complications, preventative therapy is a very important aspect of RA patient care. Patients are given appropriate immunizations (influenza, pneumococcal), osteoporosis screening and therapy, and treatment to reduce cardiovascular risk factors (smoking, hypertension, lipid control). The zoster vaccine is a live vaccine and is given to patients prior to starting biologics.

Surgical procedures used in the treatment of RA include tenosynovectomy, synovectomy, tendon realignment and repair, total joint arthroplasty, and arthrodesis. Prior to any surgical procedure an RA, patient should have their cardiovascular risk assessed since many are at risk for premature atherosclerosis. In addition, a cervical spine radiograph to rule out cervical spine instability is important to obtain.

Table 1.7 Biologic therapies for rheumatoid arthritis treatment[a]

Biologic	Dose	MOA	Precautions/monitoring
TNF inhibitors		Inhibit TNF	Bacterial, TB, fungal, viral infections, lymphoma, cytopenias, heart failure, demyelinating disorders, hepatotoxicity, DILE, psoriasis, sarcoidosis. CBC, LAEs periodically
– Etanercept	50 mg sc qwk		
– Adalimumab	40 mg sc qowk		
– Infliximab	3–5 mg/kg IV q4–8wks		
– Golimumab	50 mg sc q4wks;		
	2 mg/kg IV q8wks		
– Certolizumab	200 mg sc qowk		
Tofacitinib	5 mg BID; 11 mg qd	JAK inhibitor	Infections esp zoster, ↓Hct, ↓WBCs, ↑LAEs, ↑ lipids, ↑creatinine. CBC, Cr, LAEs, lipids q12wks
Abatacept	125 mg sc qwk; monthly IV: 500 mg (<60 kg) 750 mg (<100 kg) 1000 mg (>100 kg)	Inhibits B7-1/B7-2 binding to CD28 which inhibits T cell costimulation	Infections
Tocilizumab	162 mg sc qowk; 4–8 mg/kg IV q4wks	Binds IL-6 receptor; inhibits IL-6 binding to receptor	Infections, neutropenia, ↑ LAEs, ↑lipids, GI perforations. CBC, LAEs q1-2 mos, Lipids q 6 mos
Rituximab	1000 mg IV twice 2 weeks apart	B cell depletion; anti-CD20	Infusion reaction, infections, PML, neutropenia, hypogammaglobulinemia, hepatitis B reactivation. CBC periodically

MOA mechanism of action, *TNF* tumor necrosis factor, *sc* subcutaneously, *DILE* drug-induced lupus erythematosus, *CBC* complete blood count, *LAEs* liver-associated enzymes, *GI* gastrointestinal, *TB* tuberculosis, *PML* progressive multifocal leukoencepahopathy, *JAK* Janus kinases, *Hct* hematocrit, *WBC* white blood cells, *IV* intravenous

[a]All biologics increase both routine and opportunistic infection risk. Patients need to have a chest radiograph and be screened for tuberculosis and hepatitis B prior to use. All biologics decrease response to immunizations. Live virus immunizations are contraindicated

Prognosis: Morbidity and Mortality

RA is a systemic inflammatory disease that produces significant disability and shortens survival. Over 33% of RA patients who were working at the time of disease onset will leave the workforce within 5 years if not treated adequately. The relative risk of infection, osteoporosis with fractures, cardiovascular disease, and lymphoma is each increased two to three times compared to the general population [15, 16]. In

addition, the standardized mortality rate is 2:1 compared with people of the same sex and age without RA. Overall, RA shortens the lifespan of patients by 5–10 years. Aggressive sDMARD/biologic therapy appears to reduce disability (30%), joint replacement surgery (50%), and mortality (60%).

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Chapter 2
Rheumatoid Arthritis Pathogenesis and Pathophysiology

Jeremy Sokolove

The etiology of RA is complex, and it is likely that there may be no primary etiology attributable to all cases of RA. The final common phenotype that defines RA is itself quite heterogeneous, and the etiopathogenesis of each case is likely slightly different.

The phenotype of RA has been described and refined extensively over the past century and is now a fairly well-defined phenotype. However, understanding and defining the etiology of RA has been an iterative process with each contributing component usually studied in isolation. Over the past decades, scientific focus on the etiology of RA has focused on diverse mechanisms. Multiple different groups are studying RA in pieces, sometimes with overlapping focus, but often still studying each potential disease mechanism in isolation. This chapter will discuss the major functional processes implicated in RA pathophysiology while fully realizing it is likely that the ultimate disease pathophysiology involves various proportional contributions from each of these processes as well as other processes which are yet to be defined.

RA Etiology

It is now understood that the initiation of RA results from a combination of genetic and environmental risks which facilitate a break in immunologic tolerance and gradual accrual of pathologic immunologic processes which ultimately manifests in the phenotype of RA. Though likely simplistic, the development of RA can be thought of three phases: genetic and environmental risk followed by the initial onset

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of (usually subclinical) inflammation and finally the phase of chronic perpetuating synovitis and systemic inflammation [1].

Genetic Risk

The initiation of RA is thought to occur in the setting of an environmental exposure and on the background of a single or, more likely, multiple genetic risk factors. Although confounded by the stochastic nature of defined and undefined environmental exposures, the pattern of RA familial inheritance clearly suggests a multigenic contribution [2]. To this point, genetic studies have now suggested over 100 genetic polymorphisms which are associated with development of RA. Notably, the magnitude of most of each of these associations is relatively weak. By far the strongest genetic association is at the MHC class II locus. Select MHC class II alleles, including the HLA-DRB1*04 cluster, are most strongly associated with RA. The shared presence of a characteristic sequence of amino acids in the binding pocket of the HLA molecule has been labeled the "shared epitope" [2].

However, the magnitude of even this strongest association is still somewhat limited as demonstrated by twin studies in which only approximately 15–30% of monozygotic twin pairs both develop RA and rates of concordance in dizygotic twins are less than 5%.

Epidemiologic studies have suggested multiple environmental exposures which associate with the development of RA including most prominently tobacco smoking and exposure to other inhaled particulates [3]. Multiple infectious and/or commensal microbial exposures have been associated with RA, each with varying degrees of mechanistic support for their contribution. Many viral exposures can initiate an RA-like process which is most often transient. However, it has been hypothesized that in the predisposed individual, such processes may propagate into a chronic phenotype. It is also possible that chronic microbial colonization may, in the predisposed individual, contribute to either initial break in tolerance or propagation of inflammation required for the ultimate generation of RA.

Periodontitis is an inflammatory process of the gums characterized by chronic bacterial colonization and has been strongly associated with RA [4]. Though there is also evidence to suggest that severity of periodontal disease (PD) could be the result of shared risk factors or even a consequence of RA disease, several lines of evidence suggest that presence of PD may contribute to the development of RA [4]. Similarly, other recent studies have begun to investigate microbial colonization patterns in the gut as potential risk factors for development of RA [5]. It is most likely that any one, or perhaps any mixture of several, environmental factors could predispose to development of RA in different individuals.

Notably, the role of the environmental risk has been in tightly linked with associated genetic risk. As discussed above, it is likely that the generation of the RA immune response often requires an environmental insult in the setting of underlying

genetic risk [6]. This has been best demonstrated by the synergistic risk of concurrent cigarette smoking and the presence of the HLA-DR4 shared epitope [3].

Despite increased understanding of the genetic and environmental risks contributing to RA development, it is still not clear where in the body these processes are being initiated. The association of RA with PD could suggest the inflamed periodontium as a potential site for initiation of RA. Similarly, a microbial colonization pattern predisposing to an accelerated immunologic response in the gut could be a site for initiation and propagation of subclinical immunopathology. However, the robust risks associated with smoking and other particulate exposure have suggested that the lungs may be a major site for initiation of the RA immune response. Recent studies have demonstrated the presence of subclinical lung inflammation in the year preceding RA onset, and the inflammatory processes in these subjects suggest a pattern of immune activation similar to that ultimately observed in the RA synovium including evidence to suggest the generation of RA-related autoantibodies in the inflamed lung tissue [7]. A major question which still remains is how the process of extra-articular initiation might propagate from the site of initiation to the characteristic pattern of synovial joint inflammation.

Evolution of the RA Immune Response

Following the initial break in tolerance is a period of expansion of autoreactive T and B cells as demonstrated by a pattern of autoantibody epitope spreading and expansion [8, 9]. It is not entirely clear which are the initial types of autoantibodies generated during the preclinical phase of RA. However, it is clear from multiple studies that the major predictor associated with the development of clinical RA is the presence of a wider variety of autoantibody subtypes including the presence of rheumatoid factor (RF), various specificities of anti-citrullinated protein antibodies (ACPA), or antibodies targeting other posttranslational modifications. What is most clear is that the combined elevation of multiple autoantibody subtypes, especially ACPA and RF [9], seems the best predictor for the imminent onset of RA and may suggest that synergy between these two autoantibody responses could contribute to the development of subclinical inflammation and eventually the generation of clinically apparent arthritis.

Humoral Immunity

RA is classically divided into those who are seropositive, that is, those who have circulating autoantibodies characteristic of RA. Though there is now an expanding number of autoantibodies which have been associated with RA, the most characteristic include rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA) [10]. Beyond their role in RA diagnosis, the most actionable implication for the presence of these antibodies is their association with increased disease severity in terms of both local joint damage and extra-articular pathologies observed in RA.

RF is defined as an autoantibody targeting the Fc region of the IgG molecule. RF was described over 50 years ago due to the ability of RA serum to agglutinate sheep red blood cells [11, 12]. It was later demonstrated that these agglutinating factors were primarily IgM antibodies targeting and cross-linking IgG-coated red cells. RF can also be of the IgA or IgG isotype, but most clinical assays measure only the IgM isotype. Further study of IgM RF has demonstrated most rheumatoid factors to be germline encoded and lacking markers suggestive of T cell dependence such as extensive somatic hypermutation [13]. Despite the strong association of RF with RA, the exact contribution of RF to RA pathogenesis has been elusive. In the 1950s it was stated that "the role of RF in the pathogenesis of RA remains unclear," and today we have only made incremental progress in understanding the role of RF [14]. Building on the discovery of the more recently identified ACPA, two recent studies have suggested that RF may interact with ACPA to enhance inflammatory potential of ACPA immune complexes [15, 16].

As mentioned above, ACPA were identified many years after RF, but their recognition has added considerably both clinically and mechanistically to our understanding of RA. While ACPA and RF have a similar prevalence in RA, ACPA are generally much more specific for RA than RF [17]. The sensitivity of ACPA and RF is approximately 67% and 69%, respectively. However, the specificity of ACPA is nearly 95%, while RF specificity is 85% and lower in other cohorts [17]. The reduced specificity of RF is primarily related to the fact that RF can be observed in many other conditions including acute and chronic infection as well as other autoimmune and inflammatory conditions.

Though there have been considerably more studies investigating the pathogenic role of ACPA as a direct contributor of inflammatory arthritis, the exact mechanisms underlying this contribution remain to be defined. It should be noted that ACPA target otherwise ubiquitous proteins which have undergone a posttranslational enzymatic conversion of arginine to citrulline catalyzed by a family of enzymes known as peptidyl-arginine deiminases [18]. This process of citrullination, or deamination, occurs in multiple tissues, but of relevance to RA is the expression of PAD2 and PAD4 by many myeloid cells including monocytes/macrophage, mast cells, and neutrophils. It should thus not be surprising that citrullination is ubiquitous to sites of inflammation including many other conditions other than RA [19]. Similarly, many protein substrates for citrullination and subsequent targeting by ACPA have been described including most prominently filaggrin, fibrinogen, vimentin, enolase, and histones [20].

Perhaps the first study to suggest a direct effect of ACPA was an elegant murine study in which low-grade arthritis induced by anti-collagen antibodies was demonstrated to be exacerbated by transfer of a monoclonal antibody targeting citrullinated fibrinogen [21]. It should be noted that this antibody also displayed cross-reactivity to other citrullinated proteins as well as, at least to some degree, the native (uncitrullinated) version of several native proteins including native fibrinogen. Several studies in which mice were immunized with native or citrullinated fibrinogen further implicate fibrinogen as a critical antigenic target in RA [22, 23].

Studies of human ACPA have suggested specific mechanisms by which immune complexes containing citrullinated antigens might mediate RA-associated pathol-

ogy. These include the demonstration that immune complexes containing citrullinated fibrinogen can stimulate robust cytokine production from human macrophages [24, 25]. Additional studies have suggested that citrullinated ACPA, perhaps in part by targeting citrullinated vimentin, are capable of inducing osteoclast activation and bone erosion [26]. Furthermore, recent data suggest a role for ACPA in the induction of IL-8 and an autocrine process of neutrophil recruitment, protein citrullination, osteoclast activation, and inflammatory nociception [27–29].

As an easily measured circulating marker of RA, many groups have attempted to assess the process of development of both RF and ACPA. In all cases, the presence of these autoantibodies has preceded clinically apparent disease by years and in some cases over a decade [30, 31]. This observation has called into question the pathogenic contribution of ACPA and RF as direct mediators of RA-associated inflammation. It should be noted, however, that several processes have been observed during the preclinical phase of RA development including a pattern of epitope spreading [8] as well as changes in ACPA glycosylation patterns [32] as subjects approach the time of clinical disease onset. Thus, it is possible that evolution of the existing ACPA immune response could contribute to the inflammatory potential of these autoantibodies.

An alternative explanation for the prolonged period of inflammatory quiescence despite seropositivity is the possibility that it is not the generation of antibody that is the critical event, but rather the generation of sufficient cognate antigen to form pathogenic immune complexes that initiate and potentially propagate inflammation. Indeed, the early studies in mouse models suggested that transfer of monoclonal ACPA alone was insufficient to mediate inflammatory arthritis, but in the presence of low-grade inflammation in the joint, the presence of ACPA was an exacerbating factor [21]. This has been further supported by studies demonstrating that immunization with citrullinated histones generates a robust ACPA response but without the generation of inflammatory arthritis. However, with the induction of low-grade joint inflammation, the presence of these antibodies, either by immunization or transfer of serum from immunized animals, was able to induce a robust polyarthritis [33]. This evidence suggests that the transition from preclinical autoimmunity to clinically apparent inflammatory arthritis may be related not to the generation of pathogenic autoantibodies but the generation of cognate antigens within the synovial space in the setting of preestablished circulating autoantibodies. Whether such antigen generation may explain recent observations suggesting that extra-articular features associated with RA including lung and vascular pathology may precede synovial inflammation remains to be determined.

Role of T Cells

The importance of the HLA as well as the observation of robust T cell infiltration into the inflamed RA synovium suggested a role for T cells in RA pathogenesis [34]. The demonstration of oligoclonal T cell expansion in the RA synovia as well

as the association of RA with HLA-DR antigen binding pocket suggested the potential for the presence of an arthritogenic protein or peptide which might be driving the RA immune response [35, 36]. However, the exact contribution of the T cell to the ongoing RA inflammatory response has not been well defined. Perhaps most well supported is the requirement for the T cell in the initial break in tolerance that will eventually become RA. It is here where the studies suggesting the preferred recognition of citrulline-containing peptide antigens could suggest a mechanistic link between the HLA-DR4 shared epitope and the presence of an affinity-matured B cell response targeting citrullinated proteins.

Though presence of oligoclonal T cells in the inflamed synovium suggests an ongoing contribution to RA pathogenesis, it should be noted that therapeutic targeting including T cell depletion has met with limited success in RA [37]. This could suggest a less than critical role for the T cell once the process of RA is established or could be related to the concurrent depletion of both pro-inflammatory T cell and anti-inflammatory regulatory T cells. The disease-modifying effect of abatacept, a drug which blocks T cell co-stimulation by CD80/86 [38], suggests that there is at least some ongoing contribution of the T cell to the RA immune response.

B Cells

The fact that the first characteristic immune feature described in RA was the presence of autoantibodies strongly implicated a role of the B cell in RA pathogenesis. It was, and continues to be, easy to speculate that the generation of pathogenic immune complexes underlies the pathogenesis of RA. This was supported by studies demonstrating that B cell depletion using the anti-CD20 monoclonal antibody rituximab was effective in the treatment of RA [39]. However, even in this setting there was only incremental reduction in levels of circulating autoantibodies (both RF and ACPA) [40, 41]. This suggests that the primary source of RA-associated autoantibodies is likely the long-lived bone marrow plasma cell which notably lacks CD20 surface expression. It also suggests an autoantibody-independent contribution of B cells to RA pathogenesis which might include inflammatory cytokine production as well as antigen presentation and resultant activation of citrulline-specific synovial T cells.

Cytokines as the Final Common Pathway in RA Pathophysiology

Whatever the events which predispose to RA-associated autoimmunity as well as the adaptive immune processes which mediate upstream initiation of RA-associated inflammation, it is the final common mediators which induce synovial and

extra-articular inflammation and ultimately organ damage and destruction. Though the list of cytokines implicated in RA is large and ever growing, many studies at the cellular and tissue level have implicated a subset of cytokines most strongly associated with RA. Presently, we have dramatically improved insights into which cytokines appear critical and which are likely dispensable to the pathogenesis of RA. This insight comes as a result of many attempts at pharmacologic manipulation of individual cytokine pathways. Initial studies of RA tissues as well as animal models of RA suggested a critical role for IL-1 as a mediator of RA pathogenesis [42–44]. Disappointingly, pharmacologic targeting of IL-1 with anakinra yielded only minimal effect on RA disease activity [45]. Similarly experiences were observed for effort to neutralize IL-15 [46], interferon γ [47], as well as several chemokines implicated in RA pathophysiology [48, 49] and, most recently, antibodies neutralizing IL-17 [50].

On the opposite extreme, parallel studies implicating the cytokine TNF (also known as TNFα) led to the highly successful, and in many ways revolutionary, use of TNF-neutralizing antibodies and soluble TNF receptors [51]. However, even with the success of TNF inhibitors in RA, it has become clear that TNF is not the only pathway involved in RA-associated inflammation [52]. This is demonstrated by lack of response to TNF inhibitors in nearly 30% of RA patients and submaximal responses in well over 70% of patients. Thus, there are clearly other inflammatory pathways contributing to RA in general with individual patients, or at least patient subgroups, with disease driven by different mediators or different profiles of mediators. The success of anti-IL-6-based therapies [53] including those with previously inadequate response to TNF inhibition supports that RA is a heterogeneous disease with multiple biologic pathways contributing to disease pathogenesis. Studies are ongoing to identify additional pathways involved in RA including neutralizing additional cytokines (such as GM-CSF) [54, 55] as well as targeting shared signaling pathways downstream of multiple cytokines utilizing kinase inhibitors such as the JAK-STAT pathways [56].

Finally, we cannot ignore the cells which ultimately receive cytokine effect. These include mesenchymal cells such as the fibroblast-like synoviocytes (FLS) [57], chondrocytes [58], and the myeloid-derived osteoclast [59]. Cytokines also directly or indirectly induce chondrocyte and extracellular matrix loss resulting in joint damage and dysfunction. Similarly, in both the FLS and the chondrocyte, cytokines such as TNF, IL-1, and IL-6 induce cellular change including induction of a proliferative and invasive phenotype, with secondary production of multiple cytokines as well as prostaglandins and proteolytic enzymes such as MMPs.

Bone erosion is perhaps the most important predictor for loss of joint function and physical disability [60]. The development of bone erosion is in many ways contributed to each of the pathways discussed thus far. Bone erosion is primarily a result of osteoclast over-activation and possibly reduced osteoblastic bone generation [59]. Osteoclasts can be activated cytokines produced by synovial myeloid cells (macrophages, neutrophils, mast cells), FLS, or even chondrocytes. Multiple cell types, especially T cells, can produce RANK ligand which is a critical master regulator for differentiation of monocyte/macrophage cells to osteoclasts. Finally, there

is evolving evidence that RA-associated autoantibodies could either directly or via a short autocrine loop contribute to osteoclast activation and bone erosion [26, 29].

Extra-Articular Manifestations of RA

Though RA is primarily a disease of the synovial joint, it is clear that RA is a systemic autoimmune disease both in its inception and with clinically relevant extra-articular manifestations. Initiation of the immunologic response is likely distant from the joint [6], and there are multiple well-described extra-articular pathologic manifestations associated with RA [61]. Though there are clearly a myriad of potential organs that can be affected outside the joint, it is notable that in addition to long established and evolving documentation of clinical lung involvement, there is rapidly evolving evidence implicating the lung as a potential site of disease onset [6, 7]. Notably, though not classically characterized as a site of extra-articular involvement due to RA, there is also a suggestion that the inflamed periodontium may be both a potential site for immune initiation [4, 62, 63] and may also be a site of parallel inflammatory and osteolytic pathology to that observed in the joint [4]. Thus, it is possible that the extra-articular manifestations of RA including pathology observed in both the lung and periodontium may be not only an effect but in some cases a contributor to the etiology and pathogenesis of the end phenotype classified as RA.

Finally, the pathogenesis of the extra-articular features of RA is in many ways even more enigmatic than the pathogenesis of RA-associated synovitis. However, the common link between the joint and extra-articular sites is not clear. For instance, the common underlying pathology within the RA joint is inflammation. In the absence of active pathology, there is little evidence for disease progression. Though most extra-articular sites associated with RA also demonstrate at least some degree of inflammation, it is notable that within the lung, the primary pathology is often fibrosis without a clear preceding phase of inflammation that closely parallels the joint. The observation that extra-articular pathology including RA-associated lung disease is far more commonly observed in the seropositive RA population [61] suggests that the same RA-associated autoantibodies may contribute to both joint inflammation and extra-articular manifestations. It has been speculated that the ubiquitous generation citrullinated antigens at sites of inflammation and immune activation [19] may provide the nidus for generation of an RA-associated immune response.

Thus, although it is tempting to speculate that identical processes in the joint are simply manifest at the classic sites of extra-articular involvement, much work remains to better define both the scope and origin of the processes which initiate and drive RA within and outside the synovial joint. Ongoing research continues to define RA pathophysiology at the cellular, molecular, and systems level. It is hoped that new information, integrated with existing and evolving data, will provide a more complete understanding of the pathogenesis of RA (Fig. 2.1).

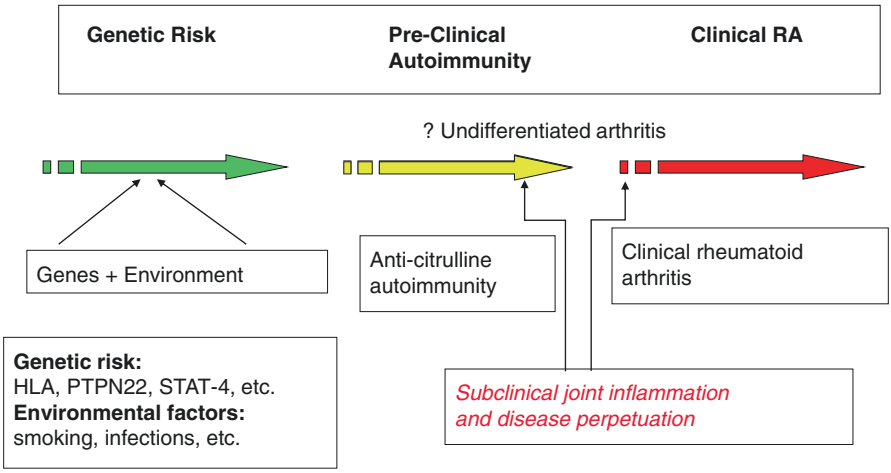

Fig. 2.1 Model for rheumatoid arthritis development

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Chapter 3
The Lungs as the Site of Initiation of RA

Lindsay B. Kelmenson, M. Kristen Demoruelle, and Kevin D. Deane

Introduction

As described in detail within other chapters in this textbook, lung disease is an important and sometimes fatal feature of rheumatoid arthritis (RA). Furthermore, RA-related lung disease can take many forms including large and small airways disease, parenchymal disease, pleural disease, and less commonly vascular disease [1].

Typically, lung involvement in RA is thought of as a late complication in patients with long-standing articular disease. However, there is established and emerging evidence that the lung can be involved early in RA [2, 3]. In addition, the lung may be a mucosal site where the autoimmunity of RA is *initiated*, particularly during a period of disease development termed "preclinical RA" where circulating RA-related autoimmunity in the form of autoantibodies is present in the absence of detectable articular inflammation [4].

In this chapter, we will review the findings to date that the lung may be a site of initiation of RA-related autoimmunity. In addition, we will discuss how the concept of RA potentially starting in the lung may be explored in future studies that could impact not only prevention and treatment of clinically significant lung disease in RA but also provide avenues for prevention of RA as a whole.

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Preclinical RA

To date, most rheumatic diseases are diagnosed once an individual develops identifiable clinical symptoms and signs of disease. RA is largely characterized by the development of joint-related symptoms and signs that can be classified as RA by established criteria such as the 1987 American College of Rheumatology (ACR) classification criteria and the 2010 ACR/European League Against Rheumatism (EULAR) classification criteria [5, 6].

However, over several decades, research by a number of investigators around the world has identified that RA develops in a series of phases that are presented in Fig. 3.1 [4]. The fine details of this model of RA development are rapidly evolving, although at this time the model includes three general phases. In phase 1, genetic and environmental risk factors for RA are present that lead to initial generation of autoimmunity and inflammation. Phase 2 is defined as a period of detectable RA-related autoimmune factors in the absence of clear joint inflammation and synovitis. This phase has largely been identified through the measurement of serum autoantibodies that include rheumatoid factor (RF) and antibodies to citrullinated protein antigens (ACPA) [4], although other antibody systems including autoantibodies to peptidyl arginine deiminase and carbamylated proteins have also been identified [7, 8]. In addition, expanding inflammation as measured by circulating cytokines, chemokines, and other factors occurs in concert with the development of autoantibodies [9]. Overall, this period of detectable circulating autoimmunity and inflammation is present for on-average 3–5 years prior to the development of clinically apparent RA [10]. Finally, phase 3 of RA development is defined as when synovitis becomes clinically apparent and classifiable as RA. Additionally, early in phase 3, there may be a period of time when there

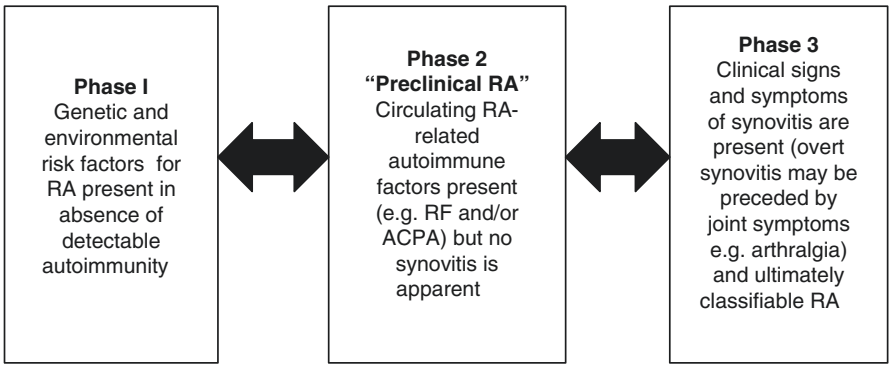

Fig. 3.1 Model of development of rheumatoid arthritis (RA). Throughout this process genetic and environmental factors may play a role in transitions from one phase to another; these factors may differ by phase. The double headed arrows indicate that these process may be reversible. Abbreviations: *RF* rheumatoid factor, *ACPA* antibodies to citrullinated protein/peptide antigens

are symptoms of inflammatory disease termed “arthralgia” prior to clearly identifiable synovitis [11].

Autoantibody and Inflammatory Evolution in Preclinical RA

Most of the studies of preclinical RA have used commercially available autoantibody tests. For the ACPAs in particular, studies have used ELISA assays to detect antibodies to cyclic citrullinated peptide antibodies (anti-CCP) that can be of several generations (e.g., anti-CCP2, anti-CCP3), with each having an assay of different antigen reactivities that are proprietary and therefore unknown to the wider community (reviewed in Demoruelle et al. [12]). Importantly, while these anti-CCP antibody assays are highly specific for both established and future RA [13], they do not allow for identification of specific antigen reactivity.

However, several studies have used ACPA arrays or other specific ACPA tests that can demonstrate autoantibodies to specific citrullinated antigens that allow investigations into the number and type of antigens recognized in RA development [14–16]. As examples, these assays can identify autoantibodies to citrullinated (cit) vimentin and cit-fibrinogen. Thus far in studies using these assays, a variety of citrullinated and even non-citrullinated antigens have been identified as autoantibody targets in preclinical RA [16]. In addition, it appears that early in preclinical RA, individuals have autoantibody reactivities to only a few antigens; then, as a diagnosis of RA approaches, there are greater numbers of antigens recognized [14]. Individuals are also more likely to have positivity for both ACPA and RF closer to diagnosis [17]. In addition, in parallel to the development of expanding numbers and types of autoantibodies, the phenotypes of autoantibodies change with alterations of glycosylation likely rendering antibodies more pathogenic [18]. Furthermore, inflammation as measured in the circulation by broad ranges of cytokines and chemokines increases in preclinical RA [17].

However, despite the intriguing finding that autoantibody reactivity is limited in early preclinical RA, no single antigen has been discovered as the dominant target in the initial break in immune tolerance. In addition, no specific antigen has been found that is strongly associated with the transition from preclinical to clinically apparent RA (phase 2 to phase 3—Fig. 3.1), although in one cross-sectional study of first-degree relatives (FDRs) of probands with RA as well as patients with established RA, antibodies to citrullinated fibrinogen and vimentin were specific for those with RA suggesting that these particular ACPAs may be important to the transition to clinically apparent synovitis [19].

The issue of which antigens are initially targeted in RA will need to be explored further, especially with newer techniques that are already in use in RA, such as single-cell analyses of plasmablasts and T cells [20, 21], which could identify early antigenic targets as well as explore the possibility that the earliest antigenic targets in RA are not citrullinated [22]. In addition, as discussed below, understanding the

location at which RA-related autoimmunity may initially be generated could shed light on the pathophysiology and mechanisms of disease development.

The Natural History of RA Suggests That Initial Autoimmunity Starts Outside of the Joints

While in patients with established RA it is known that RA-related autoantibodies are generated within the joint [23], several factors strongly suggest that the joints are not the initial site of generation of these autoantibodies. These factors include the on-average duration of 3–5 years of elevations of RA-related autoantibodies in the circulation prior to the development of synovitis [10]. Importantly, even beyond physical examination, multiple studies have shown that in many individuals who exhibit circulating RA-related autoantibodies and later develop synovitis, there is initially no evidence of synovitis by imaging (ultrasound and magnetic resonance imaging [2, 24] and even synovial biopsy [25]. These findings all support that the site of generation of these autoantibodies in preclinical RA is outside of the joint.

As to the specific anatomic site of generation, a growing evidence suggests that it is a mucosal site. This evidence includes data linking infections and other environmental exposures that are "mucosal" such as smoking and occupational dust to risk for RA [26, 27]. In addition, studies have suggested links between periodontal, gut, and lung inflammation with the development of RA (reviewed in Catrina et al. [28]). A number of studies have also identified that IgA RA-related autoantibodies (RF and ACPA) are present in preclinical RA. Studies using longitudinal biobank samples from subjects from preclinical RA have not clearly shown that IgA autoantibodies precede IgG [29]; however, in cross-sectional studies of at-risk populations such as FDRs, IgA ACPA seems to be the dominant isotype. Specifically, Barra and colleagues studied FDRs and patients with RA and found that in the FDRs, IgA and IgG ACPA were positive in 26 and 2% of subjects, respectively [30]. In contrast, in established RA, IgA and IgG ACPA were present in 27 and 56% of patients, respectively. In addition, a cross-sectional analysis by Kinslow and colleagues identified that IgA plasmablasts are a dominant feature of RA-related autoantibody-positive individuals without synovitis [21]. While these latter studies have not yet been followed up with longitudinal evaluations of the transition from early IgA to later IgG autoantibody dominance, they overall suggest that in very early RA development, IgA autoantibodies and, therefore, mucosal responses are important.

The Lung Is a Particularly Important Site of Possible Initiation of RA

As for a specific mucosal site where RA-related autoimmunity may be initiated, there are multiple lines of evidence that suggest that the lung may play a prominent role in the initiation of RA. These include (1) biologic machinery such as inducible

bronchus-associated lymphatic tissue (iBALT) that is present within the lung that can generate immune and autoimmune responses [31], (2) epidemiologic evidence linking inhaled exposures such as smoking and occupational dust to increased risk for RA (reviewed in Karlson and Deane [26]), and (3) studies that have demonstrated the generation of RA-related autoimmunity within the lung, including during the preclinical period of RA [32]. Each of these factors will be discussed in more detail below.

Biologic Machinery Within the Lung to Generate Immune (and Autoimmune) Responses

Because of its position as an interface between the environment and the body, the lung and, in particular, the airways are required to manage inhaled particulates as well as microbial factors and still maintain gas exchange [33]. A particular feature of the lung that responds to antigenic stimuli is iBALT.

iBALT is secondary ectopic lymphatic tissue that develops in the lungs in proximity to airways. It is comprised of aggregates of B and T cells as well as stromal cells, high endothelial venules, and lymphatic vessels [33]. Humans normally lack iBALT, but it can develop in response to infection or inflammation. In particular, the formation of iBALT is thought to bring together immunologic machinery that can generate local immune responses that protect against infection such as influenza or other viral infections or bacteria [34, 35]. iBALT appears to persist for several months after resolution of infection, and can participate in immune responses to pulmonary antigens, even those that are different from the initial antigens (e.g., infections) that triggered iBALT [33].

iBALT has been demonstrated in a variety of chronic lung diseases including emphysema and asthma [33, 36]. Importantly, iBALT has also been demonstrated in RA [31, 37]. Specifically, Rangel-Moreno and colleagues have shown in lung biopsies from patients with long-standing RA and known lung disease that plasma cells generating both ACPA and RF are present within iBALT [31].

The specific timing and triggers for the appearance of these autoantibody-generating plasma cells are unknown, but their presence raises the possibility that some initial event led to iBALT and perhaps over time RA-related autoantibodies began to be generated in the lungs of these individuals that contribute to local tissue injury. Furthermore, as discussed in more detail below, the presence of these RA-related autoantibody-generating plasma cells within the lung in established RA raises the issue that perhaps RA-related autoimmunity could be initiated within the lung prior to joint disease.

Epidemiologic Data Linking Inhaled Factors to Risk for RA

Multiple epidemiologic studies have identified associations between inhaled factors and an increased risk for developing RA. One of the earliest environmental exposures associated with increased risk for RA was exposure to occupational dust, identified

among miners in the United Kingdom [26]. In addition, more recent studies have consistently demonstrated that the strongest environmental risk factor for RA is smoking, with estimates that exposure to tobacco smoke explains up to ~30% of the overall risk for RA [38] and a possibly stronger risk in males [39]. In particular, smoking is associated with increased risk for ACPA- and RF-positive RA. In addition, there is a particularly strong association between smoking, the presence of certain human leukocyte antigen (HLA) proteins called the "shared epitope," and ACPA-positive RA [40, 41].

Certainly inhaled exposures may have immunologic effects outside of the lung. For example, smoking is known to introduce systemic toxins that can lead to bladder cancer or other non-pulmonary disease [42]. However, these associations do raise the possibility that inhaled factors act within the lung to drive initiation of RA-related autoimmunity, and a more detailed discussion on how these factors could combine to drive the development of RA in the lung is included below.

Lung Disease in the Absence of or Preceding Synovitis in RA

If RA-related autoimmunity were to begin in the lung, it follows that lung disease may precede the development of articular disease in RA. While most symptomatic lung disease is diagnosed after the onset of arthritic symptoms in RA, there are multiple case reports/series that have identified lung disease in early RA [3], as well as even preceding the appearance of arthritis in RA [43]. In particular, Fischer and colleagues identified 74 subjects with symptomatic lung disease and high-titer anti-CCP positivity in the absence of articular RA, several of whom later developed clinically apparent RA [44]. In addition, in a prospective study of individuals who had elevations of anti-CCP and/or RF in the absence of clinically detectable synovitis, Demoruelle and colleagues identified that on high-resolution computed tomographic (HRCT) imaging of the lung, ~70% of 42 autoantibody positive individuals without arthritis had airways disease [2], with two of these subjects later developing articular RA as reported in the paper and a total of five developing RA in longer-term follow-up (unpublished data).

Importantly, in all of these studies, the predominant form of lung disease was airways disease, suggesting that airways inflammation (and perhaps iBALT) likely plays a special role in the relationship between the lung and presence of RA-related autoimmunity.

Generation of RA-Related Autoimmunity Within the Lung in the Absence of Synovitis

While the above information supports that RA-related autoimmunity can develop in the lung, confirming the generation of autoimmunity, and in particular generation during the preclinical period of RA development, has been a difficult task. However,

following their work identifying airways disease abnormalities in serum RA-related autoantibody-positive individuals without RA, Demoruelle and colleagues performed comparative autoantibody studies of serum and induced sputum in individuals at risk for future RA [32]. Specifically, they identified that RA-related autoantibodies (both RF and ACPA) were present in the sputum and not the serum of ~25% of individuals at risk for future RA because they had a first-degree relative with RA, suggesting these autoantibodies were generated in the lung.

Additional studies of patients with established RA have also demonstrated the generation of RA-related autoantibodies within the lung. As discussed above, Rangel-Moreno and colleagues demonstrated plasma cells within iBALT in the lung generating ACPA and RF [31]. In addition, Reynisdottir and colleagues demonstrated ACPA generation within the lung in patients with established RA [45]; in addition, Harlow and colleges found a novel autoantibody to citrullinated heat-shock protein-90 that was highly specific for RA-related ILD and furthermore appeared to be generated within the lung [46].

Finally, in further support that the lung can be a site of generation of RA-related autoimmunity, lung generation of RF has been demonstrated in non-RA-related diseases; in particular, Schiotz and colleagues demonstrated the generation of RF in the lungs of individuals with cystic fibrosis and presumed due to chronic local infection-induced inflammation [47].

Putting It All Together: A Model of RA Where Autoimmunity Starts in the Lung and Later Involves the Joints

Putting an overall model together, RA development may start with an inflammatory process at a mucosal site that triggers generation of RA-related autoimmunity. This may propagate and transition from IgA- to IgG-related autoimmunity, as well as increased targeting of epitopes evidenced by increased number and specificities of ACPAs and development of multiple autoantibodies systems (e.g., RF and ACPA). Over time, the pathogenicity of these autoantibodies may change due to alternations in glycosylation, and perhaps combinations of autoantibodies are more likely to trigger and/or drive synovitis because of increased ability to form immune complexes and activate complement or involvement of other cell types (e.g., macrophages) [48]. Furthermore, paralleling the expansion of autoimmunity is expanding inflammation with a variety of cytokine and chemokine abnormalities that may reflect both growing tissue injury and direct participation in development of disease.

The precise mechanisms by which environmental exposures could initiate RA-related autoimmunity at a mucosal surface and in particular the lung and then propagate to articular RA are as of yet unknown. However, as Klareskog and colleagues elegantly proposed in a landmark 2006 article, it could well be that smoking or other inhaled factors drive initial inflammation in the lung [27]. Following this,

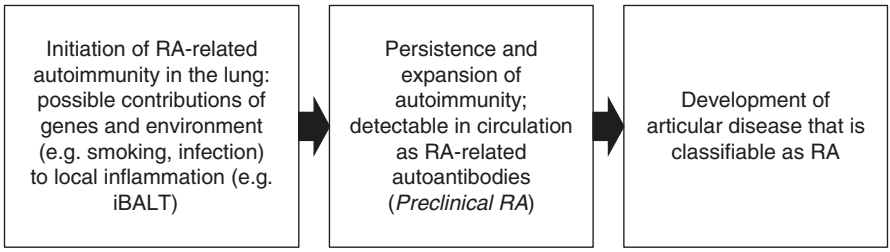

Fig. 3.2 Model of development of rheumatoid arthritis (RA)-related autoimmunity in the lung. In this model RA-related autoimmunity is initially generated in the lung. Over time this autoimmunity may resolve, or progress through regional lymphatics to systemic autoimmunity that can be detectable through circulating autoantibodies that may progress to the point where clinically-apparent synovitis develops that is classifiable as RA. In some individuals, the lung may serve as site of generation of autoimmunity, but otherwise be spared significant damage; in others, local or systemic RA-related factors may lead to substantial lung disease

and in the setting of the certain genetic backgrounds and other factors (e.g., iBALT formation, microbiologic factors), RA-related autoimmunity is generated locally, later spreading to regional lymphatics and then systemically leading to joint disease (Fig. 3.2). Supporting this model, citrullinated proteins are known to be elevated in the lungs of smokers as well as in other inflammatory lung conditions [49], and the HLA molecule containing the shared epitope may preferentially present citrullinated antigens to the immune system [50]. Therefore, perhaps locally generated inflammation and citrullination in the right genetic background drive the generation of RA-related autoimmunity in the lung, although as Quirk and colleagues have demonstrated, a high proportion of patients with non-RA-related bronchiectasis demonstrate circulating autoantibodies to non-citrullinated targets, and therefore it is possible that the initial autoantigens in RA are not citrullinated [22].

Future Directions

An overall model where RA-related autoimmunity begins at a mucosal surface and in particular the lung is a reasonable hypothesis based on currently available knowledge. However, multiple aspects of this model need to be explored in greater detail. Importantly, large, prospective studies of humans who are at risk for future RA need to be conducted to explore the progression of autoimmunity, early antigenic targets (citrullinated or non-citrullinated) and factors (e.g., genetics, smoking, microbiome) and cellular processes that drive the initiation and propagation of autoimmunity. Importantly, as discussed above, Demoruelle and colleagues found that ~25% of relatives of patients with RA had elevations of sputum RA-related autoantibodies. That number is in excess of the 3–5% that one would expect would ultimately develop RA based on current understanding of risk for RA within FDR populations [51], and because of that, it may be that RA-related autoimmunity develops at a

mucosal site as part of "natural" autoantibody responses and resolves in most individuals. This needs to be explored in future studies that include large numbers of individuals to determine the prevalence of RA-related autoantibody generation in the lung, as well as the factors that may lead to persistence and expansion of this autoimmunity locally as well as systemically. Following on that, additional studies are needed to understand the progression of initial mucosal disease and then articular symptoms in the early steps of RA development [52]. As part of these studies, it will be necessary to establish informative methodologies that can robustly assess mucosal as well as joint inflammation in a simultaneous fashion, so the timing of inflammation at each of these sites can be well-quantified in comparative analyses to determine at which site inflammation is truly initiated. Finally, while the lungs are an attractive site to investigate for the initiation of RA, other mucosal sites including the oral cavity and gut may also be important sites [53], and studies that can integrate evaluations of multiple mucosal surfaces in preclinical RA are necessary in order to discover the full scope of how mucosal inflammation may influence the development of RA.

In addition, there are increasing numbers of patients being identified who have symptomatic lung disease as their initial symptoms and systemic elevations of RA-related autoantibodies, yet no arthritis [44]. The precise classification of these types of patients is currently being evaluated, and an international task force has proposed that they be classified as "interstitial pneumonia with autoimmune features (IPAF)" [54]. The clinical management of these patients including treatment, as well as prediction of future development of articular RA, needs to be better studied; in addition, these subjects need to be incorporated into research studies to learn more about how the lung and joints are related in RA. Furthermore, as discussed above, while many patients with classifiable RA may have some form of lung disease, few of these develop clinically severe disease. If RA truly starts in the lungs, future studies need to determine how RA could be initiated in the lungs and then leave the lungs relatively functional in most subjects yet in a subset trigger more severe disease.

Fortunately, many such studies are underway using a variety of at-risk populations including FDRs, Native Americans, and subjects who present to clinics with arthralgia and RA-related autoantibody positivity in the absence of synovitis [11, 19, 55]. Importantly, as reported by Fischer and colleagues, pulmonologists may be the first to identify individuals who have lung disease and elevations of systemic RA-related autoantibodies [44], and these patients may be incredibly valuable to study to learn more about the natural history of lung disease, RA-related autoimmunity, and development of synovitis as well as the factors that may lead to more severe lung disease in some individuals; hopefully, there will be an expansion of mechanisms to study these types of individuals in more detail.

Furthermore, there are several RA prevention studies currently underway [56, 57], and the natural history and biologic data that will be available from these trials should do much to advance our understanding of the field. Finally, researchers are evaluating new ways of using animal models of disease to shed light on mucosal and in particular pulmonary processes that are important in the

very early steps of RA development [58], and these will be important contributors to our understanding of how mucosal processes can drive RA-related autoimmunity. In particular, understanding the role of the lung in the earliest steps of RA development may provide insights into how to treat or prevent clinically apparent lung disease in patients with established RA. Finally, given the advent of prevention studies in RA, understanding these processes may ultimately provide novel ways to prevent articular RA altogether.

Conclusion

While the lung is known to be clinically involved in patients with established RA, there is a growing evidence that the lung may be a site of initial generation of RA-related autoimmunity. Further studies are needed to identify the specific mechanisms by which RA may be initiated at a mucosal site and then develop into an articular disease, so that these mechanisms can ultimately be targeted to improve treatment and prevention of RA and RA-related lung disease.

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Chapter 4
The Epidemiology of Rheumatoid Arthritis-Associated Lung Disease

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Introduction

Rheumatoid arthritis (RA), characterized by inflammatory joint destruction, is the most common connective tissue disease, affecting 1% of the US population [1]. The global prevalence of RA is 0.24% (or 16 million people), and it ranks as the 42nd highest contributor to global disability [2]. The annual excess health cost related to RA in the USA is estimated at $19.3 billion [3].

Extra-articular manifestations (ExRA) are common in RA [4], may involve nearly any organ, and lead to excess mortality [5, 6]. Lung involvement occurs in 60–80% [7–9] of RA patients, many of whom (29–68%) are asymptomatic [7, 9, 10]. Although any component of the respiratory tract may be affected [11], the parenchyma, airways, and pleura are the most common sites of involvement [12]. In addition to direct pulmonary involvement from RA, patients are at risk for secondary pulmonary complications such as drug-induced lung disease and opportunistic infections.

Challenges of Epidemiologic Studies in RA Lung Disease

There are unique challenges in determining the epidemiology of RA-related lung disease. A three-patient case series of RA patients with "reticulation" on chest radiograph was published in 1948 [13], but the first well-described case of "rheumatoid

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lung" wasn't published for another decade [14]. In the subsequent years, authors tried to link RA and interstitial lung disease (ILD), but they remained limited by available detection methods [15, 16]. Since the 1970s, the connection between RA and lung disease has become well-established and, more recently, strongly confirmed with the advent of chest computed tomography (CT). Without CT, it was nearly impossible for investigators to detect subtle changes of ILD and extremely difficult for them to distinguish bronchiectasis and small airways disease. Thus, in the pre-CT era, epidemiological estimates of RA-related lung disease must be viewed as unreliable.

More recently, studies of the epidemiology of RA-related lung disease have yielded inconsistent results because of differing case definitions and case detection modalities. For example, studies using respiratory symptoms as a trigger for screening may underestimate prevalence, particularly in RA patients with severe articular disease and limited mobility. Evaluation for secondary causes of respiratory symptoms or lung disease (e.g., drug-related lung toxicity) has not been standard among epidemiologic studies. Studies that rely on health-care databases to determine incidence and prevalence are subject to issues related to diagnostic coding and classification bias. Tackling these issues will help investigators develop systematic approaches to identifying the true epidemiological burden of this disease.

Rheumatoid Arthritis-Associated Interstitial Lung Disease

Prevalence and Cumulative Incidence of RA-ILD in Patients Known to Have RA (*Table 4.1*)

Population-based studies that rely on medical records data to calculate incidence and prevalence estimates of RA-ILD are hindered by reporting bias and typically only include people with clinically significant disease. Studies of the US RA population have yielded cumulative incidence estimates of clinically significant RA-ILD in 5% of patients at 10 years [17], 6.3% at 15 years [18], and 6.8% over 30 years of follow-up [4]. Investigators from the Mayo Clinic reviewed data from 582 RA patients captured by the Rochester Epidemiology Project and estimated a lifetime risk of developing clinically significant ILD of 7.7% [19]. A large study of over 40 million US death certificates identified 160,000 records of decedents with RA; investigators found clinically significant ILD (defined as a contributor to death) in 6.8% of women and 9.8% of men [20]. Additional results from this study suggest that death from ILD among decedents with RA is on the rise [20]. However, these data should not be interpreted as incidence estimates.

A large study looking at the changing prevalence of severe ExRA from 1985 to 2006 in over 35,000 RA patients in the US Department of Veterans Affairs (VA) system found a decline in all ExRA (Felty syndrome, vasculitis, carditis) with the exception of rheumatoid lung disease, defined as ILD and pleurisy, which was increasing over this time in both outpatients and hospitalized patients [21]. These

Table 4.1 Prevalence and cumulative incidence of interstitial lung disease in rheumatoid arthritis

Cumulative incidence of RA-ILD	5% at 10 years [17]
	6.3% at 15 years [18]
	6.8% at 30 years [4]
Lifetime risk of RA-ILD	7.7% [19]
Clinically significant RA-ILD (defined as contributing to death)	6.8% in women [20]
	9.8% in men [20]
Prevalence of RA-ILD in ethnic subgroups	3% in Koreans [23]
	4.2% in Italians [24]
	3.7% in Spaniards [25]
	4.8% in Turks [26]
Prevalence of RA-ILD in "high-risk" patients (symptoms or abnormalities on PFTs or CXR)	91% [28]
Prevalence of RA-ILD in unselected patients	19–67% [8, 10, 29, 31–34]
Prevalence of RA-ILD using a multimodality approach	58% [29]

RA-ILD rheumatoid arthritis-associated interstitial lung disease, *PFTs* pulmonary function tests, *CXR* chest X-ray

investigators hypothesized that these trends may be due to the fact that newer therapies have improved the treatment of joint disease in RA thus decreasing extrapulmonary-related death, while treatments for ExRa, in particular fibrotic lung disease, are lacking. In addition, the increased awareness of RA-associated ILD, as well as the increasing use of high-resolution computed tomography (HRCT) over time, is likely also contributing to an increase in the prevalence of disease.

Prevalence rates of RA-ILD have been reported for certain ethnic groups. Researchers from the University of California San Francisco (UCSF) analyzed medical records from Hispanic and Asian outpatients in a rheumatology clinic and calculated a prevalence of RA-ILD of 3.6% [22]. Prevalence of RA-ILD in other ethnic subgroups has also been calculated: 3% in Koreans [23], 4.2% in Italians [24], 3.7% in Spaniards [25], and 4.8% in Turks [26].

Prevalence of RA-ILD in Patients with Respiratory Symptoms

As mentioned, when different imaging modalities and screening criteria are used for ILD screening, disease rates can vary markedly. For example, prevalence rates of RA-ILD are typically higher when using highly sensitive imaging techniques (i.e., HRCT) as compared to lower-sensitivity studies (i.e., chest radiograph). In fact, due to its sensitivity, HRCT is the preferred method of screening for ILD. RA-ILD prevalence rates are also typically lower when screening studies are applied broadly to any RA patient rather than only to RA patients with respiratory symptoms. For instance, a study looking at patients with a documented lack of pulmonary symptoms (cough or dyspnea) found "subclinical" ILD in 33% [27]. Conversely, a

screening study looking at selected patients at high risk for ILD (with either symptoms, impaired lung function or suspicious finding on chest X-ray (CXR)) identified ILD in as many as 91% [28] of patients.

Symptoms suggestive of lung disease are common in patients with RA. In 54 consecutive patients coming into a rheumatology clinic, 41% were found to have respiratory symptoms upon questioning, though symptoms did not correlate with either HRCT or PFT abnormalities [10]. Clinically significant ILD, defined as radiographic or physiologic changes in the setting of respiratory-related symptoms, occurs in approximately 10% of patients with RA [29–31]. A study of 252 RA patients found respiratory symptoms in 23% of patients; further investigation of these symptoms found ILD found in 9.1% of the entire cohort [31]. Clinically significant ILD was found to be associated with a 2.8-fold increased risk of death [5].

Prevalence of RA-ILD in Unselected Patients

Those with RA who undergo screening regardless of symptoms commonly have abnormalities on HRCT. The prevalence of radiographic ILD is variable and ranges from 19 to 67% depending on the population screened [8, 10, 29, 31–34]. A screening study of 150 RA patients irrespective of symptoms found interstitial changes (defined as reticular lines or ground glass) in 19% (with changes on CXR noted in less than 3%) [32], and these interstitial abnormalities correlated with reductions in the diffusing capacity for carbon monoxide (DLCO) and elevations in the forced expiratory volume in 1 s (FEV1)/forced vital capacity (FVC) (suggestive of restrictive disease). Another study screening unselected RA patients with HRCT found findings consistent with ILD (defined as a reticulonodular pattern) in 42% [8]. The large differences in the prevalence of imaging abnormalities between these studies may be due in part to differences in RA disease duration or severity or differences in smoking history. Investigators looking at early RA (defined as a joint disease duration of <2 years) found HRCT changes consistent with ILD in 27–33% with a majority of those being defined as "mild" (with only 10–14% defined as clinically significant disease) [29, 30]. When lifelong non-smokers with RA are screened, ILD is less common, found in only 5% in one study [35]. In another unselected group of hospitalized patients with RA, 49% of patients had HRCT abnormalities with the majority of these being ILD [34].

Prevalence of RA-ILD Using CXR, Pulmonary Function Tests (PFTs), and Multimodality Approach

Early studies looking at the prevalence of lung disease on CXR found interstitial abnormalities in 1–12% of unselected RA patients [14, 29, 32, 33, 36, 37]. However, CXR is a notably insensitive tool for identifying ILD. For example, in a study

screening hospitalized patients with HRCT, 48% of patients with an abnormal HRCT had a normal CXR, highlighting its insensitivity [34, 38].

PFTs can also be used to screen for ILD but, similar to CXR, are a less sensitive indicator of ILD compared to HRCT. In one study, PFTs were normal in 37% of people with HRCT evidence of ILD [8]. DLCO seems to be the best indicator of disease with reductions in DLCO correlating with the presence of interstitial abnormalities across a number of studies [28–30, 32]. In one study, reductions in DLCO were seen in 82% of patients with ILD on HRCT, and DLCO was the only PFT variable associated with ILD [32]. FVC is associated with ILD [34] though it has a weaker correlation compared to DLCO [28]. This may be contributed by the prevalence of smokers with obstructive physiology in this group (in one study of HRCT scans in 150 consecutive patients with RA, 43% of those with ILD had concomitant emphysematous changes [32]).

Overall, screening with multiple modalities finds a higher incidence of lung abnormalities in RA patients. A study looking at a combination of clinical symptoms, lung physiology, radiology (HRCT and CXR), bronchoalveolar lavage (BAL), and ^{99m}Tc-DTPA nuclear scan found abnormalities suggestive of ILD in 58% of patients, with 14% of those patients having clinically significant ILD [29].

Risk Factors for RA-ILD (Table 4.2)

RA is clearly a risk factor for ILD, conferring an increased risk of ILD with an odds ratio of 8.96 [19]. There are many reported risk factors for the development of ILD in RA, though few have strong supporting data.

Smoking

Smoking is a well-documented risk factor for RA in general [39, 40]—as well as RA-ILD [27, 33, 35, 41]. A multivariate analysis of risk factors for physiologic or radiographic abnormalities suggestive of ILD in patients with RA found that

Table 4.2 Possible risk factors for rheumatoid arthritis-associated interstitial lung disease

Stronger evidence
Smoking
Male sex
Advanced age
Rheumatoid arthritis disease score
Weaker evidence
Methotrexate
Anti-TNF agents
Anti-cyclic citrullinated antibodies
Genetics

TNF tumor necrosis factor

pack- years of smoking was associated with reductions in FVC and DLCO (even after exclusion of those with airflow obstruction as defined by an FEV1/FVC ratio <0.65) as well as interstitial changes on CXR [33]. A dose response was noted, with a higher incidence of ILD in those with ≥25 pack-years of smoking. A study of patients with RA but without pulmonary symptoms also found a strong association between longer smoking histories and the presence of subclinical ILD [27]. A much lower incidence of ILD is found when HRCT screening of RA patients is limited to lifelong non-smokers (5% in non-smokers [35] compared to 19–67% in all comers [8, 10, 29, 31–34]). In spite of these suggestive data, smoking has not been associated with ILD in all studies [8, 32, 42, 43], and smoking may not influence the pattern of ILD [28].

Sex

Although the prevalence of RA is more common in women [1, 44], male sex has been associated with the development of RA-ILD in multiple studies [19, 29, 31, 33, 45]. A study that longitudinally followed RA patients for a mean of 16 years found that males were more likely to develop ILD with a HR of 4.37 (95% CI 2.43–7.88) [19], although these estimates were not adjusted for smoking. A cross-sectional analysis of 252 RA patients found male sex was associated with the presence of clinically apparent ILD on multivariate analysis (OR 3.29, 95% CI 1.59–6.80, $p = 0.0013$) [31]. The association between male sex and ILD applies also to early RA [29]. However, not all studies find an association between sex and ILD [18, 43].

Age

Advanced age has been associated with RA-ILD in a number of studies [8, 18, 19, 33, 34, 41, 43]. Indeed, the average age across multiple studies ranges from 57 to 74 [4, 18, 28, 41, 46]. A population-based study following 582 patients over a mean of 16 years found age associated with the development of ILD with a HR of 1.41(95% CI 1.11–1.79) for every 10-year increase in age [19]. The analysis of an inception cohort with a 20-year follow-up found that every 10-year increase in age increases the likelihood of ILD by 64% [18]. Age is also predictive of ILD in studies utilizing multivariate analysis of other cofounders [8, 33].

RA Disease Activity

Disease activity, as measured by higher scores on the Health Assessment Questionnaire (HAQ) [18] and/or higher scores on the disease activity score 28 (DAS28) [30], has been associated with the presence of ILD, the HAQ showing

further association with declines over time in the FVC and DLCO [33]. Erythrocyte sedimentation rate (ESR), as a measure of RA disease activity, has been associated with the presence of ILD and declines in DLCO over time [8, 18, 19] with one study showing an increased likelihood of ILD by 11% for every 10-unit increase in ESR [18]. Other measures of disease activity such as rheumatoid factor (RF) [8], erosions or destructive joint changes, and rheumatoid nodules [19] have been associated with the development of ILD [19] as well.

RA Disease Duration

Multiple studies suggest that duration of RA is not a risk factor for ILD [8, 27, 34, 47]. One group looked at HRCT screening in patients with early (<1 year) and long-standing (>3 years) RA and found no difference in the incidence of ILD [47]. The duration of RA, however, may influence the presence of clinical versus subclinical disease [27] or the subtype of ILD in these patients [28].

RA Treatment

Medications have been implicated as risk factors for the development of ILD. Methotrexate (MTX) is well known to cause lung disease [48], but its effect on the development of ILD in RA is not clear, with some studies concluding no association [18, 32] and others finding associations with decline in lung function [33], the presence of honeycombing [41], or the development of ILD over time [19]. There is no current consensus on the association between biologic agents and ILD. There have been case reports of exacerbations of existing ILD or new interstitial pneumonitis in patients with RA taking infliximab [49–51]. Etanercept has been linked to granulomatous lung disease and exacerbation of preexisting lung disease in patients with RA [52, 53]. In spite of these reports, a recent review of 367 patients with RA-ILD treated with either anti-TNF agents or traditional RA treatments found no difference in mortality [54], and a report using a databank to evaluate the associations between therapies for RA and ILD found no increased risk of hospitalization with the use of TNF inhibitors [55].

Genetics

There is limited data to determine whether genetics play a role in the development of RA-ILD. The presence of the HLA shared epitope (SE) is a known risk factor for RA in general, but older studies did not find associations between presence of SE alleles and ILD [8, 18, 56]. However, a recent study looking at 450 Japanese RA patients found associations between HLA-DR2 and ILD [57].

RA-Related Antibodies

Studies have suggested that RF and anti-cyclic citrullinated peptide (CCP) antibodies may be a risk factor for RA-ILD [43]. One study found that elevated levels of anti-CCP2 were associated with ILD (OR 1.49, 95% CI 1.25–1.78, $p < 0.0001$). In addition, a retrospective evaluation of 220 Greek patients with ILD found an association between anti-CCP2 levels and the presence of all ExRA manifestations, including pulmonary fibrosis ($p = 0.004$) [58]. Furthermore, an expanded repertoire of antibodies to citrullinated protein/peptide antigens (ACPA) that was defined as reactivity to multiple citrullinated targets was associated with an increased risk of ILD [59]. However, these associations may be confounded by the presence of smoking that has been linked to both anti-CCP positivity and RA-ILD.

Rheumatoid Arthritis-Associated Airways Disease

Prevalence and Cumulative Incidence of Airways Disease in RA (Table 4.3)

In addition to parenchymal lung disease, the prevalence of airways disease is also elevated in RA patients. While RA-ILD is associated with significant mortality, it is important to consider airways disease in RA as well because it can also lead to increased morbidity and even increased mortality [60, 61].

Airways disease in RA can involve the large airways (e.g., bronchiectasis and arthritis of the cricoarytenoid joint) or the small airways (e.g., asthma, chronic obstructive pulmonary disease (COPD), bronchiolitis). Airways abnormalities can be identified using PFTs and/or HRCT, and, as in RA-ILD, many RA patients display airways abnormalities in the absence of respiratory symptoms. Similar to

Table 4.3 Prevalence and cumulative incidence of airways disease in RA

Obstructive lung disease	
Cumulative incidence	4% at 10 years [61]
	7% at 20 years [61]
	10% at 30 years [61]
Prevalence in unselected RA patients	32% [62]
Clinically significant disease stratified by smoking	26–45% in ever smokers [62, 63]
	14–30% in never smokers [62, 63]
Prevalence using highly sensitive screening (e.g., HRCT)	66–92% [68, 69]
Bronchiectasis	
Prevalence in unselected RA patients	17% [69]
Clinically significant disease	3–6% [63, 70]

RA rheumatoid arthritis, *HRCT* high-resolution computed tomography

RA-ILD, the prevalence rates of airways disease in RA can vary widely depending on the screening criteria used (e.g., all patients with RA, those with early RA, those with respiratory symptoms), the definition of airways disease (e.g., decreases in FEV1/FVC, decreases in forced expiratory $flow_{25–75}$), and the level of dysfunction on PFTs that is considered to be abnormal. Another complicating factor in establishing the prevalence of airways disease in RA is the differences in patient populations studied, particularly related to smoking histories, as smoking is a known risk factor for RA, RA-ILD, and airways disease.

The prevalence of obstructive airways abnormalities in RA is reported to be in the range of 15–44% [10, 62–64]. In a study of 100 consecutive RA patients who had normal CXRs, screening PFTs found 32% of patients had airflow obstruction as measured by decreased FEV1/FVC and/or forced expiratory flow at 25%-75% of the FVC [62]. The prevalence of these abnormalities is higher in RA patients than in matched controls. A population-based cohort that included 603 RA patients from the Rochester Epidemiology Project and based on chart review found COPD to be more common in RA patients, even after adjusting for smoking [61]—suggesting that RA patients may be more susceptible to the effects from smoking.

Multiple studies demonstrate an association between smoking and the presence of airways disease in RA patients [61, 62, 65]. One study found that the hazard ratio for symptomatic obstructive lung disease in RA ever smokers was 4.38 (95% CI 2.14–8.99). However, it is important to note that even RA patients who are never smokers are also reported to have higher rates of airways disease, seen in 14–30% [62, 63]. In addition to the strong association of airways disease and smoking, airways disease has also been associated with longer RA disease duration [65]. One study found that the 10-, 20-, and 30-year cumulative incidence of symptomatic obstructive airways disease was 4, 7, and 10%, respectively. This incidence was significantly higher than in matched controls whose 10-, 20-, and 30-year incidence was 3, 5, and 6% [61]. Another study found a 13% incidence of airways abnormalities at 5-year follow-up in RA patients [66]. However, it is important to note that not all studies have found an association between RA disease duration and increased prevalence or incidence of airways disease [67] . In addition, airways abnormalities are reported at high rates in early RA as well based on HRCT imaging. Specifically, 66–92% in RA subjects with <1 year disease duration demonstrated airways abnormalities on HRCT [68, 69], although many of these patients were asymptomatic. Airways disease does have an impact on mortality in RA. In a study looking at women followed prospectively over 36 years in the Nurses' Health Study, there was an increased risk of death in those with RA and respiratory disease with the majority of those deaths being attributable to COPD [60].

Bronchiectasis or bronchial dilation is also prevalent in RA, although studies dedicated to determining the epidemiology of bronchiectasis in RA are limited. Clinically significant bronchiectasis is estimated to have a prevalence of approximately 3% of RA patients [70]; however the overall prevalence of bronchiectasis in RA is likely much higher. For example, a study of 105 consecutive early RA patients found that 17% demonstrated evidence of bronchiectasis on HRCT imaging [69]. Importantly, bronchiectasis in RA patients has been linked with an increased risk of

mortality [71, 72] supporting the need for additional research in this area. One study of 32 patients with RA and bronchiectasis found a 7.3-fold higher mortality compared to the general population and a fivefold higher mortality compared to an age- and sex-matched control group with RA alone [71].

While the prevalence of airways disease is consistently higher in RA patients, the pathogenesis of this link is not entirely clear. Inflammatory airways abnormalities have been suggested to play a role in the generation of RA-related autoantibodies [68]. In addition, while airways abnormalities are seen with higher frequency in RA non-smokers [67], studies have suggested that perhaps smoking can potentiate or exacerbate RA-associated airways disease [65]. Another factor at play may be infections; RA patients often get respiratory infections related to immunosuppressing medications, and airways disease including bronchiectasis can result from recurrent infections.

Rheumatoid Arthritis-Associated Pleural Disease

In the 1940s and 1950s, it was recognized that patients with RA had a higher incidence of pleural adhesions at biopsy, though a direct relationship between RA and pleural disease was not established until the 1960s [73]. Since then, pleural disease has been recognized as one of the most common intrathoracic manifestations of RA. In postmortem studies, pleural involvement is described in up to 73% of patients with RA [16, 74, 75]. In an earlier study utilizing chest radiographs, pleural thickening and/or effusion was reported in 24% of men and 16% of women [37]. Pleural effusions are more common in men over the age of 35 with rheumatoid nodules, have been associated with HLA-B8 [76, 77], and have an annual incidence of 1.54% in males and 0.34% in females [78]. Though the prevalence of pleural disease is high, symptomatic disease is less common. Only 20% of patients with RA have pleurisy [73], and clinical pleural disease, including symptomatic effusions, is seen in less than 5% [36, 76, 79].

Summary

In summary, the epidemiology of RA-associated ILD, airways disease, and pleural disease is complex. The prevalence and cumulative incidence depend on the mode of detection, the definition used to define disease, the duration of disease, and exposure to cigarette smoke. Clinically significant ILD appears to occur in approximately 10% of patients and is associated with a worse outcome. RA-ILD has been associated with a number of risk factors; further studies are warranted to determine more precisely how these risk factors confer disease. Clinically significant airways disease appears to occur in approximately 10% of patients. And while symptomatic pleural disease is uncommon, RA commonly affects the pleura. The role of not only

smoking but also autoantibodies in the initiation and progression of RA lung disease needs further investigation. With a better understanding of the underlying mechanisms—for RA-ILD, RA-associated airways disease, and RA-associated pleural disease—ultimately, we may be able to reduce the incidence and impact of the pulmonary complications of this disease.

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Chapter 5
Risk Factors and Biomarkers of RA-ILD

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Introduction

Lung disease in rheumatoid arthritis (RA) is one of the leading causes of death in RA patients [1]; interstitial lung disease (ILD) is the most common clinical manifestation of lung involvement in RA and the only complication of RA increasing in prevalence [2] with substantial risk for progressive morbidity and mortality [3]. Despite this, RA-ILD often goes unrecognized, highlighting the need for improved recognition and management of disease, including identification of targets for disease prevention; clinical tools that classify early stages of disease, such as clinical prediction models; and a personalized approach to diagnosis and treatment. As such, the focus of this chapter will be on risk factors and protein biomarkers of RA-ILD with a brief discussion on other potential molecular and genetic markers extrapolated from ongoing research in idiopathic pulmonary fibrosis (IPF) and other connective tissue disease-ILD (CTD-ILD), such as systemic sclerosis (SSc).

RA-ILD Phenotypes

RA-ILD has well-described radiologic and histopathologic subtypes that are shared with the idiopathic interstitial pneumonias (IIPs) [4, 5], in particular, the usual interstitial pneumonia (UIP) pattern seen in IPF and the non-specific interstitial

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pneumonia (NSIP) pattern [6, 7]. The majority of individuals with clinically evident RA-ILD have a UIP pattern and a corresponding natural history that parallels the poor survival rates seen in IPF [6, 8–10]. Clinically evident disease occurs in about 10% of the RA population [1, 2, 11–13] with subclinical ILD [14] (no previous ILD diagnosis but interstitial lung abnormalities (ILA) [15] on CT) present in up to 30% of individuals [2, 16], with 34–57% demonstrating radiologic progression over 1–2 years [17, 18], supporting the hypothesis that some subclinical RA-ILD could eventually progress to clinically evident disease. Early detection of ILD in RA patients at risk for disease progression could lead to a meaningful change in clinical outcomes given the availability of numerous disease-modifying antirheumatic drugs (DMARDS), biologics [19], and novel anti-fibrotic therapies [20, 21].

Risk Factors

According to the World Health Organization, a risk factor is any attribute, characteristic, or exposure of an individual that increases the likelihood of developing a disease [22]. Risk factors for a spectrum of ILD in individuals with RA include demographics, RA disease severity, functional status, and tobacco exposure; furthermore, recent data suggests that some of these risk factors can help identify susceptible individuals that are at greater odds of having poor clinical outcomes and increased mortality [Table 5.1]. Demographic parameters that are associated with an increased risk for RA-ILD include older age and male gender [12, 23–25]. RA-ILD specifically has been associated with older age at the time of RA diagnosis [12], as well as older age at time of ILD diagnosis [23]. This is similar to IPF, which usually develops in the sixth or seventh decade of life [4]. This age-related onset may be related to genetic mutations that lead to telomere shortening thus limiting tissue renewal capacity in the lung; short telomeres have been demonstrated in approximately a quarter of familial and sporadic pulmonary fibrosis patients [26] and are associated with worse survival [27, 28]. Although RA is a female predominant disease [29], ILD is more common in male RA patients [12, 23–25], similar to IPF, which is also a male-predominant disease [30]. In addition, RA disease activity and severity are risk factors for the development of RA-ILD, as well as extra-articular disease in general [31]. A higher incidence of RA-ILD is seen in those with increased severity of joint disease, increased erosions or destructive changes and rheumatoid nodules, and high erythrocyte sedimentation rate (ESR) levels [12]. Increased incidence of ILD is also seen in individuals with RA and decreased functional status [12]. Although there is no primary evidence in RA studies, based on ongoing research in IPF and other IIPs, gastroesophageal reflux disease (GERD) [32, 33] is another potential risk factor for ILD that can be further explored in RA.

Although identifying risk factors associated with disease presence helps facilitate understanding of the epidemiology of disease and highlights opportunities for increased recognition, risk factors that can be associated with disease progression and outcomes have additional prognostic implications. Importantly, some of the

Table 5.1 Risk factors and biomarkers of RA-ILD

	Risk factors for disease presence	Risk factors for poor outcomes	Biomarkers of disease
Demonstrated in a spectrum of RA-ILD	Older age Male gender Increased respiratory symptoms Function decrements Physiologic decrements Tobacco smoking Increased severity of RA joint disease	Older age Male gender Low baseline FVC% Low DLCO% >10% FVC% decline UIP pattern	High-titer RF Anti-CCP antibodies MMP7 CCL18/PARC SP-D KL-6
Potential targets in RA-ILD	GERD		SP-A IL-6 YKL-40 CCN2 IL-8 ICAM-1 VCAM-1 CXCL9, CXCL10 CRP

RA-ILD rheumatoid arthritis-associated interstitial lung disease, *FVC%* forced vital capacity (% predicted), *DLCO%* diffusion capacity of carbon monoxide (% predicted), *UIP* usual interstitial pneumonia, *RF* rheumatoid factor, *CCP* cyclic citrullinated peptides, *MMP* matrix metalloproteinase, *CCL18* CC chemokine ligand 18, *PARC* pulmonary and activation-regulated chemokine, *SP* surfactant protein, *KL-6* Krebs von den Lungen-6, *GERD* gastroesophageal reflux disease, *IL* interleukin, *CCN2* connective tissue growth factor, *ICAM-1* intracellular adhesion molecule-1, *VCAM-1* vascular cell adhesion molecule-1, *CXCL* CXC chemokine ligand, *CRP* C-reactive protein

above risk factors of RA-ILD are also associated with ILD severity, poor outcomes, and increased mortality. Disease progression and increased mortality in RA-ILD have been associated with older age and male gender, as well as low baseline percentage predicted forced vital capacity (FVC%), low baseline percentage predicted diffusion capacity for carbon monoxide (DLCO%), and a significant decline (>10% FVC%) in lung function at follow-up [9, 18, 23, 34]. Low functional status, as measured by the Heath Assessment Questionnaire Disability Index, has also been associated with a decline in DLCO% [35]. In addition, it has been well established that the UIP pattern is associated with poor outcomes in RA subjects when compared to a non-UIP pattern [6, 8–10, 23], with significant predictors of radiologic progression of RA-ILD including extent of interstitial changes on high-resolution CT scan, bibasilar crackles, and low DLCO% [18]. Although not specifically validated in RA-ILD, additional clinical measures that may define disease severity and progression and predict early mortality in clinically-evident RA-ILD can be drawn from the IPF and lung transplant literature, including extent of honeycombing on high-resolution computed tomography (HRCT), new onset of desaturation during exercise, presence of pulmonary hypertension, and level of dyspnea [4, 34].

Chronic environmental exposures like tobacco smoking have also been shown to be risk factors for RA-ILD [17, 36, 37], as well as both RA [38] and fibrotic lung

diseases in general [4, 39–42]. Smoking promotes protein citrullination in the lungs, which may lead to generation of anti-citrullinated protein antibodies (ACPA) and subsequent lung injury [43], especially in individuals with the HLA-DRB1 "shared epitope" [44]. These findings suggest that anti-cyclic citrullinated peptides (CCP) antibodies [45] and HLA-DR serotype are risk factors for the development of RA-ILD [44, 46].

The overlap among RA, fibrotic lung disease, and smoking supports the importance of smoking cessation in all RA patients as a key component of the management of individuals at risk for ILD. Increased understanding and detection of RA-ILD and recognition of modifiable risk factors can improve clinical outcomes by identifying targets for secondary prevention, such as smoking cessation, as well as opportunities for early intervention, such as with immunosuppressive therapy. Furthermore, in light of the recent discovery of anti-fibrotic therapies that can reduce the decline in lung function in IPF patients with mild to moderate fibrotic lung disease [20, 21], clinical trials with anti-fibrotic therapy for RA-ILD are ongoing.

Biomarkers

A biomarker has been defined as, "a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" [47]. There are many commonly used lung biomarkers in clinical and research settings, such as physiologic variables, patient-reported outcomes, radiologic parameters, and, more recently, protein biomarkers [36], which will be the focus of this section. Although protein biomarkers can be measured in a variety of compartments, we will focus the discussion on peripheral blood and bronchoalveolar lavage fluid (BALF) protein biomarkers as they appear to be more sensitive, better standardized, more reproducible, and, in the case of peripheral blood biomarkers, minimally invasive, cost-effective, and easily obtained in clinical settings. Peripheral blood biomarkers also have been shown to correlate with mortality and other important clinical outcome measures in IPF and SSc. In addition, we will extrapolate from emerging IPF and CTD-ILD research to identify other innovative peripheral blood-based biomarkers that may be useful to identify RA-ILD, measure disease outcomes, and/or response to treatment.

Autoantibodies

Multiple independent studies have shown that select autoantibodies, specifically high-titer RF [24, 48, 49] and anti-CCP antibodies [23, 24, 45, 48, 50], are associated with the presence of both clinically evident and subclinical ILD in RA

patients. Others have also demonstrated that high-titer RF is associated with a decreased DLCO [49]. In addition, the notion that RA may at times be initiated in the lungs is suggested by the recent description of a cohort of patients with anti-CCP positivity and lung disease in the absence of existing RA or other connective tissue disease, some of whom developed articular disease within a short period of follow-up [51].

There is also emerging research describing novel autoantibodies that may prove to be useful targets. Using a novel "reverse immunophenotyping" approach based on mass spectrometric sequencing of proteins preferentially immunoprecipitated by RA-ILD sera, anti-citrullinated HSP90 autoantibodies have been defined as modestly sensitive, but highly specific, markers of RA-ILD [52]. Coupling this immunoprecipitation strategy with refined difference in-gel electrophoresis (DiGE) techniques [53] may permit detection and quantification of additional autoantigens/autoantibodies that can be assessed for their relationship to RA-ILD as well as their predictive capacity for disease progression [54].

Experimental Serum Biomarkers

Given the radiologic and histologic overlap between RA-ILD and IPF [6, 8], it is not surprising that biomarkers associated with outcomes in IPF patients, including matrix metalloproteinase-7 (MMP7), CC chemokine ligand 18 (CCL18)/pulmonary and activation-regulated chemokine (PARC), surfactant protein-D (SP-D), and Krebs von den Lungen-6 (KL-6), have also been associated with RA-ILD. Increased levels of MMP7, CCL18, and SP-D, associated with disease progression and reduced survival in IPF [55–63], have been found in multiple independent cohorts with a spectrum of RA-ILD [37, 64]. There is additional evidence to suggest that Krebs von den Lungen-6 (KL-6), associated with disease severity and prognosis in IPF [65, 66], can be useful in evaluating the severity of RA-ILD, as well as distinguishing between fibrotic from non-fibrotic disease [67]. Other biomarkers that have been associated with IPF [68] and/or subclinical fibrosis may provide additional targets for RA-ILD research, including surfactant protein-A (SP-A) [63, 69, 70], interleukin (IL)-6 [56, 71], YKL-40 [72], connective tissue growth factor (CCN2) [73], IL-8, intracellular adhesion molecule (ICAM)-1, vascular cell adhesion molecule (VCAM)-1 [56], and various matrix metalloproteinases (MMPs) [55, 56, 74].

In addition to biomarkers of IPF, CTD-ILD, most notably SSc, may also prove useful in identifying biomarkers for the assessment of disease activity and prognosis in RA-ILD. SP-D, CCL18, and KL-6 have been demonstrated as markers of disease activity in SSc, strengthening their potential to become standard markers of ILD in RA [58, 75, 76]. In addition, CCL18 has also been associated with pulmonary function deterioration, lung fibrosis progression, and reduced survival [77]. KL-6 levels may be useful in predicting FVC decline in SSc [78], suggesting that these biomarkers may also prove useful for assessing progression and survival

in RA-ILD. Based on additional research in other connective tissue disease-related ILD, other potential biomarkers that may prove useful include surfactant protein-A (SP-A) [79], CXC chemokine ligand 9 (CXCL9), CXCL10, and C-reactive protein (CRP) [80].

Alveolar Protein Biomarkers

Another potential compartment for biomarker exploration is the alveolus through bronchoscopy. Levels of certain alveolar proteins, including platelet-derived growth factor (PDGF)-AB, PDGF-BB, transforming growth factor (TGF)-β_2, and interferon gamma (INFγ), differed significantly based on the degree of RA-ILD [17]. In addition, IgG and/or IgA antibodies targeting citrullinated HSP90 proteins/peptides also have been demonstrated in RA-ILD-derived BALF specimens [81]. The potential of this compartment for biomarker identification has been further substantiated by the profiling of cytokines in BALF of individuals with systemic sclerosis, in which IL-8 and monocyte chemoattractant protein 1 (MCP-1) were associated with lung fibrosis and prognosis [82, 83].

Other Potential Markers of RA-ILD

Ongoing research in IPF and other idiopathic interstitial pneumonias has highlighted the potential for genetic markers and should be further explored in RA-ILD, especially given the potential for incorporating genomic and molecular profiles into strategies for diagnosis, treatment, and prevention of RA-ILD [84]. Some of the most robust genomic targets include peripheral blood mononuclear cell gene expression profiles [85] and microRNAs [86]. Several genetic factors such as MUC5B polymorphisms [87, 88], surfactant protein gene mutations in SFTPC and SFTPA2 variants [89, 90], telomerase mutations in TERT and TERC genes [91, 92] and/or short telomere length in general [93], and genes involved in inflammation and immunity (TOLLIP [94, 95], ELMOD2 [96], and TLR3 [97]) have been associated with IPF. Next-generation sequencing (NGS) will lead, in the near future, to the discovery of additional gene candidates that could enhance our understanding of disease pathogenesis, risk factors, and their potential role as prognostic markers. Lastly, other markers of RA-ILD could be derived from changes in cell populations (fibrocytes [98], T-cell subtypes [99], monocytes), transcriptional changes (genes, microRNAs, noncoding RNA, exosomes), proteomics, and metabolomics [100–102]. Elucidation of these molecular markers has the potential to inform RA-ILD disease mechanisms, novel treatments, and prevention and to advance the development of personalized management of RA-ILD.

Clinical Predictive Modeling

Clinical prediction rules [103], or risk prediction models, use evidence-based medicine to provide an individualized approach to diagnosis, outcomes, and treatment. By combining a number of characteristic disease parameters, these models can help physicians make predictions pertinent to disease development and/or prognosis, with far-ranging implications for screening, diagnostic work-up, and choice of therapy in high-risk groups. Prediction models have become increasingly utilized, particularly in the areas of public health, surgery, oncology, and cardiology [104]. Biomarkers have the potential to augment these prediction rules, such as the use of cardiac biomarkers in the TIMI risk score [105].

In pulmonary medicine, prediction models have been used to predict outcomes in COPD (BODE index—body mass index, airflow obstruction, dyspnea, and exercise capacity) [106, 107], IPF (GAP model, gender, age, and physiology, and CPI, composite physiologic index) [108, 109], and chronic ILD, including CTD-ILD (ILD-GAP model) [110]. Several recent biomarker studies in IPF have demonstrated that a panel of peripheral blood molecular markers can complement and enhance the assessment and prognostication of individuals with ILD when added to established clinical parameters [36, 56, 60]. Kinder and colleagues demonstrated that the addition of SP-A and SP-D to an IPF clinical prediction model improved performance in the prediction of 1-year mortality [60]. Richards and colleagues have shown that a clinical prediction rule with MMP7 in it (the combined clinical and molecular outcome index—PCMI) predicts mortality better than clinical rules alone [56].

In RA, risk algorithms have been used to predict RA disease progression [111] and cardiovascular events [112], with recent data to suggest that the GAP, ILD-GAP, and CPI risk prediction models can predict mortality in RA-ILD. Of note, there is also an HRCT staging system based on one developed in SSc-ILD [113], which predicts prognosis in clinically evident RA-ILD, with limited disease (involving <20% of the lung parenchyma) demonstrating a better prognosis than borderline (20–25% lung involvement) or advanced (>25% lung involvement) disease [114]. But, there are no validated clinical predictive models to identify subclinical RA-ILD or subclinical ILD in general. We recently proposed a model composed of clinical risk factors (age, gender, smoking), autoantibodies (RF, CCP), and investigational biomarkers (MMP7, CCL-18, SP-D) that is useful in identifying both subclinical and clinically evident RA-ILD [37]. From this model, we derived a diagnostic algorithm for subclinical RA-ILD (Fig. 5.1), which yielded strong positive and negative likelihood ratios. These data suggest that clinical prediction models can be useful in a spectrum of RA-ILD, including the application of existing ILD models to accurately estimate mortality in clinically evident RA-ILD, as well as models incorporating risk factors and biomarkers that can identify RA patients at risk for developing ILD.

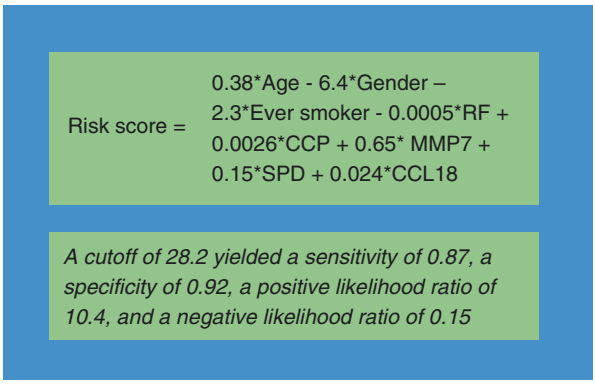

Fig. 5.1 Diagnostic algorithm for subclinical RA-ILD. *RA-ILD* rheumatoid arthritis-associated interstitial lung disease, *RF* rheumatoid factor, *CCP* cyclic citrullinated peptides, *MMP* matrix metalloproteinase, *SP* surfactant protein, *CCL18* CC chemokine ligand 18

Conclusion

RA-ILD is a heterogeneous disease with multiple pathologic (UIP/NSIP) and radiologic (subclinical/progressive/end-stage) phenotypes. A better understanding of risk factors and molecular markers could help not only to distinguish between these different phenotypes and predict outcomes but could also impact diagnosis, management, treatment, and prevention. A recent National Institutes of Health (NIH)-sponsored panel on the "Primary Prevention of Lung Disease" highlighted the need to understand better the natural history of early stages of pulmonary fibrosis in order to identify modifiable risk factors and, in turn, develop timely interventions to prevent disease progression [115]. To address this important unmet need, the NIH-sponsored panel concluded that research efforts should focus on better defining phenotypic and molecular traits associated with subclinical ILD in susceptible populations, including patients with RA. Identification of risk factors, biomarkers, and genetic factors associated with both clinically significant and subclinical RA-ILD, and their incorporation into clinical predictive models, can help to achieve this important goal. Moving forward, the study of large RA cohorts with detailed clinical phenotyping and longitudinal follow-up will be required. These future studies could ultimately lead to a better understanding of the pathobiology of RA-ILD and the rate of progressive subclinical disease and will therefore have the potential to positively impact clinical outcomes of RA patients with progressive lung fibrosis.

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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

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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

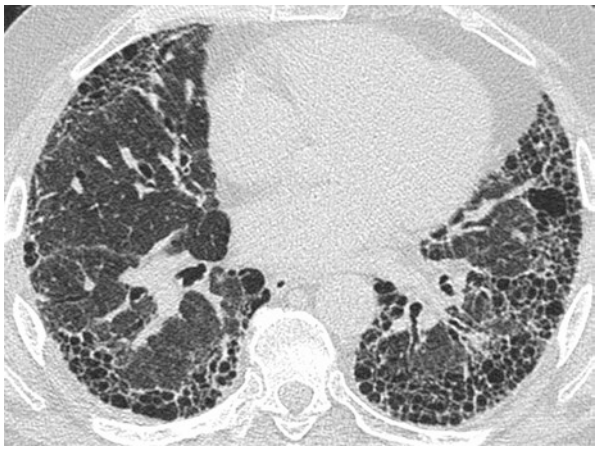

Fig. 6.1 Axial HRCT image of the lower lobes in a patient with rheumatoid arthritis-related usual interstitial pneumonia (UIP). The basal predominant, subpleural distribution of honeycombing is characteristic of this entity

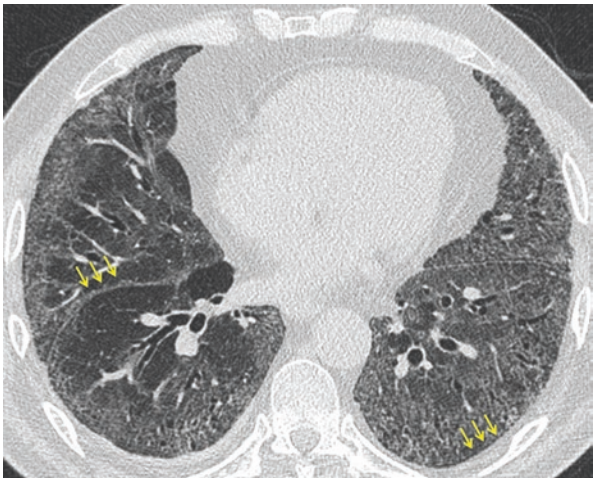

Fig. 6.2 Axial HRCT image of the lower lobes in a patient with rheumatoid arthritis-related nonspecific interstitial pneumonia (NSIP). In this patient, diffuse but predominantly subpleural textured ground-glass opacification is demonstrated containing areas of traction bronchiectasis particularly in 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

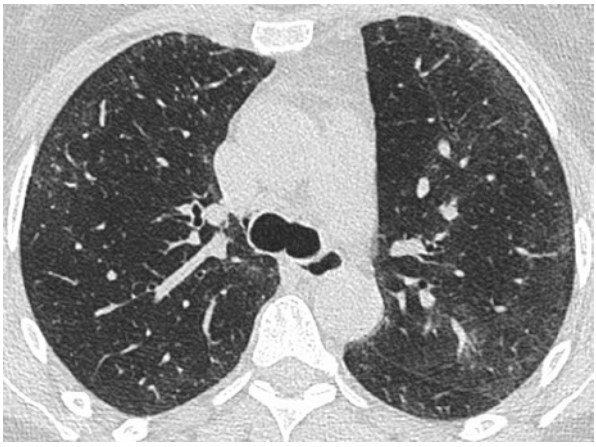

Fig. 6.3 Axial HRCT image of the upper lobes in a patient with rheumatoid arthritis-related NSIP. In the left upper lobe, the subpleural ground-glass opacification spares the juxtapleural lung

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

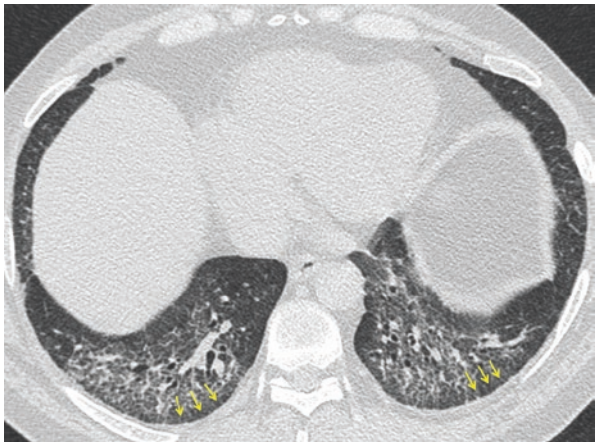

Fig. 6.4 Axial HRCT image of the lower lobes in a patient with rheumatoid arthritis-related NSIP. The lower lobe ground-glass opacification has admixed areas of reticulation and traction bronchiectasis but no honeycombing

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

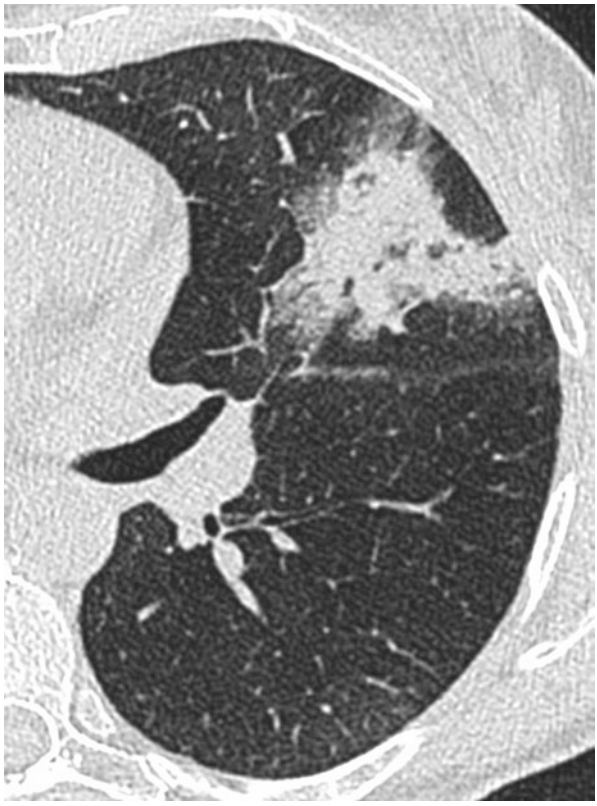

Fig. 6.5 Cropped HRCT image of the left upper lobe of a patient with rheumatoid arthritis. An area of bronchocentric consolidation with perilobular sparing is demonstrated consistent with organizing pneumonia

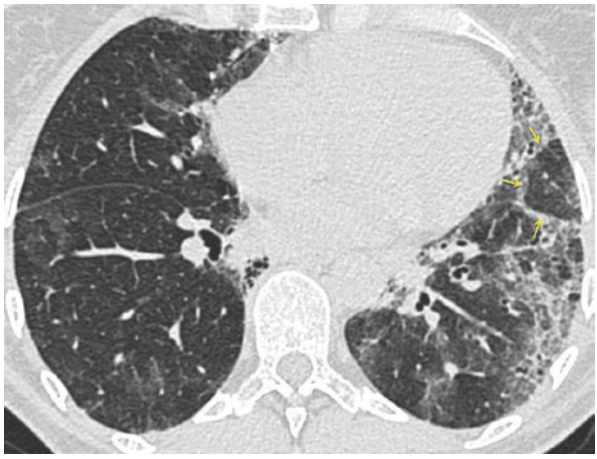

Fig. 6.6 Axial HRCT image of the lower lobes in a patient with rheumatoid arthritis-related NSIP characterized by subpleural reticulation, ground-glass opacification and traction bronchiectasis. In addition to the fibrotic lung disease, there is evidence of subpleural perilobular sparing indicating admixed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

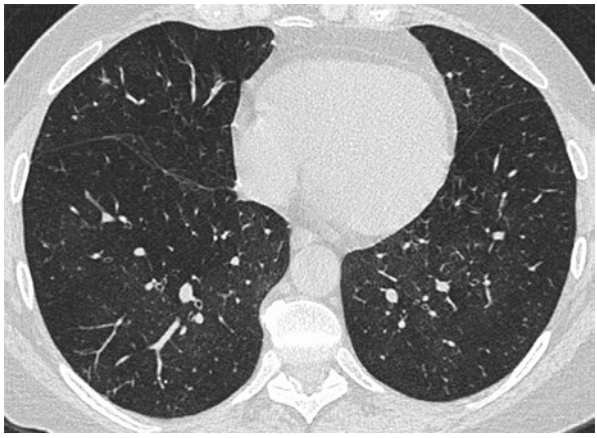

Fig. 6.7 Axial HRCT image of the lower lobes in a patient with rheumatoid arthritis demonstrating subtly the mosaic pattern of obliterative bronchiolitis, characterized by areas of normal lung interspersed with areas of low attenuation (dark lung)

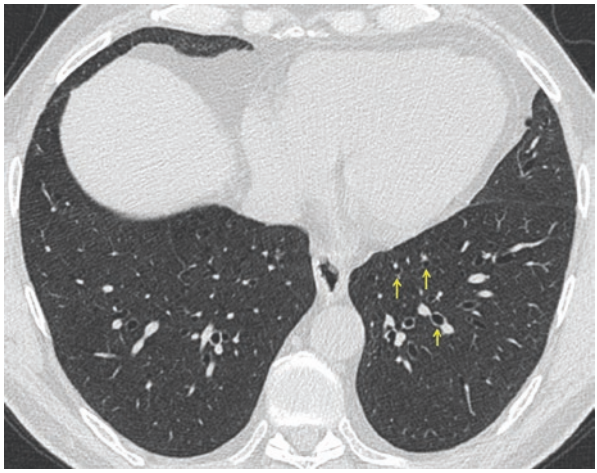

Fig. 6.8 Axial HRCT image of the lower lobes in a patient with rheumatoid arthritis demonstrating mild cylindrical bronchiectasis involving the segmental and subsegmental airways of both lower lobes. The affected bronchi are larger in cross-sectional diameter than the accompanying pulmonary artery, a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

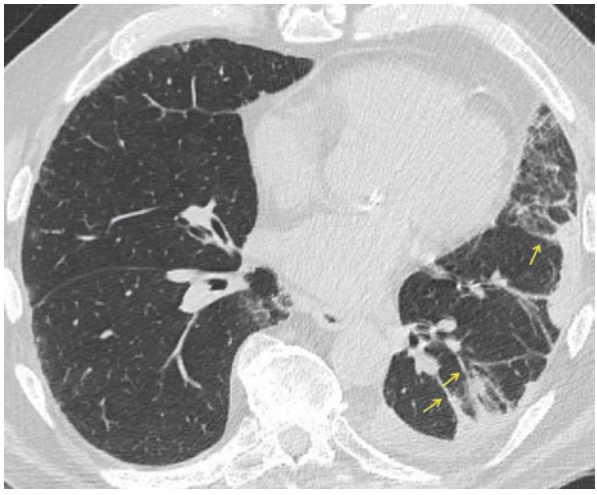

Fig. 6.9 Axial HRCT image of the lower lobes in a patient with rheumatoid arthritis demonstrating a shallow left-sided pleural effusion with overlying regions of rounded atelectasis. Each region of rounded atelectasis has bands of linear atelectasis arising from it, extending into the lung parenchyma—the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

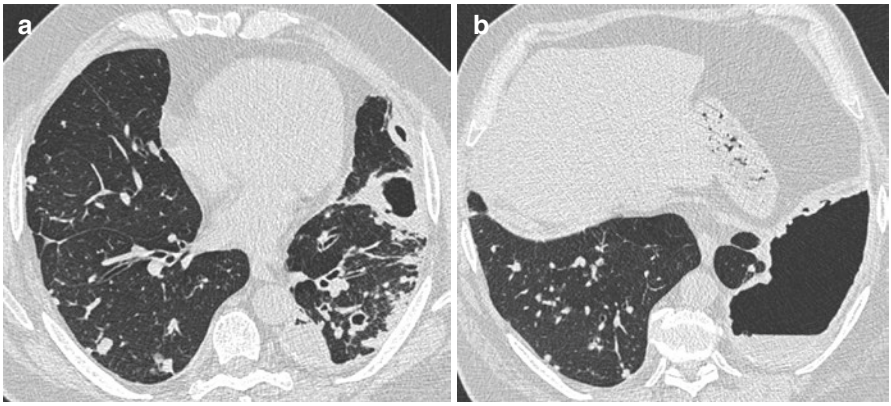

Fig. 6.10 (**a**) Multiple solid and cavitating pulmonary nodules are demonstrated throughout both lungs in a patient with rheumatoid arthritis. Areas of pleural thickening and subpleural round atelectasis are demonstrated in the left lower lobe. A nodule has cavitated into the left pleural space (**a**)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

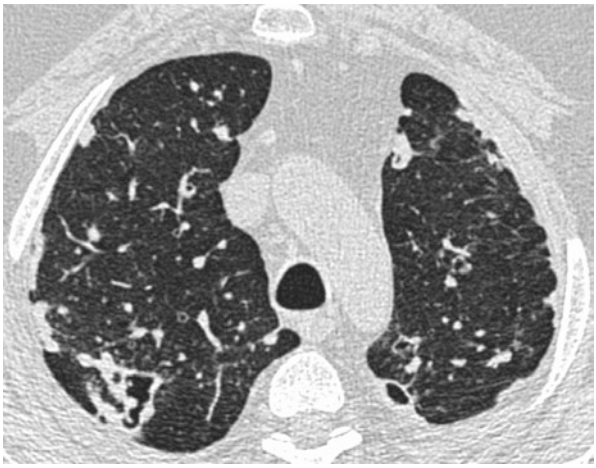

Fig. 6.11 Axial HRCT image of the upper lobes in a patient with rheumatoid arthritis demonstrating multiple irregular-shaped pulmonary nodules, some of which are cavitating. Nodules located along the pleura may cavitate into the pleural space resulting in bronchopleural fistula (Fig. 6.10a, b)

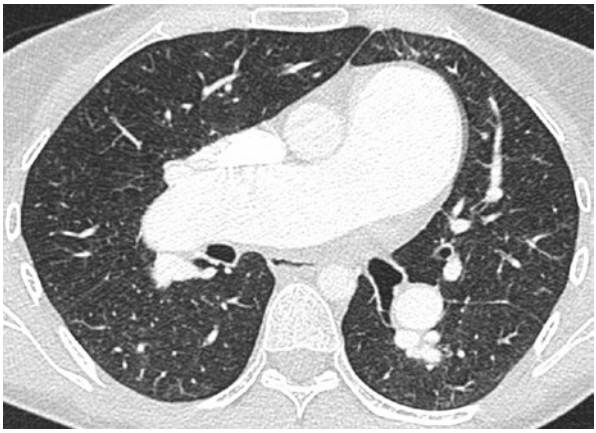

Fig. 6.12 Axial HRCT image in a patient with rheumatoid arthritis and confirmed pulmonary artery hypertension on right heart catheterisation studies. There is gross enlargement of the main pulmonary artery

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-

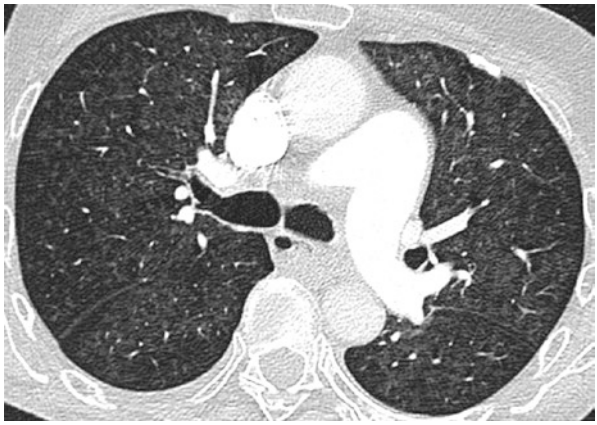

Fig. 6.13 Methotrexate toxicity in a patient with rheumatoid arthritis. There are subtle nodular regions of ground-glass opacification in the upper lobes, also seen in patients with hypersensitivity pneumonitis

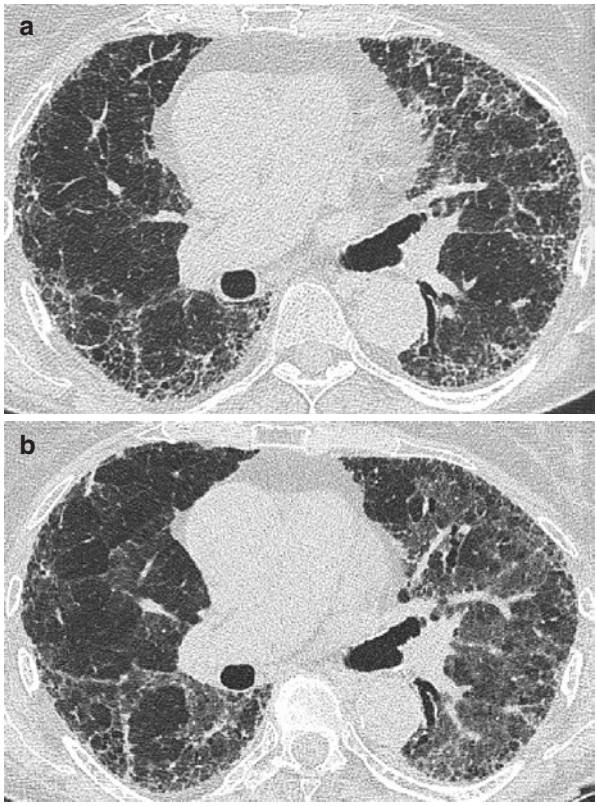

Fig. 6.14 TNF inhibitor pulmonary toxicity in a patient with rheumatoid arthritis and pre-existing interstitial lung disease. (**a**) Before treatment there are subpleural reticular abnormalities with traction bronchiectasis consistent with fibrotic lung disease. (**b**) Following treatment with TNF 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*.

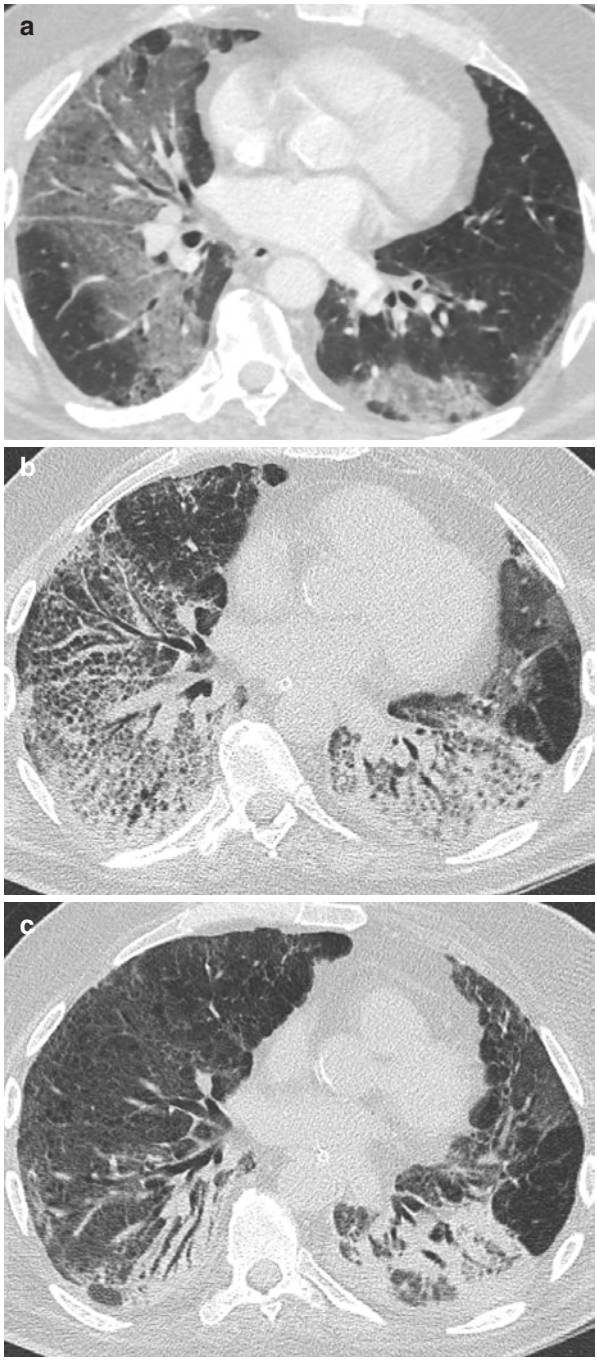

Fig. 6.15 Series of HRCT images of a RA patient receiving rituximab therapy. Soon after commencing therapy, the patient presented with acute dyspnoea. The HRCT (**a**) demonstrated diffuse ground-glass opacities representing DAD. Fifteen days later, a repeat HRCT showed (**b**) DAD with areas of incorporated 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**)

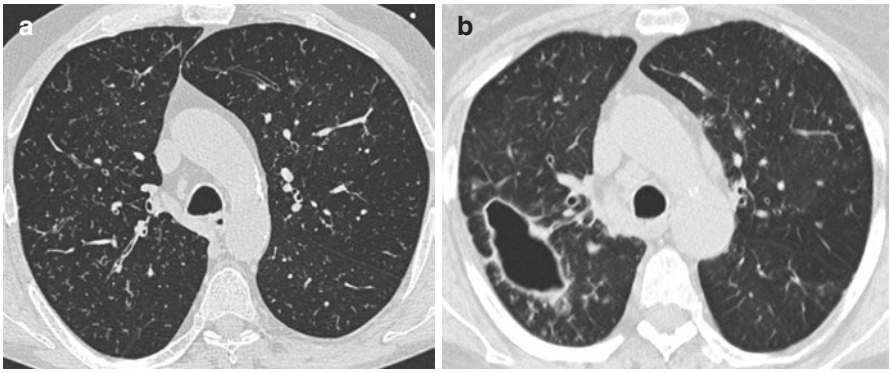

Fig. 6.16 Nontuberculous mycobacterial infection in two patients being treated with TNFi therapy. (**a**) Axial HRCT image in a RA patient demonstrating tree-in-bud-type opacities throughout both lungs consistent with exudative bronchiolitis seen in nontuberculous mycobacterial infection. (**b**) Axial 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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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

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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.

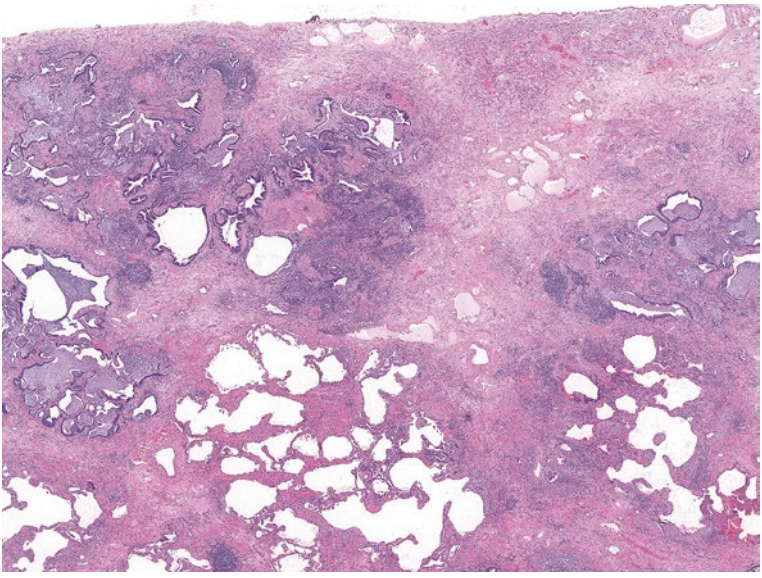

Fig. 7.1 Usual interstitial pneumonia. Low magnification view shows subpleural fibrosis with microscopic honeycombing (*top*) which transitions into less fibrotic alveolar septa (*mid-lower*)

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].

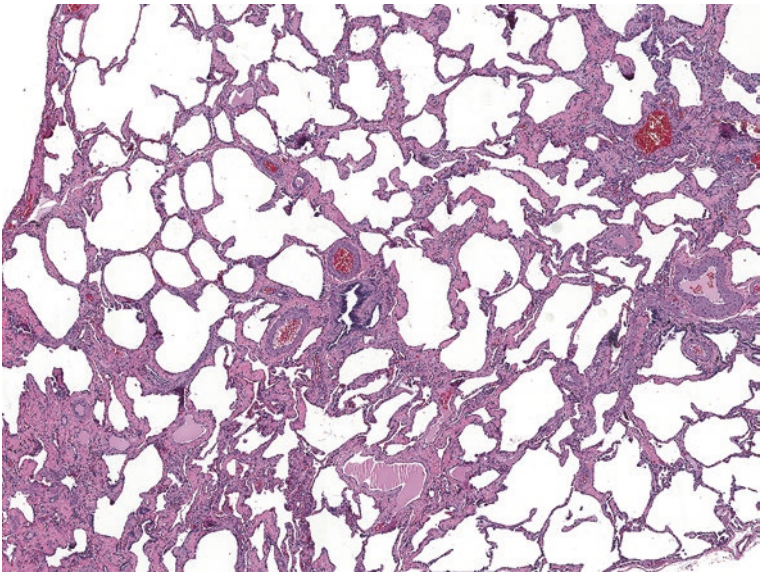

Fig. 7.2 Non-specific interstitial pneumonia. Low magnification view shows uniform alveolar septal thickening by fibrosis

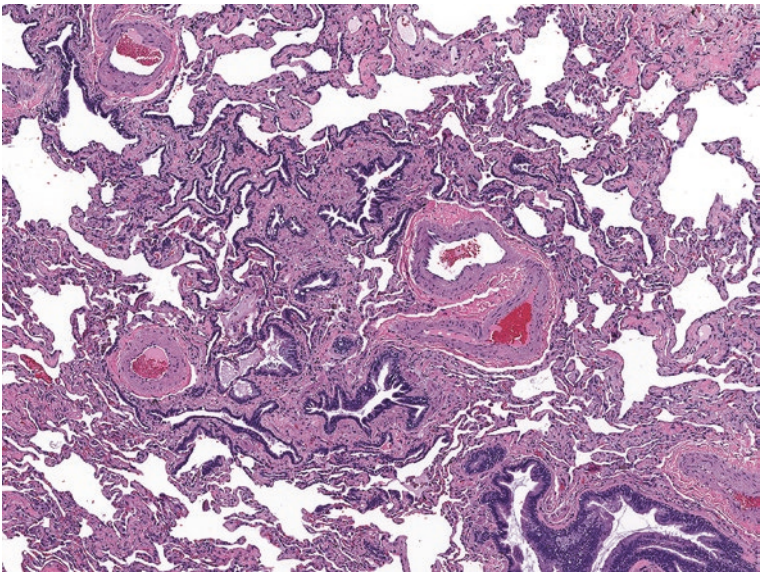

Fig. 7.3 Bronchiolocentric fibrosis. Low magnification view shows fibrosis of the peribronchiolar alveolar septa with bronchiolar-type epithelial metaplasia lining the thickened walls

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).

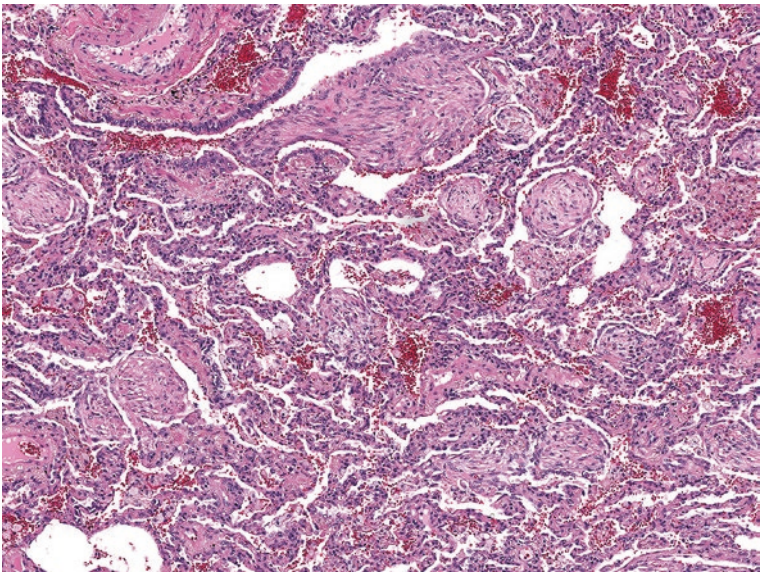

Fig. 7.4 Organizing pneumonia. Low magnification view shows alveolar spaces with patchy consolidation by rounded elongate plugs of granulation tissue-like fibrosis

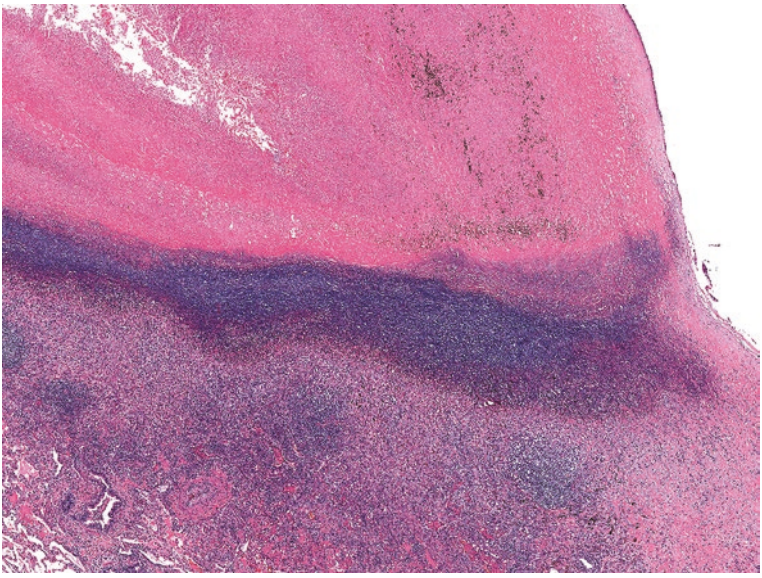

Fig. 7.5 Rheumatoid nodule. Low magnification view shows a large pleural-based nodule. There is eosinophilic acellular necrosis (*top*) and basophilic necrosis with adjacent palisading histiocytes (*bottom*). A small amount of the normal lung is present (*lower left*)

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

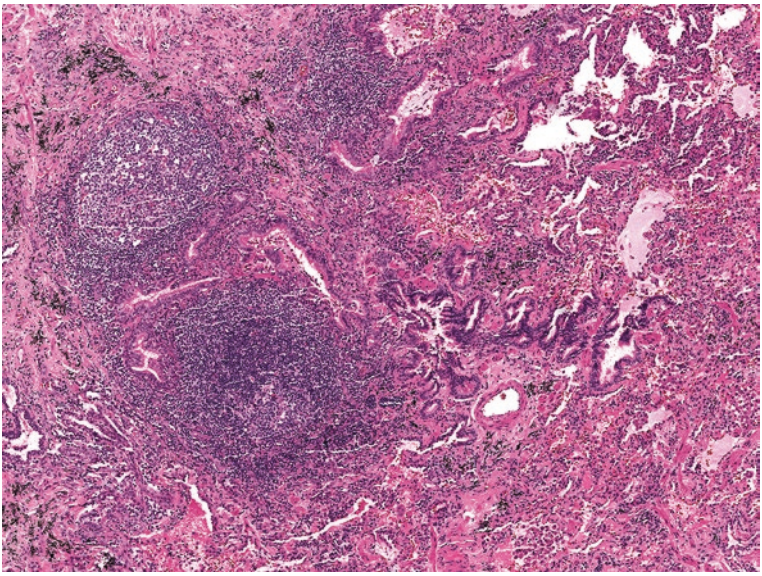

Fig. 7.6 Follicular bronchiolitis. Low magnification view shows lymphoid follicles with germinal centers that surround a bronchiole

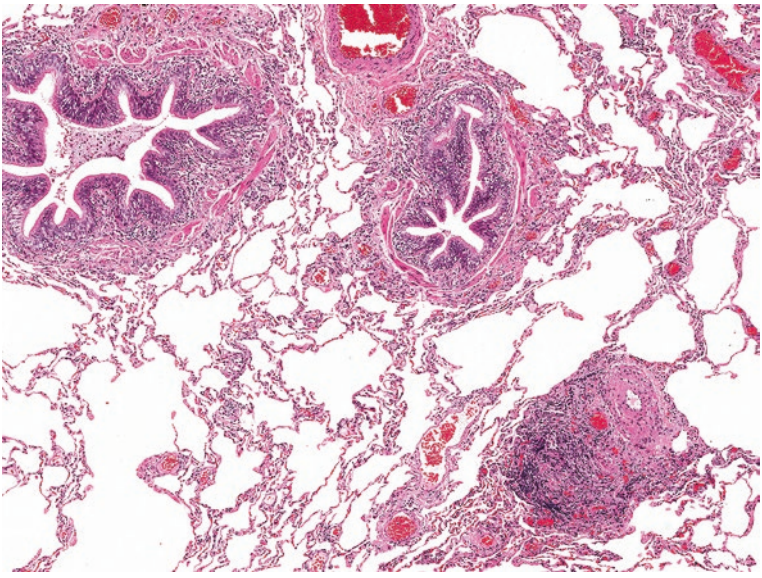

Fig. 7.7 Obliterative bronchiolitis. Low magnification view shows two bronchioles (*upper left*) with subepithelial chronic inflammation and fibrosis and a bronchiole with fibrous obliteration (*lower right*, identified by its proximity to a paired pulmonary artery)

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].

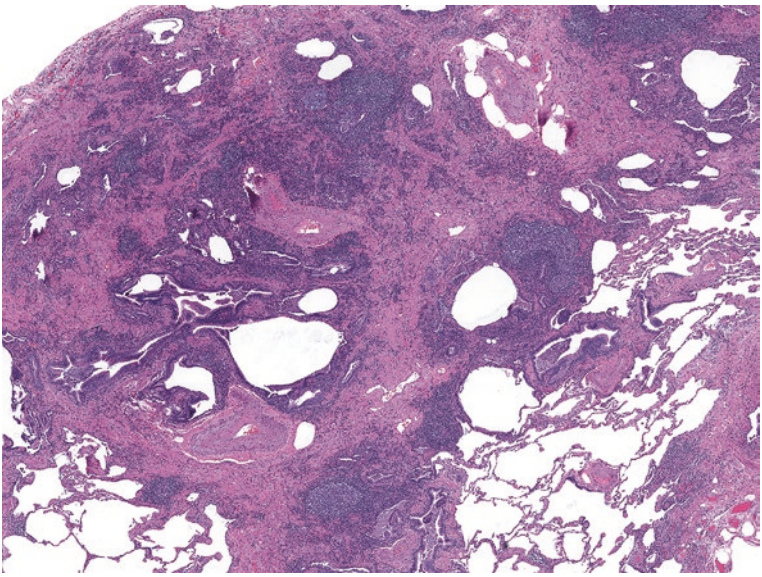

Fig. 7.8 Usual interstitial pneumonia with lymphoid hyperplasia. Low magnification view showing marked interstitial fibrosis with microscopic honeycombing (*upper left*) and the nearly normal lung (*lower right*). There are several lymphoid aggregates around bronchioles consistent with follicular bronchiolitis

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.

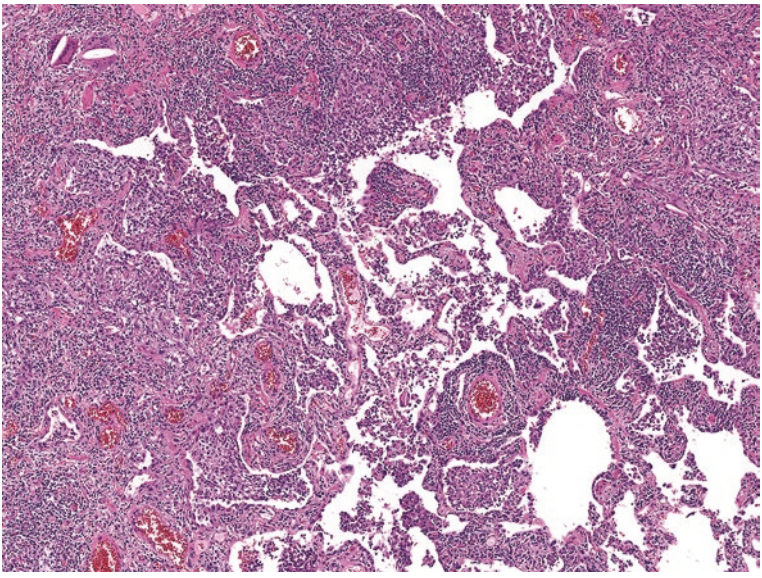

Fig. 7.9 Methotrexate toxicity. There is diffuse alveolar septal thickening by lymphocytic interstitial inflammation. A poorly formed granuloma is present (*upper left*) composed of two multinucleate histiocytes with cytoplasmic cholesterol clefts

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

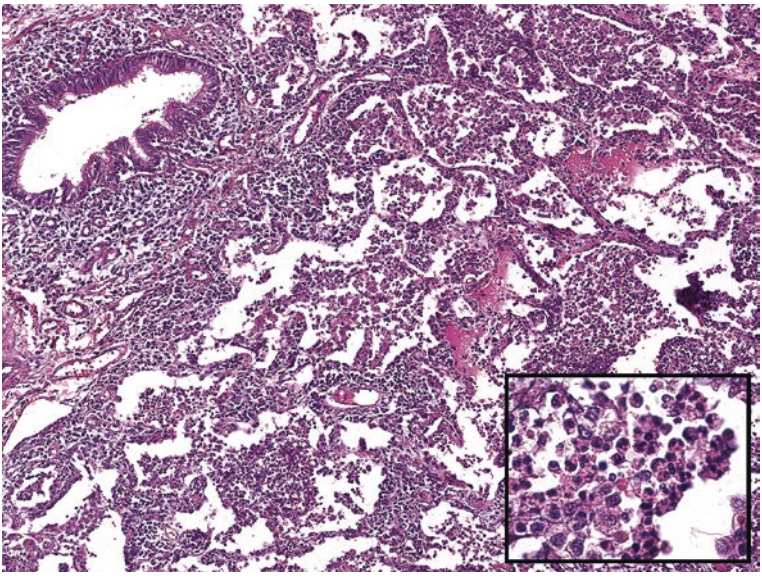

Fig. 7.10 Acute bronchopneumonia. Low magnification view shows alveolar filling with neutrophils and fibrin (inset shows high magnification of alveolar space)

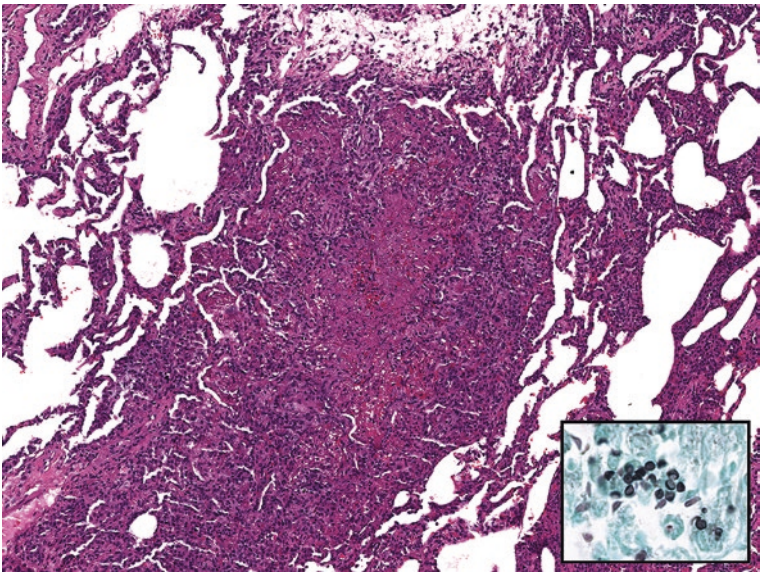

Fig. 7.11 *Pneumocystis* pneumonia. Low magnification view shows a nodular region of fibrin-rich necrosis with surrounding mixed lymphohistiocytic inflammation. High magnification (inset, GMS stain) shows typical irregular spherical structures of *Pneumocystis*

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.

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Chapter 8
Rheumatoid Arthritis-Associated Interstitial Lung Disease

Julie Morisset and Joyce S. Lee

Introduction

Interstitial lung disease (ILD) is a frequent extra-articular manifestation of rheumatoid arthritis (RA) [1]. RA-ILD significantly impacts prognosis and is associated with increased morbidity and mortality [2–4]. The diagnostic process can be challenging as the initial symptoms can be minimal or go unrecognized. Moreover, the differential diagnosis of diffuse lung disease in RA encompasses a wide variety of diagnoses ranging from drug-induced lung toxicities to opportunistic infection and other types of RA lung disease (see Chap. 10). Due to its impact on prognosis and quality of life, RA-ILD requires prompt diagnosis to ensure optimal care.

Epidemiology of RA-ILD

In 1948, Ellman and Ball reported the first case series of patients with rheumatoid lung disease [5]. These three patients presented with diffuse lung disease on chest x-ray, and the two available autopsies revealed chronic fibrotic pneumonitis. Since then, the prevalence estimates of RA-ILD differ depending on the diagnostic definition, the population being studied, and the mode of detection being used. A wide range of prevalence estimates, varying between 1 and 58%, has been reported [1, 3, 6–16].

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High-resolution computed tomography (HRCT) is more sensitive than conventional chest x-ray to detect ILD [17]. In a cohort of patients with a recent diagnosis of RA, HRCT identified abnormalities compatible with ILD in 33% of patients, while chest x-ray detected abnormalities in only 6% of patients [14]. HRCT has also been shown to allow identification of subclinical ILD or interstitial lung abnormalities (ILA) in patients with RA without any respiratory symptoms. These radiographic abnormalities are seen in up to 44% of RA patients [7, 14, 18, 19]. Furthermore, in population-based studies, the 30-year incidence of clinically significant RA-ILD has been reported to vary between 6 and 8% of patients with RA [2, 20]. Although ILD is a common extra-articular manifestation of RA, it is believed to still remain under-recognized [21].

Risk Factors

Several risk factors have been linked to the development of RA-ILD (Table 8.1). Increased age has been identified as a significant predictor of RA-ILD [21, 22]. On multivariable regression analysis in a cohort of 356 RA patients, age greater than

Table 8.1 Risk factors for the development of rheumatoid arthritis-associated interstitial lung disease (RA-ILD)

Risk factor	Study/year	Details
Age	Doyle et al. [21]/2015	Older age associated with clinically evident RA-ILD (AUC = 0.8)
	Mori et al. [22]/2012	Age > 65; relative risk ratio for RA-ILD: 4.58 95%CI (1.67–12.53)
Male gender	Mori et al. [22]/2012	Male gender relative risk ratio for RA-ILD: 1.45 95%CI (0.36–5.84)
	Kelly et al. [23]/2014	Male gender associated with RA-ILD: OR 1.67 95% CI (1.2–2.2)
	Weyand et al. [24]/1998	RA-ILD more frequent in male patients ($p < 0.001$)
Smoking history	Doyle et al. [21]/2015	Ever-smoking history associated with clinically evident RA-ILD (AUC = 0.56)
	Kelly et al. [23]/2014	Ever-smoking history associated with RA-ILD: OR 1.91 95% CI (1.3–2.7)
Rheumatoid factor (RF)	Doyle et al. [21]/2015	Positive RF associated with clinically evident RA-ILD (AUC = 0.69)
	Mori et al. [22]/2012	Positive RF relative risk ratio for RA-ILD: 3.14 95% CI (1.17–8.42)
	Kelly et al. [23]/2014	Positive RF associated with RA-ILD: OR 2.81 95% CI (1.8–4.1)
Anti-cyclic citrullinated peptide (CCP) antibody	Doyle et al. [21]/2015	Positive CCP antibody associated with clinically evident RA-ILD (AUC = 0.76)
	Mori et al. [22]/2012	Positive CCP antibody relative risk ratio for RA-ILD: 2.73 95% CI (0.91–8.23)
	Kelly et al. [23]/2014	Positive CCP antibody associated with RA-ILD: OR 2.81 95% CI (1.8–4.1)
	Giles et al. [27]/2014	Higher titers of CCP antibodies associated with higher ILD score ($p = 0.001$)

AUC area under the curve, *OR* odds ratio

65 years was associated with a 4.58-fold increased risk of ILD [22]. Male gender is also independently associated with RA-ILD [22–24]. In a multicenter cohort of 230 RA patients, male gender was found to be a significant predictor of RA-ILD (OR 1.67, 95% CI = 1.2–2.2) [23]. Smoking history is associated with an increased risk of RA [25, 26] and a greater risk of developing RA-ILD [21, 23]. The severity of RA may also be influenced by smoking exposure in a dose-dependent manner [26].

The presence of either rheumatoid factor (RF) or anti-cyclic citrullinated peptide (CCP) has also been found to be significant predictors for the development of ILD in RA [21–23]. There may be a relationship between the titer of CCP antibodies and the risk of ILD, as higher titers of CCP have been shown to correlate with more extensive RA-ILD on HRCT [27]. Finally, a model including a combination of these risk factors (older age, male sex, ever-smoking history, positive RF, and positive CCP) has an area under the curve between 0.82 and 0.86 to predict clinically evident RA-ILD and between 0.89 and 0.98 to predict subclinical ILD [21].

Clinical Presentation of RA-ILD

ILD can be diagnosed in the setting of long-standing RA, be identified at the time of RA diagnosis, or precede the onset of the articular symptoms [23, 28–33]. Patients with RA-ILD commonly report dyspnea (at rest and/or on exertion), exercise limitation, and dry cough [32, 34–37]. Shortness of breath can be minimal or difficult to recognize in the earlier stage of the lung disease given the physical limitation associated with their articular disease [38]. Less frequently, patients may present with chest pain, wheezing, and productive cough [39, 40].

Some patients with RA are identified to have subclinical ILD or ILA and don't report clinical symptoms, although their high-resolution computed tomography (HRCT) and/or pulmonary function tests are abnormal [14, 18, 21]. In a cohort of RA patients, Doyle et al. described the clinical characteristics of patients with ILA on HRCT [41]. Although patients with ILA had an array of disease severity and functional impairment, they were more likely to have lower forced expiratory volume in 1 s (FEV1) and forced vital capacity (FVC) % predicted than patients without ILA [41]. The clinical significance of subclinical ILD in RA remains to be determined, although some data suggest that the radiological abnormalities will progress over time in a subset of patients [7, 42].

Diagnostic Evaluation of Patients with Suspected RA-ILD

Although RA-ILD frequently presents as respiratory symptoms in patients with a known diagnosis of RA, the onset of ILD has been reported to occur prior to the diagnosis of RA [23]. Accordingly, patients being investigated for a new diagnosis of an ILD should be questioned about symptoms that may suggest an underlying connective tissue disease (CTD). Moreover, physicians often perform serologic testing (including RF and CCP antibodies) in their initial work-up to

screen for the presence of an occult CTD [43]. Sometimes the work-up of ILD will lead to a clear diagnosis of RA, while another subset of patients with ILD will have a positive serologic profile without clinical evidence of RA [29]. A cohort of 74 patients with lung disease and positive CCP antibodies but no clinical evidence of RA has been described [29]. In this cohort, only 3 patients (9%) went on to develop articular manifestations of RA after a median follow time of 449 days [29]. This study supports the hypothesis that the lung may be an initial site in the pathogenesis of RA [33, 44, 45]. More studies are needed to better understand the natural history of these patients with ILD and positive serologies for RA but no clear RA diagnosis [46].

The development of respiratory symptoms in patients with RA or the presence of articular symptoms in a patient being evaluated for ILD should raise the suspicion of RA-ILD (Fig. 8.1). In patients with RA, other types of RA lung disease need to be considered [47], as well as the exclusion of drug toxicity and opportunistic infection [38]. ILD has been reported as a potential complication of many drugs used for the management of RA like methotrexate, TNF-alpha inhibitors, rituximab, tocilizumab, cyclophosphamide, and leflunomide [48–52]. Patients on immunosuppressive medications are at higher risk of opportunistic infections that can cause diffuse

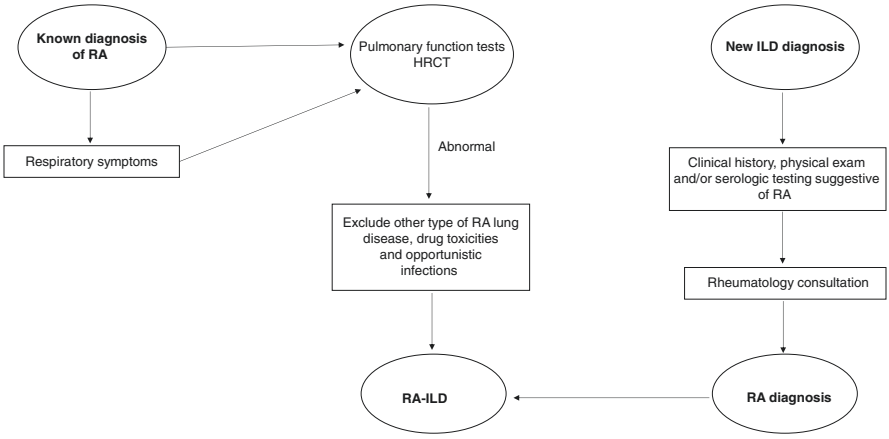

Fig. 8.1 Diagnostic approach to patients with rheumatoid arthritis-associated interstitial lung disease. When evaluating patients with a known diagnosis of rheumatoid arthritis (RA) presenting with respiratory symptoms, clinicians should perform appropriate investigations to exclude other types of RA lung disease, drug toxicities, and opportunistic infections. Pulmonary function tests and high-resolution computed tomography should be performed to better characterize the lung disease and its functional impairment. In patients being evaluated for a new ILD diagnosis, symptoms and signs, on either clinical history and physical exam or serologic testing suggestive of RA, should prompt a referral to rheumatology. In either clinical scenario, RA-ILD can be diagnosed when both a diagnosis of RA and ILD can be established. Abbreviations: *RA* rheumatoid arthritis, *HRCT* high-resolution computed tomography, *ILD* interstitial lung disease, *RF* rheumatoid factor, *CCP* anti-cyclic citrullinated peptide

lung disease and mimic ILD (e.g., *Pneumocystis jirovecii*, *Mycobacterium*, or fungal infections) [53].

A complete clinical history and physical exam are the first steps in the evaluation. Patients may report non-specific respiratory symptoms such as shortness of breath, cough, wheezing, or chest pain [32, 33, 37]. The physical exam may reveal crackles, but clubbing, wheezing, or signs of right heart failure can also be present [6, 7].

HRCT is essential in the evaluation of patients with suspected RA-ILD. It allows for the characterization of the radiological pattern and assessment of the disease severity [11, 39, 54]. Ground-glass opacities and reticulations are the most common HRCT findings [54]. The most frequently encountered HRCT patterns are usual interstitial pneumonia (UIP), non-specific interstitial pneumonia (NSIP), and organizing pneumonia (OP) [54]. Similar to IPF, HRCT has been shown to be an effective tool to identify the UIP pattern in RA-ILD. The presence of UIP pattern on HRCT is highly specific for the presence of UIP pattern on surgical lung biopsy [55].

Pulmonary function tests (PFTs) are also fundamental to assess the physiologic severity of RA-ILD and are a useful test to monitor disease activity over time. Among patients with RA, up to 30% of patients will have abnormal PFTs [40]. Common findings on PFTs include evidence of restriction and a reduced diffusion capacity (DLCO) [36, 37, 41].

Bronchoscopy and bronchoalveolar lavage (BAL) are often not required in the work-up of patients with RA-ILD because it adds little value to the diagnostic process, unless there is a high suspicion for infection [56]. Cellularity may be increased in the BAL of these patients [57], although this does not correlate with extent of disease on HRCT [56]. BAL can be useful to exclude an opportunistic infection when clinically suspected [38, 56].

Similar to other forms of CTD (e.g., scleroderma), a surgical lung biopsy is rarely required in the diagnosis of RA-ILD [38]. At this time, the identification of the underlying histopathologic pattern is not part of the diagnostic and treatment algorithm of patients with RA-ILD. Surgical lung biopsy may be indicated in cases where the etiology of the lung disease is not clear in an RA patient. In patients with RA-ILD who undergo a surgical lung biopsy, the most frequently reported histopathologic patterns are UIP, NSIP, OP, lymphocytic interstitial pneumonia, and diffuse alveolar damage [58, 59].

Currently, there are no biomarkers that are diagnostic for RA-ILD or have utility in predicting disease progression. Doyle et al. recently demonstrated that the addition of a biomarker signature to a model of clinical and serologic variables (age, gender, smoking history, RF, and CCP antibodies) can increase the model's ability to predict the presence of RA-ILD and potentially facilitate an earlier diagnosis of RA-ILD [21]. The biomarker signature they proposed consists of matrix metalloproteinase-7 (MMP-7), pulmonary and activation-regulated chemokine (PARC), and surfactant protein D (SP-D). The role of these biomarkers in disease progression is unknown.

Phenotypes of RA-ILD

As previously mentioned, many different radiologic and histopathologic patterns have been described in patients with RA-ILD. Often, patients are categorized as having either a UIP or a non-UIP pattern of disease. There are accumulating data suggesting that RA patients with a UIP pattern exhibit a different phenotype, clinical evolution, and prognosis compared to RA patients without a UIP pattern of disease [4, 11, 32, 56, 58, 59]. In RA-ILD, the UIP pattern has been more frequently described in older, male patients with a history of smoking [4, 11, 58–60]. Notably, this is the clinical phenotype often associated with the idiopathic form of UIP (i.e., idiopathic pulmonary fibrosis) [43]. Moreover, RA-ILD patients with a UIP pattern appear to have a worse overall prognosis than RA-ILD patients with a non-UIP pattern, and a survival pattern appearing similar to patients with IPF [4, 61], though the data are conflicting [62]. RA-ILD patients with a UIP pattern are also reported to have more respiratory-related hospitalizations [32].

Natural History and Prognosis

ILD is one of the leading causes of death in patients with RA [63, 64]. A population-based study demonstrated that the mortality rate in RA-ILD is increasing despite the overall decline in RA mortality [3]. Patients with RA-ILD tend to die younger and are more likely to die from their lung disease or have an RA-related death compared to RA patients without ILD [3].

Various predictors of mortality in patients with RA-ILD have been described [4, 59, 65–69]. Patient-specific variables (e.g., age, male sex, and low socioeconomic status), ILD-specific variables (e.g., DLCO, FVC, extent of fibrosis on HRCT, and UIP pattern either on HRCT or surgical lung biopsy), and RA-specific variables (e.g., baseline pain, disease activity score, and disability score) have been shown to be associated with mortality in RA-ILD [69]. Of these variables, only a few have been identified to be independent predictors of mortality in multivariable models (Table 8.2) [69]. Age is the only variable that has been identified as a significant predictor on multivariable analysis in multiple studies. A recent systematic review highlighted the variable methodological quality of studies evaluating predictors of mortality in RA-ILD as many of them lacked multivariable analysis [69].

In general, patients with RA-ILD tend to experience disease progression over time [7, 42, 62]. Acute exacerbations (AE) have been described in some patients with RA-ILD [62, 70]. Risk factors for AE in RA-ILD include older age at ILD diagnosis, UIP pattern on HRCT, and use of methotrexate [70]. AE of RA-ILD is associated with increased mortality [70]. Finally, patients with RA-ILD are at risk of serious infections requiring antibiotic therapy and hospitalization [53]. Pneumonia is the most frequent infection (3.9 cases per 100 person-year), and a prednisone dose greater than 10 mg daily is associated with an increased risk of serious infection [53].

Table 8.2 Independent predictors of mortality on multivariate analysis in rheumatoid-associated interstitial lung disease

Study/year	Sample size	Predictor	Hazard ratio (95% CI)
Dixon et al. [66]/2010	367	Age (per decade)	2.28 (1.64–3.15)
		Disease activity score (DAS28 score [71])	1.43 (1.11–1.85)
Kim et al. [4]/2010	82	Female sex	0.30 (no CI provided) (*p*-value, 0.008)
		Baseline DLCO% predicted	0.96 (no CI provided) (*p*-value, 0.003)
		Definite UIP pattern on HRCT	2.34 (no CI provided) (*p*-value, 0.05)
Koduri et al. [67]/2010	52	Age at onset	1.04 (1.00–1.09)
Solomon et al. [59]/2013	48	Age (per year)	1.04 (no CI provided) (*p*-value, 0.01)
		Presence of fibrosis on surgical lung biopsy	2.1 (no CI provided) (*p*-value, 0.02)
Solomon et al. [68]/2015	137	Age (year increase over 64.7)	1.06 (1.03–1.10)
		Ever-smoking history	2.05 (1.03–4.08)
		FVC % predicted (10% lower than mean baseline FVC % predicted)	1.36 (1.16–1.60)

CI confidence interval, *DLCO* diffusing capacity of the lung for carbon monoxide, *UIP* usual interstitial pneumonia, *HRCT* high-resolution computed tomography, *FVC* forced vital capacity

Conclusion

RA-ILD is a prevalent pulmonary manifestation of RA. It is associated with reduced survival and substantial morbidity. Early diagnosis remains a challenge in RA-ILD due to the non-specific symptoms at initial presentation. There may be important disease phenotypes within RA-ILD, but the current paradigm does not support identification of radiologic or histopathologic forms of RA-ILD to guide management. Further research is needed to better characterize and identify these phenotypes in order to provide personalized and comprehensive care to RA-ILD patients.

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Chapter 9
Management of the Rheumatoid Arthritis Patient with Interstitial Lung Disease

Meghna Jani, William G. Dixon, and Eric L. Matteson

Introduction

The management of rheumatoid arthritis (RA) has changed dramatically over the past 15–20 years. New classification criteria for RA have been introduced [1] that allow the study of patients earlier in their disease course, and recommendations have been developed to treat patients with RA using a strategic

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approach by targeting an optimal outcome, with the primary goal of joint disease remission [2, 3]. The armamentarium of treatments available for the treatment of RA has also expanded. However, with the introduction of novel therapies comes a wider choice in selecting the best treatment for the individual patient not only in terms of comparative efficacy but also safety in the presence of comorbidities.

Interstitial lung disease (ILD) is one of the most common respiratory manifestations in patients with RA and is a major cause of morbidity and mortality. RA-ILD encompasses several histopathologic patterns; the most frequent considered here are usual interstitial pneumonia (UIP), nonspecific interstitial pneumonia (NSIP), and obstructive pneumonia (OP). The development of respiratory complications of treatment is thus particularly problematic in patients with such coexistent lung disease, and there have been many reports of respiratory complications of both non-biologic disease-modifying antirheumatic drugs (nbDMARDs) and biologic DMARD (bDMARD) therapy. Clinicians are frequently encountered with decisions about balancing risk and benefit of treatments in patients with RA-ILD who have active articular disease. Serious respiratory adverse events (SRAEs) in the patient with RA on treatment for their joint disease may be due to induction of 'pneumonitis' or idiosyncratic adverse drug reactions (ADRs), acceleration of pre-existing ILD or increased predisposition to infection in a susceptible host. Several nbDMARDs and bDMARDs have been implicated in the development of ILD. Conversely, treatment of the underlying disease process may be beneficial in halting the progression of the lung disease. This chapter first considers methods for assessing drug safety and then reviews the available evidence for respiratory outcomes of nbDMARDs and bDMARDs in RA-ILD and the role of additional immunosuppression and overarching recommendations for patient assessment and management of ILD.

Detection Safety Assessment Methods

Clinical Trials

Whilst randomised controlled trials (RCTs) are considered the gold standard in assessing efficacy of treatments, they have limited utility in terms of assessing safety. Although safety has been evaluated as part of a number of RCTs, uncommon events such as new-onset ILD may not be captured. RCTs often have restrictive eligibility criteria to ensure a homogenous population (leading to exclusion of patients with known RA-ILD), small numbers of patients and a short follow-up period. This also limits their external validity, as real-life patients may be older and have multiple comorbidities compared to trial patients. Open-label extension (OLE) studies are often an adjunct to double-blind RCTs, and although they do allow surveillance of participants for a longer duration, patients who are intolerant to the drug

during the previous study will not be able to participate in the extension period, therefore potentially leading to underreporting of adverse events (AEs). OLE studies also lack a comparator group and are prone to loss to follow-up, making it difficult to interpret the rate of AEs.

Spontaneous Pharmacovigilance

Post-marketing spontaneous pharmacovigilance involves the reporting of suspected adverse drug reactions by healthcare professionals or patients. This is done either in the form of case reports/series to medical journals or to national or international monitoring centres, such as the UK Medicines and Healthcare products Regulatory Agency (MHRA) 'Yellow Card Scheme', European Medicines Agency EudraVigilance database and the US Food and Drug Administration (FDA) MedWatch programme. Whilst these are useful for drug safety signal detection, there is no available denominator to calculate rates of AE or to determine whether these reported cases represent an increased incidence above the background population rate.

Observational Cohort Studies

Observational cohorts have the advantage of being able to examine drug safety in a 'real-world' setting and can follow large numbers of patients for long periods of time. They can therefore study the medium- to long-term side effects of a drug that might otherwise be missed in clinical trials or spontaneous pharmacovigilance. However these come with the challenge of interpreting results in the context of clinical decisions, with their consequent biases and confounding.

Each of these methods can employ a wide array of terminology to describe various forms of respiratory AEs. For example, parenchymal lung disorders are called many things from 'pulmonary fibrosis' to 'allergic pneumonitis'. There are also challenges in differentiating between respiratory conditions with different aetiologies but similar clinical presentations. RCTs, for example, can report on culture-negative pneumonias or 'community-acquired pneumonitis', which may indeed be idiosyncratic drug reactions or pneumonias secondary to a resistant microorganism: often patients are administered a combination of glucocorticoids and antibiotics due to initial uncertainty of the diagnosis.

The data available for this chapter come from all of the above study designs. Having been in use for RA for the longest duration, nbDMARDs and tumour necrosis factor inhibitors (TNFis) have the most observational evidence, but not in all cases. Newer TNFis, nbDMARD and emerging novel therapies recently licensed for RA have not had the opportunity for longer follow-up; therefore, experience about pulmonary safety may be restricted to clinical trials and spontaneous pharmacovigilance.

Respiratory Safety of Non-Biologic Disease-Modifying Antirheumatic Drugs

Methotrexate

Methotrexate (MTX) has been described as the anchor drug in RA treatment, as it is often used first line at diagnosis, in combination with other nbDMARDs and concomitantly with biologics, following failure of traditional nbDMARDs for controlling articular disease. It inhibits folic acid and purine metabolism along with T-cell activation. MTX-induced pulmonary injury was initially reported in children with leukaemia in the 1960s [4], followed by a case series in treated patients with RA in 1983 [5]. Following a review of 123 cases of methotrexate pneumonitis in the year 2000, 63% of cases arose in patients with RA (dose range 2.5–15 mg/week), 23% occurred during intensification/consolidation treatment for leukaemia (dose range 20–80 mg/week), and 8% were in patients treated for other malignancies (dose range 15–1400 mg/week) [6]. Whilst mortality rates have been reported up to 17%, hypersensitivity pneumonitis is reported to be a rare AE in RA patients. In a systematic literature review of 3463 patients with RA on MTX, 84 patients (2%) had some type of lung toxicity, but only 15 patients were felt to be definitive cases of pneumonitis attributable to methotrexate (0.43%) [7]. Estimates of reported incidence vary between 0.43 and 1% of treated patients (in up to 3-year follow-up) [8, 9].

Classification of MTX Pneumonitis

The clinical presentation of acute MTX pneumonitis is generally nonspecific, with symptoms (fever, rigors, malaise, nonproductive cough, dyspnoea, chest pain) that can be progressive over several days. Criteria proposed by Searles and McKendry [10] and Carson et al. [11] are generally accepted for defining MTX pneumonitis and can sometimes help in differentiating the disease from RA-ILD and respiratory infections, although it is possible to fulfil the criteria with conditions other than pneumonitis, for example, infection or a progression of pre-existing RA-ILD (Table 9.1). Searles and McKendry criteria have since been adapted by Kremer et al. [12] categorising them into major and minor. All rely on a combination of clinical features, radiological, histology and exclusion of infection.

Studies have explored other factors that might differentiate these clinically similar respiratory diseases. Histological findings in MTX pneumonitis such as cellular interstitial infiltrates, diffuse alveolar damage, tissue eosinophils and granuloma formation are nonspecific and have all been seen in RA lung disease [6]. High-resolution computer tomography (HRCT) studies in MTX pneumonitis typically show ground-glass changes, centrilobular nodules +/− diffuse parenchymal opacification [13]. Bronchoalveolar lavage (BAL) cell profiles in MTX pneumonitis show a lymphocyte alveolitis with a preferential increase in CD4+ cells compared to normal RA controls [14, 15], though comparisons have not been made between BAL in

Table 9.1 Various criteria for diagnosis of methotrexate-associated pneumonitis

Carson et al. [11]	Searles and McKendry criteria [10]	Kremer et al. [12]
Clinical 1. Clinical course consistent with hypersensitivity *Radiology* 2. Resolving infiltrates on chest radiograph after discontinuing methotrexate *Exclusion of infection* 3. Exclude infection or other pulmonary disease *Histology* 4. Pathology consistent with drug-induced injury (i.e. hypersensitivity pneumonitis or toxic drug reaction Probable: 3 or 4 criteria Possible: 2 criteria Unlikely**:** 1 criterion	*Clinical* 1. Acute onset dyspnoea 2. Fever >38.0 °C 3. Tachypnoea ≥28/min and dry cough 4. Radiological evidence of pulmonary interstitial or alveolar infiltrates *Laboratory* 5. White blood cell count ≤15.0×10^9 with or without eosinophilia 6. PO_2 <7.5 kPa on air *Exclusion of infection* 7. Negative blood or sputum cultures (mandatory) *Pulmonary function tests* 8. Restrictive defect and decreased diffusion capacity on pulmonary function tests *Histology* 9. Consistent with bronchiolitis or interstitial pneumonitis with giant cells and without evidence of infection Definite ≥6 criteria Probable 5 of 9 criteria present Possible 4 of 9 criteria present	Major criteria *Histology* 1. Hypersensitivity pneumonitis by histopathological examination (without evidence of pathogenic organisms) *Radiology* 2. Radiological evidence of pulmonary interstitial or alveolar infiltrates *Exclusion of infection* 3. Blood (if febrile) or initial sputum cultures negative for pathogenic organisms Minor criteria *Clinical* 1. Shortness of breath <8 weeks 2. Dry cough *Laboratory* 3. Oxygen saturation <90% 4. White blood cell count ≤15.0×10^9 *Pulmonary function tests* 5. DLCO <70% predicted *Definite* – Major criteria 1 – Major criteria 2 and 3 and at least 3 minor criteria *Probable* – Major criteria 2 and 3, and 2 minor criteria

DLCO diffusing capacity of the lungs for carbon monoxide

MTX pneumonitis and RA-ILD. A challenge with all these studies is the problem of measuring the accuracy of a test against no accepted gold standard.

Prevalent RA-ILD and MTX Pneumonitis

It has been argued on several counts that MTX hypersensitivity pneumonitis is a unique hypersensitivity reaction rather than the development or progression of RA-ILD. Firstly, MTX-associated lung injury tends to occur early in the

course of MTX therapy [16], the close temporal relationship arguing in favour of causality. Secondly, acute lung injury has resolved after discontinuation of the drug and treatment with high-dose glucocorticoids [5]. Lastly, case reports of ILD have been reported in other conditions including psoriatic patients treated with MTX [6, 17] as well as in other conditions not typically associated with ILD.

However, there are issues with each of these arguments. Clinicians are more likely to diagnose and report MTX pneumonitis if there is a close temporal relationship. If cases in question are identified by asking rheumatologists to identify them [16], it is inevitable that a strong temporal relationship will be found. The second argument of resolution on drug withdrawal would be more convincing if there were no concurrent glucocorticoid treatment. Acute exacerbations of ILD, which may resemble drug pneumonitis, tend to be responsive to glucocorticoids. That said, there are cases of improvement on MTX withdrawal with no increase in pre-existing glucocorticoid dose [14]. Third, dose and duration of MTX treatment does not appear to be associated with pulmonary toxicity in the reported literature [6]. Furthermore a recent systematic review and meta-analysis evaluating the risk of pulmonary disease amongst MTX-treated patients with psoriasis, psoriatic arthritis and inflammatory bowel disease in RCTs concluded no increased risk [18].

It is not clear whether pre-existing RA-ILD increases the risk of MTX pneumonitis with studies both supporting and opposing this view. The largest study was a multicentre case-control study from the USA [12, 19], which identified 29 cases and 82 controls matched for MTX use. The strongest predictors of lung injury were diabetes, hypoalbuminaemia, previous use of nbDMARDs, rheumatoid pleuropulmonary involvement (OR 7.1 (95% CI 1.1–45.4)) and older age (>60). A history of COPD was modestly associated with MTX-induced lung injury. Since all the cases were identified following clinical presentation, the observed association between pre-existing lung disease and MTX pneumonitis may represent an increased likelihood of presentation (because of a reduced physiological lung reserve) or a surveillance bias rather than an increased predisposition to pneumonitis. Meta-analysis of six studies that suggested an association between pre-existing lung disease (of varying definitions) and an increased risk of MTX pneumonitis found a pooled odds ratio of 7.5 (95% CI 3.6, 15.8) [20]. However, two studies that suggested no such association [11, 21] were not included in the meta-analysis for reasons that are not clear. Howes et al. [22] followed 120 patients who received MTX for RA for a median treatment duration of 15 months, all of whom had baseline PFTs. Three patients developed pulmonary toxicity according the established criteria [5], all of whom had abnormal baseline PFTs. Of the patients studied, 3/120 patients had a transfer factor of <70% at baseline, one of whom developed pulmonary toxicity. The authors report a relative risk for pneumonitis of 10, though this estimate is not robust given the small numbers.

Progression of RA-ILD on MTX

There is currently no conclusive evidence that lung function is likely to decline faster in patients with RA-ILD on MTX who do not develop pneumonitis. In a retrospective cohort analysis, following 6 weeks of high-dose glucocorticoid treatment, one study reported treatment with MTX vs. leflunomide or azathioprine was associated with an improvement in FVC at 6 months in patients with less fibrosis at baseline, although there were no another differences in other major outcomes such as mortality [23]. Another study by Dawson et al. [7] followed 128 patients with RA for 2 years, 43% of whom were on low-dose MTX (mean 10.7 mg/week), with HRCT in all patients at baseline and pulmonary function tests (PFTs) at baseline and at 4-month follow-up intervals. There was no significant difference in the change in PFTs over the follow-up period either between the MTX and non-MTX patients or between MTX and non-MTX patients with proven ILD on HRCT at baseline. The authors concluded that they found no association between MTX therapy and progression of chronic pulmonary fibrosis.

Current guidelines on the use of MTX recommend that all patients should have a baseline chest radiograph with or without PFTs. There appears to be little evidence to support this; however, PFTs may be useful in patients with RA deemed to be at high risk of ILD or known to have RA-ILD to assess for progression (discussed further in section "Patient Management and Treatment"). In summary, diagnostic uncertainty and the lack of any gold standard test for MTX pneumonitis leaves ambiguity about the true pattern of disease. However MTX has not been shown to consistently accelerate the progression of underlying RA-ILD. Whilst few studies have been conducted in pre-existing RA-ILD stratified by severity of lung disease, the risk of pneumonitis means that it may not always be the safest first-line nbDMARD in patients with RA who have severe pre-existing lung disease.

Leflunomide

Leflunomide is an isoxazole derivative, which inhibits de novo pyrimidine synthesis, resulting in several downstream anti-inflammatory effects such as suppression of TNF-induced cellular responses and inhibition of matrix metalloproteinases and osteoclasts. Leflunomide-induced pneumonitis is rare but well reported. A signal of concern was raised in 2004 after an investigation by the Japanese Ministry of Health following post-marketing surveillance in 16 (0.5%) of the first 3000 Japanese patients treated with leflunomide, resulting in five fatalities [24, 25] and the Committee on the Safety of Medicines also reporting 17 cases in the UK of which five were fatal.

Further case reports have subsequently been reported especially in the Japanese and Korean populations [26–28]. However leflunomide is often used second line

after MTX exposure or in combination with MTX in patients with active articular disease, which make studies evaluating leflunomide-induced pneumonitis difficult to interpret. In a report of 14 such cases from Australia and New Zealand, 12 were co-prescribed MTX [29]. Chikura et al. [30] reported on 32 pneumonitis cases following leflunomide exposure, classified using Searles and McKendry criteria (Table 9.1), and found 97% had a history of MTX exposure, whilst 41% were on concomitant MTX at the onset of ILD. The majority presented within 20 weeks of initiation. Clinical features of those who died were pre-existing ILD and diffuse alveolar damage on histology (n = 6/32). Pre-existing ILD was also shown to be a risk factor for leflunomide-induced pneumonitis in a large case-control study using a Canadian claims database [31]. The risk of ILD was increased with the use of leflunomide (adjusted RR 1.9 [95% CI 1.1–3.6]); however, in patients without previous MTX exposure or ILD history, the risk associated with leflunomide treatment was not elevated (RR 1.2 [95% CI 0.4–3.1]). However, it was acknowledged given the probable association between prior ILD and MTX pneumonitis; clinicians may be more likely to prescribe leflunomide than MTX to patients with prevalent ILD, leading to channelling bias explaining the increased risk observed.

Leflunomide-induced pneumonitis appears to occur more frequently in Japanese and Korean population (reported rate ~1%) [26, 32], whilst in the Western Caucasian population, a rate of <0.1% is reported [33]. Genetic susceptibility in Japanese patients has been described in a study which investigated human leukocyte antigen (HLA) class I associations with MTX pneumonitis in Japanese patients with RA and found HLA-A × 31:01 as a possible predictor. The prevalence of this allele is proportionally higher in the Japanese population (8.7%) than in the Caucasian population (3.9%) [34]. Therefore such genetic differences and undiscovered genetic predictors may explain some of the differences in frequency observed in such populations.

Several risk factors of leflunomide-induced pneumonitis have been reported in small numbers of patients in case series and retrospective studies including pre-existing lung disease [32, 35, 36], a prescribed loading dose, smoking, low body weight [32] and increased C-reactive protein, hypoalbuminaemia, hypoxia and lymphopaenia [36]. Treatment includes cessation of the drug, treatment with glucocorticoids with some benefit reported with activated charcoal and cholestyramine as washout treatments. Whilst conclusions of use in RA-ILD are limited from studies due to channelling bias, leflunomide should be avoided in patients with previous MTX pneumonitis and should be used with caution in patients with pre-existing ILD.

Sulphasalazine

Sulphasalazine is a 5-aminosalicyclic acid (5-ASA) derivative metabolised to sulphapyridine, which is the active moiety in RA. Pulmonary hypersensitivity reactions such as eosinophilic pneumonias [37, 38], fibrosing alveolitis and

bronchiolitis obliterans have been well described, with over 50 case reports in the literature [39, 40]. Drug reaction with eosinophilia and systemic symptoms (DRESS) is also reported [41, 42]. Typical presentation of sulphasalazine-induced lung disease reported is with new-onset dyspnoea and infiltrates on chest radiograph (with or without peripheral eosinophilia with eosinophilic pneumonitis). Cough and fever are the most common symptoms with sputum production, whilst allergy history, rash, chest pain and weight loss were inconsistent findings [40]. Histology is often variable; the most frequent appears to eosinophilic pneumonia with interstitial inflammation with or without fibrosis. Drug cessation often results in resolution of symptoms in patients who develop eosinophilic pneumonia [43]. The role of systemic glucocorticoids is not well-studied, as most patients improve with withdrawal of sulphasalazine. There are no studies that have systematically evaluated the safety of sulphasalazine in pre-existing RA-ILD; however, it is worth observing that the rates of SRAEs with sulphasalazine appear much lower than those seen with methotrexate and leflunomide in the literature.

Hydroxychloroquine

Hydroxychloroquine is an antimalarial drug and is a 4-aminoquinoline derivative, often used in combination with other nbDMARDS. It is usually well tolerated and serious AEs are rare. Few cases of drug-induced pneumonitis exist [44], with some reports in association with drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome [45, 46]. Hydroxychloroquine has been tried in childhood ILD (diffuse parenchymal lung diseases) in case reports given the lack of therapeutic options. In a systematic review from 1984 to 2013 [47], 85 case reports were identified: a favourable response to hydroxychloroquine was reported in 35 cases (41%), with an unclear effect in the rest. Whilst idiosyncratic reactions leading to lung toxicity have been reported, no studies have demonstrated a benefit or harm of this drug in RA-ILD.

In summary, case report evidence for drug-induced pneumonitis exists for all nbDMARDs commonly used to treat joint disease; therefore, incident ILD may be a theoretical risk in most treated patients. With treat-to-target guidelines [2] and the eventual aim of abrogation of joint inflammation as soon as possible, most patients with RA are likely to be treated with a nbDMARD early in the course of their disease. Whether the risk of progression of RA-ILD or SRAEs increases with nbDMARDs is not clear and may vary according to the individual patient profile including their comorbidities, concomitant treatments, severity of ILD at the outset of treatment and their genotype. Evidence to date suggests caution should be exercised whilst treating patients with pre-existing RA-ILD with all nbDMARDs, particularly MTX and leflunomide, with careful monitoring of disease progression and vigilance for (sometimes rare) SRAEs associated with such treatments (summarised in Table 9.4).

Respiratory Safety of Biologic Disease-Modifying Antirheumatic Drugs

Tumour Necrosis Factor Inhibitors (TNFis)

Five TNFi agents have been approved for treating patients with RA: three monoclonal antibodies (infliximab, adalimumab and golimumab), the recombinant soluble TNF receptor etanercept and pegylated certolizumab. As biologic therapies such as TNFis target key cytokines and cells in the inflammatory cascade with pleiotropic effects on the immune system, there have been particular concerns regarding their long-term safety profile. Although these drugs are highly effective in controlling joint disease, and often are used as first-line biologics in combination with MTX, they are reported to be associated with various autoimmune AEs [48]. Whilst the most common of these appear to be lupus- and vasculitis-like events, TNFi-associated lung injury has been reported [49]. The safety of these drugs in patients with established RA-ILD continues to be scrutinised.

Conversely elevated levels of TNF-α have been detected in the lungs of both experimental animal models [50] and patients with idiopathic pulmonary fibrosis (IPF) [51]. Interestingly serum levels of TNF-α have also been found to be elevated in patients with rituximab-induced ILD [52]. Etanercept has been used in a randomised double-blind placebo-controlled exploratory trial in clinically progressive IPF subjects, however failed to show a difference in primary endpoint of improvement in FVC over 48 weeks. The study was underpowered; however, a non-significant reduction in disease progression was seen in several physiologic (including transfer factor), functional and quality-of-life endpoints amongst participants receiving TNFi. Importantly there was no decline in lung function or higher incidence of SRAEs in the etanercept group compared to placebo. Therefore whilst legitimate concerns about pulmonary toxicity have been highlighted, TNFi treatments may have plausible bidirectional effects. The next section will review the levels of evidence for both incident ILD and safety in pre-existing RA-ILD.

Randomised Clinical Trials and Case Reports

Clinical trials of TNFi therapy have been significantly underpowered to detect even a large increase in the incidence of serious RA-ILD. The original RCTs leading to eventual approval of TNFi provided no RA-ILD safety signals. In the first reported phase III trial of infliximab and MTX versus placebo and MTX over 30 weeks, there was a death in both the placebo arm due to ILD and the infliximab arm due to cardiopulmonary failure as a result of suspected pulmonary embolism or ILD [53]. In a two-year extension of this trial, there was a single death attributed to ILD in the infliximab arm; however, it was not clear whether this is the same patient reported in the previous paper.

A clinical trial of etanercept versus MTX in early RA reported three cases of pneumonitis in the MTX group at 1 year follow-up [54] and four cases at 2 year

follow-up [55] with no reported cases in the etanercept arm despite a ratio of etanercept/MTX of 2:1. There was one case of death from respiratory failure in the 5-year OLE of this study in the etanercept arm [56]. No cases of ILD were reported in the 7-year OLE of etanercept [57]. ILD was not reported in any of the initial adalimumab clinical trials, in either the adalimumab or placebo arms [58]. However, within an adalimumab OLE study [59], SAEs coded as 'parenchymal lung disorders' occurred at a rate of 0.2–0.3/100 patient-years, accounting for 20% of all SAE's. In this trial, however, there was no placebo-controlled or nbDMARD-exposed arm, making the interpretation of these figures challenging. Similarly no signal of concern for incident ILD was observed in the initial golimumab-RA trials [60, 61] in the two-year [62] or five-year [63] extension studies. In the certolizumab RAPID 1 and RAPID 2 trials [64, 65], and subsequent OLEs [66], no cases of drug-induced pneumonitis were reported in any arms.

Therefore original RCTs of TNFi agents did not raise concern over the potential development of ILD. These trials typically had short duration, included between 210 and 340 patients in the TNFi arm each and excluded patients with RA-ILD at baseline. Concerns regarding the respiratory safety of TNFi agents arose initially following three case reports of rapid fatal exacerbations of RA-associated fibrosing alveolitis following commencement of infliximab in 2004 [67], which was extended in a later publication to five cases [68]. Of these cases, three patients were taking concomitant azathioprine, and one taking leflunomide developed rapid progression of RA-ILD (known UIP preceding treatment). The fifth patient did not have a history of lung disease pretreatment and, following infliximab, developed nonfatal cryptogenic organising pneumonia (COP or bronchiolitis obliterans organising pneumonia [BOOP]) [68]. In a case series of autoimmune diseases associated with TNFi, 24/226 (~10%) were reported to develop ILD (interstitial pneumonitis in 18 patients, sarcoidosis in three, pulmonary haemorrhage in two and BOOP in one patient) [49]. Exacerbation of previous ILD was reported in four patients. Perez-Alvarez et al. described a further series of 122 patient case reports from the literature (89% with RA), with incident ILD or exacerbation of pre-existing ILD (20 patients, 38%) [69]. The outcome was available in 52 of the described cases: 21 (40%) had complete resolution, improvement or partial resolution in 13 (25%) and no resolution reported in 18 (35%). Case reports of incident ILD have been reported with newer TNFis such as certolizumab [70–73] and golimumab [74], including possible deterioration of pre-existing ILD in a patient with RA treated with certolizumab and leflunomide after 3 months of therapy [75]. Whilst the temporal association with onset of ILD and repeated reporting of such events provides a signal of concern, the interpretation of such data for extrapolation into clinical practice is limited by a likely reporting bias, a possible 'bandwagon' effect (a phenomenon where following the publication of an index case, further cases are consequently more likely to be reported), and lack of an adequate denominator. Furthermore, reports of stabilisation of RA-ILD in patients exposed to TNFi therapy have also been published [76–78], suggesting a further bidirectional influence of TNFi on ILD.

Observational Studies

To accurately evaluate the risk of incident ILD or exacerbation in patients with RA-ILD on TNFi in patients who are most likely to receive them in the real world, observational studies offer the best design to examine rare outcomes. However all studies evaluating such events have faced methodological issues, namely, with channelling bias and challenges with classification. Using the National Databank for Rheumatic Diseases, Wolfe et al. used a combination of hospital records, patient descriptive reports and physician and mortality records to classify patients who had severe RA-ILD (requiring hospitalisation or who died) [79]. They reported a significant association with previous use of infliximab (HR 2.1, 95% CI 1.1–3.8) and etanercept (HR 1.7, 95% CI 1.0–3.0). However the study was confounded by the fact that physicians were, at the time, prescribing TNFis for treatment of RA-ILD, possibly accounting for such an association. The incidence of hospitalisation for ILD requiring hospitalisation was reported 260 per 100,000 patient-years with a 27% mortality, likely reflecting the types of patients included in this analysis. Whilst the authors concluded that there was no evidence of an association between TNFi and hospitalisation for ILD as the observed effect with TNFi was likely to be due to confounding by indication, the specific effect of TNFi on patients with RA-ILD at baseline was not assessed [79].

Two claims database studies have evaluated ILD incidence in patients treated with biologics including TNFis. To assess the risk of incident ILD in 8417 patients with autoimmune diseases who were members of Kaiser Permanente, Northern California, Herrington and colleagues compared new users of TNFi and nbDMARDs [80]. ILD cases were identified using ICD codes, with a pilot of the first 100 cases verified using CT reports. The study demonstrated no increased risk in the TNFi-exposed group of new ILD; however, patients with known ILD at baseline were systematically excluded. Using data from the commercial claims and benefit (Medicare) databases, Curtis et al. assessed the ILD incidence and exacerbation amongst users of rituximab, abatacept and tocilizumab to TNFi agents [81]. Two definitions of ILD were used (one more sensitive, the other more specific in the absence of CT results and lung histology). There were no significant differences in the risk of ILD and its related complications between patients with RA receiving TNFis and those on non-TNFis. Of the patients' studies, 419 patients had a history of ILD, of which 232 were put on TNFi agents [81]. However there were clear baseline differences between the groups receiving the different drugs, which were not adjusted in the analysis. Therefore the true risk in the TNFi group may be confounded if patients with higher levels of RA joint disease or ILD disease severity were channelled to specific therapies, which may have led to an overall underrepresentation of risk in this group.

In a recent single-centre retrospective evaluation from Japan, Nakashita et al. described up to one-year outcomes of 163 RA patients with (n = 58) or without (n = 105) established ILD on a biologic drug [82]. In patients with established RA-ILD, 14 (24%) had an exacerbation of ILD, which the authors concluded was greater in patients exposed to TNFi agents using descriptive statistics. None of the

patients on tocilizumab ($n = 9$) or abatacept ($n = 3$) were reported to have an exacerbation; however, conclusions were limited due to low numbers. Similar to Curtis et al.'s study [81], it did not adjust for severity of RA or any confounders potentially introducing channelling bias. In this case, it is likely that patients on TNFi (approved earlier than the non-TNFi drugs in this study) had more severe disease at the outset, in turn is known to be associated with the outcome.

Data from the British Society for Rheumatology Biologics Register for RA (BSRBR-RA) evaluated the effect of TNFi in patients with RA who have established ILD [83] and reported no difference in all-cause mortality between patients on TNFis and nbDMARDs. However RA-ILD as an underlying cause of death was reported in a higher proportion of TNFi-treated patients than nbDMARD-treated patients (21 vs. 7%), suggesting a signal for concern. Methodological challenges included potential for misclassification, as prevalent ILD was identified from clinician questionnaires since attempts to retrospectively verify such cases were unsuccessful. Whilst it could be that TNFi truly increased the proportion of deaths attributable to RA-ILD, given the well-publicised respiratory concerns with TNFi, it may be that physicians at that time were more inclined to report RA-ILD on death certificates of patients exposed to TNFis leading to the observed relationship. PFTs, imaging or nonfatal exacerbation of ILD details were not available to examine the effect of treatment on such outcomes.

Challenges in interpreting the data common to all studies is delineating the effect of TNFi on RA-ILD in the presence of nbDMARDs, the majority of which are linked to reports of pneumonitis or exacerbation of RA-ILD. Furthermore, it can be difficult to ascertain if severity of RA associated with both development of ILD and also being the indication for TNFi could explain the association between TNFi and RA-ILD exacerbation. However, no studies have completely excluded a clinically meaningful risk, and the multiple case reports, observational evidence and possible increase in ILD-specific mortality in patients with known RA-ILD indicate that careful monitoring and caution is required when considering use in this setting.

Biosimilar Drugs

With several biologics approaching patent expiration, substantial interest has been in the development of biosimilar products that are not bioidentical but highly similar to already approved reference products listed above [84]. To date, biosimilar infliximab CT-P13 (marketed as Remsima and Inflectra) and biosimilar etanercept SB4 (marketed as Benepali) have been approved for use by the FDA and EMA. There were no cases of pneumonitis or ILD in the biosimilar infliximab CT-P13 trials in RA [85, 86] or ankylosing spondylitis [87], although there was a case of non-infective dyspnoea reported within the CT-P13 arm of the latter trial felt to be related to the drug by the investigators. Open-label extensions of these trials have not suggested a signal for concern [88, 89]. Similarly no cases of new ILD were reported with biosimilar etanercept SB4, albeit treatment-emergent AEs in ≥2% of patients were reported only [90]. One patient in the SB4 arm died due to cardiorespiratory

failure (felt to be unrelated to the drug by the investigators), and further details of the event were not provided [90]. Whilst this provides some initial reassurance, biosimilars should be considered as having similar risks to the originator reference products and therefore be used with vigilance in the context of established RA-ILD.

Non-tumour Necrosis Factor Inhibitor Biologics

Rituximab

Rituximab is a monoclonal chimeric anti-CD20 antibody licensed for the treatment of non-Hodgkin lymphoma and RA in TNFi nonresponders. Rituximab-induced ILD has been a well-described AE in haematology patients often presenting as acute/subacute hypoxaemic organising pneumonia, NSIP or hypersensitivity pneumonitis [91–93]. Whilst its pathogenesis is unknown, it may involve induction and release of cytokines, and it has been reported to occur in patients receiving rituximab for several months [94]. In RA, a number of rituximab trials have reported incident ILD [95–97], including subsequent deaths from acute respiratory distress syndrome (ARDS) [98] and culture-negative (non-infective) bronchopneumonia [99]. Hadjinicolaou et al. identified >120 cases of rituximab-associated ILD up to June 2010 in a systematic review of published studies and reports to the FDA and EMA [100]. In addition, UK spontaneous pharmacovigilance reporting systems (via its Yellow Card system) have recorded hundreds of rituximab-associated cases of non-infectious respiratory disorders till March 2016 (Table 9.2). Of the patients with possible rituximab-associated ILD/pneumonitis, 15 deaths have been reported (Table 9.2). Further observational evidence has been discussed in section "Other Agents with Limited Agents in RA-ILD").

Abatacept

Abatacept is a selective T-cell costimulation modulator. It is a fully human recombinant protein that comprises of the extracellular domain of CTLA4 and the Fc portion of an IgG1 molecule that has been modified to prevent complement activation. Pooled safety data from eight trials of abatacept involving 3173 patients with RA reported incident ILD in 11 patients (0.11 cases per 100 person-years), with no events reported in the placebo control groups [101]. Patients with pre-existing RA-ILD were excluded from all of the initial abatacept trials [101]. Therefore limited conclusions can be drawn from existing trial data, which may suggest a small increase in incident ILD in patients with RA.

Despite its FDA licence back in 2005, few case reports exist describing abatacept-induced lung injury. One case reported drug-induced respiratory failure, 2 weeks after the second abatacept dose [102], however was unable to distinguish if infection was the reason for deterioration by the time of death. Relatively few respiratory

Table 9.2 Non-infectious respiratory events related to non-tumour necrosis factor-targeted biologic agents reported to UK regulatory agencies

Drug	Licensing date (in RA unless otherwise stated)	Reported to UK MHRA to 2016	
		Type of event	Number (*n*, fatal)
Rituximab	1997 for lymphoma 2006 for RA by both the EMA and FDA	Interstitial lung disease[a] Obliterative bronchiolitis Alveolitis (including allergic) Pneumonitis Pulmonary vasculitis ARDS	36(8) 6(1) 5(1) 18(4) 1 6(1)
		Total non-infectious respiratory disorders	431
Abatacept	2005: FDA 2007: EMA	Pneumonitis	1
		Total non-infectious respiratory events	23
Tocilizumab	2009: EMA 2010: FDA	Interstitial lung disease[a] Obliterative bronchiolitis Alveolitis (including allergic) Pneumonitis ARDS	8(4) 1 2 3 3(1)
		Total non-infectious respiratory events	94
Anakinra	2002: EMA 2001: FDA	Interstitial lung disease[a]	1
		Total non-infectious respiratory events	19
Tofacitinib	2012: FDA Not approved by EMA by 2016	NA	

ARDS acute respiratory distress syndrome, *EMA* European medicines agency, *FDA* Food and Drug Administration, *MHRA* medicines and healthcare products regulatory agency, *NA* data not available, *RA* rheumatoid arthritis

[a]Includes cases reported as idiopathic pulmonary fibrosis, pulmonary fibrosis and pulmonary toxicity

ADRs have been reported to the regulatory agencies after treatment with abatacept compared with other biologic agents (Table 9.2). Indeed, only one case of pneumonitis and 23 cases of non-infectious respiratory events had been reported through the UK Medicines and Healthcare Products Regulatory Agency (MHRA) 'Yellow Card' system by March 2016. However it is worth noting at exposure to abatacept may be limited in the UK due to lack of its initial approval by the National Institute of Health and Care Excellence (NICE) until 2010 as a second-line biologic (following TNFi failure and if rituximab was contraindicated) and first-line biologic approved in 2013.

Whilst experience of using abatacept in the context of pre-existing ILD is limited, a case report of rapid-onset interstitial pneumonia 2 days post initiation of

treatment has been described in a Japanese patient [103]. Conversely, there are reports of stabilisation of RA-ILD on abatacept [104] and improvement in some patients [105]. In a case series of 16 patients with RA-ILD (with varying grades of severity at baseline), all patients completed 52 weeks of abatacept treatment, and no one was reported to have an exacerbation of their pulmonary disease [105]. In the three patients with RA-ILD on abatacept, as part of Nakashita and colleagues' retrospective study [82], none had ILD-related complications reported by one-year follow-up. However using claims data, in the Curtis et al. study [81], of the 102 patients with RA-ILD on abatacept, there was no significant decreased risk of ILD events compared to TNFis.

In comparison with other biologic agents introduced to the market at around the same time, the spontaneous pharmacovigilance and case report figures are cautiously encouraging. The lack of a clear denominator or the number of patients treated with each drug in these settings makes accurate interpretation challenging. Whilst experience in baseline RA-ILD is limited, emerging observational data thus far appears tentatively reassuring. Additionally patients on abatacept may have a more favourable infection profile in comparison to other biologics in those who have experienced a hospitalised infection previously [106]. This study also forms the basis of its use as a conditional recommendation in the context of prior serious infection in the ACR 2015 guidelines for RA [107]. Therefore given the limitations of spontaneous pharmacovigilance and inconsistent findings from observational data, more observational data is required before robust conclusions can be formed regarding safety of abatacept in RA-ILD. However, there may be a role for abatacept particularly in patients in whom serious infection is a concern.

Tocilizumab

Tocilizumab is a humanised monoclonal antibody that inhibits IL-6 receptor signalling through its membrane-bound and soluble forms. In the treatment of active joint disease, where MTX is contradicted or not tolerated, tocilizumab monotherapy has been shown to be as effective as combination treatment with MTX [108, 109]. Given the potential concerns regarding the respiratory safety profile of MTX, there may be a preference for using this drug over other biologics in RA-ILD by some physicians. Experimental work has demonstrated profibrotic effects of IL-6 on lung fibroblasts, which may have the potential to be antagonised by blocking the IL-6/IL-6 receptor pathway, suggesting a potential benefit of tocilizumab in RA-ILD [110]. However, clinical data on the use of tocilizumab in pre-existing RA-ILD is sparse and inconclusive.

Unlike other biologics, early RCTs of this biologic agent have raised some concerns regarding an association with development of ILD. A single case of 'allergic pneumonitis' after tocilizumab monotherapy exposure in 109 patients with RA was reported in 2004 by Nishimoto et al. [111]. In 2008, two of 419 patients treated with tocilizumab and MTX in the OPTION study [112] developed ILD at weeks 9 and 13, with a further two cases of 'culture-negative pneumonia'. A similar case was

also reported in the SATORI [113] trial, which included patients on tocilizumab monotherapy. In one of the few head-to-head biologics studies, the 2013 ADACTA trial compared tocilizumab monotherapy with adalimumab monotherapy and reported two deaths in the tocilizumab arm, one of which occurred suddenly in a 56-year-old man with multiple comorbidities, including pre-existing ILD [114]. Further deaths due to interstitial pneumonitis have been reported in tocilizumab-exposed arms in recent trials such as the SURPRISE (tocilizumab + MTX arm) [109], as well as the SUMMACTA trial, the latter reporting one death due to ILD and ARDS each [115]. Of note other anti-IL-6 drugs being evaluated for RA, such as sarilumab (a fully human anti-IL-6Rα mAb that binds membrane-bound and soluble human IL-6Rα), have also reported SRAEs within trials. Of the two deaths reported in the SARIL-RA-MOBILITY trial (sarilumab +MTX), one was due to ARDS (investigator felt was drug-related) [116]. Within the phase III study published to date, four deaths in the sarilumab arms were described [117], one due to unspecified respiratory complications post surgery.

Whilst the consequences of such reports are not clear at present for the patient with pre-existing ILD, such observations suggest the need for alertness especially since most trials exclude patients with multimorbidity. Case reports have suggested an association between incident ILD and tocilizumab exposure in patients on a concurrent nbDMARDs both in RA [118–120] and adult-onset Still's disease [121]. Spontaneous pharmacovigilance figures from the UK have reported five deaths due to SRAEs in tocilizumab-exposed patients to date, four due to ILD and one secondary to ARDS (Table 9.2). Whilst the total number of patients exposed to treatment (denominator) is not available, cautious comparison of these figures with abatacept, which was approved earlier than tocilizumab by FDA and EMA, is of interest. Furthermore, the REACTION study, a retrospective study of 229 tocilizumab-exposed patients with RA in Japan, reported interstitial pneumonia in two of the 229 patients followed up over 6 months and an additional six discontinuations for pneumonia (presumed infective), raising further concerns of pulmonary toxicity in this population.

RA-ILD was found to have improved in one patient with pre-existing RA-ILD within 16 weeks after administration of tocilizumab [122], whereas another patient with biopsy-proven UIP and emphysema developed a fatal exacerbation of ILD after treatment with tocilizumab [119]. Of the 23 ILD events reported in 3881 patients who received tocilizumab every 4 weeks over 28 weeks (1.28 per 100 patient-years) in a post-marketing surveillance programme in Japan, the presence of a known ILD was a risk factor for acute presentation with ILD exacerbation and serious infections [123]. Recent small retrospective observational studies demonstrate limited reassurance. In the nine patients with RA-ILD selected to receive tocilizumab treatment over 1 year in the Nakashita et al. study [82], no patients were reported to have an ILD exacerbation. However patients who did not complete at least 1 year of follow-up lacked imaging data or discontinued treatment because infections were excluded from the study leading to a likely selection bias of reported outcomes. In a retrospective case-control study in RA, patients were stratified according to the presence of baseline RA-ILD ($n = 78$) or without ($n = 317$) [124].

During observation period of 148.8 patient-years and 629.7 patient-years for the RA-ILD and non-ILD groups, respectively, six patients developed an acute exacerbation in the RA-ILD group (none in the non-ILD group). Interesting all the patients who developed an exacerbation of ILD were on tocilizumab monotherapy, and there was a suggestion that all patients who developed an exacerbation had more uncontrolled articular disease that may in turn be associated with the outcome [124]. The administrative data study by Curtis et al. concluded no significant differences between tocilizumab and other biologic drugs in the risk of ILD or its exacerbation [81]. However exacerbation of ILD can be difficult to define in such databases as recognised by the authors. Hence surrogate measures such as hospitalisations for ILD, pneumonia or lung transplant were used, which as expected were observed infrequently and capture a heterogeneous overall outcome that includes infection. Therefore, whilst current evidence does not allow robust conclusions about the pulmonary safety of tocilizumab in RA-ILD, ongoing vigilance is recommended if used in this context in the absence of clear predictors of ILD exacerbation.

Anakinra

Anakinra is a recombinant IL-1 antagonist, which binds competitively to the type I IL-1 receptor and therefore acts as a competitive antagonist to IL-1. Initial trials that supported the licensing in RA did not demonstrate a signal of concern in relation to incident ILD either as monotherapy [125–127] or in combination with MTX [128]. Whilst such data supported the initial licensing of anakinra in RA, in clinical practice, it is not widely used in RA for active joint disease as it appears less efficacious than TNFi agents and of no additional value in early RA [129]. Moreover, combination of anakinra and etanercept provided no added benefit compared to etanercept monotherapy, and indeed increased serious safety concerns were reported including two patients with new ILD and pneumonitis in the combination biologic arms [130]. There are sparse reports of non-infective SRAEs on anakinra from spontaneous pharmacovigilance (Table 9.2), possibly reflecting fewer exposed patients with RA. Therefore apart from one case of improvement in tocilizumab-induced pneumonitis following anakinra in a patient with adult-onset Still's disease [121], there is no further literature indicative of non-infective SRAEs with its use [33] but also minimal evidence to suggest a potential beneficial role in RA-ILD.

Janus Kinase Inhibitors

Janus kinase (JAK) inhibitors, such as tofacitinib and baricitinib, are synthetic orally administered compounds that block JAK, a protein that mediates signal transduction of multiple cytokines. Although these are not biologic drugs, though they interact with biological pathways, they have been classed as targeted synthetic

DMARDs (tsDMARDs) for use in moderate to severe RA, who are nonresponders or intolerant to MTX [3, 131]. Tofacitinib has been approved in several countries, such as in the USA, Latin America and Asia although not in the European Union or UK. Baricitinib has completed phase III trials, and early results from head-to-head trials even suggest that it may be more efficacious than a TNF inhibitor [132].

RCT data thus far with regard to respiratory safety of JAK inhibitors are inconclusive. Phase III trials of tofacitinib with concomitant MTX in patients with RA have reported cases of new-onset ILD and pulmonary sarcoidosis [133]. Other SRAEs reported in tofacitinib-treated arms in RCTs include bronchopneumonia [134] and a death due to ARDS [135]. A combination of pulmonary fibrosis and chronic obstructive pulmonary disease has been observed in such trials using tofacitinib monotherapy [136]. However data from two long-term extension studies from Japan following up 4102 tofacitinib-treated patients over 5963 patient-years reported no additional ILD events [137], nor did subsequent meta-analysis of tofacitinib trials [138]. In addition phase IIb studies and phase III studies of baricitinib also have not reported incident ILD cases [139, 140] and is currently under regulatory review. In 2015, the FDA released a Risk Evaluation and Mitigation Strategy (REMS) document highlighting the known concerns with tofacitinib, instructing the pharmaceutical company to send information out to healthcare professionals regarding the risk of serious infections, malignancies, decreases in peripheral lymphocyte counts, neutrophil counts and haemoglobin and derangement in lipid profiles [141]; lung toxicity was not mentioned. No case reports or regulatory reports of ILD have been published to date, although tofacitinib was licensed for the treatment of RA a few years ago in November 2012 in the USA and remains unlicensed in most of Europe, limiting the numbers of exposed patients. Conclusions drawn regarding the association between JAK inhibitors and ILD in patients with RA are therefore restricted, given limited data and further observational evidence are required to assess its effect on pre-existing RA-ILD.

Immunosuppressive Agents to Treat Rheumatoid Arthritis-Related Interstitial Lung Disease

Although RA-ILD is a fairly heterogeneous extra-articular manifestation of RA, the majority of cases mimic the two idiopathic interstitial pneumonia patterns of NSIP and UIP. Whilst NSIP and organising pneumonia appear to be more responsive to glucocorticoid treatment, the presence of the UIP pattern on HRCT in patients with RA may be associated with a significantly shorter survival compared to other forms of interstitial disease [142]. As a general clinical guidance, lung disease features that may be predictive of treatment benefit include histopathologic patterns other than UIP (especially NSIP and OP, younger age of the patient and worsening of symptoms, PFTs or finding on HRCT over the preceding 3–6 months [143–145]. A DLCO of less than 54% is associated with progression and poor prognosis and may identify patients who could be considered for treatment [7]. Numerous medications

have been described for potential therapies for RA-ILD, but currently there are no large RCTs to help guide physicians specifically in the management of the pulmonary manifestations of RA-ILD. In addition to immunosuppressive treatments, general considerations for management of RA-ILD include smoking cessation and age-appropriate vaccinations for pneumonia and influenza, as well as prophylaxis for *Pneumocystis jirovecii* pneumonia in patients who are profoundly immunosuppressed [145].

Glucocorticoids and Azathioprine

Typically glucocorticoids were used as first-line therapies in an attempt to stabilise and improve the disease course of RA-ILD based on limited evidence from IPF. Because RA-ILD is a heterogeneous spectrum of histopathologic patterns beyond UIP (IPF), experience extrapolated from management of idiopathic ILD suggests that some forms, including NSIP and OP, may respond to glucocorticoid therapy [145]. Given the paucity of evidence in RA-ILD, it was felt that the addition of azathioprine maybe beneficial in glucocorticoid-responsive patients and could result in improved survival compared to glucocorticoids alone, again based on historic data from IPF studies [146]. However, the 2012 multicentre Prednisone, Azathioprine, and (N) acetylcysteine [NAC]: A Study That Evaluates Response in IPF (PANTHER-IPF) trial had to be prematurely stopped as it is found that combination of prednisone, azathioprine and NAC was associated with greater mortality (eight vs. one death), more hospitalisations (23 vs. 7) and more serious AEs (24 vs. 8) compared to placebo in IPF patients with mild to moderate disease [147]. A large proportion of deaths were due to pulmonary infection, highlighting the need for adequate precautions to be taken against respiratory infections in patients with RA-ILD who are susceptible to serious infections [148]. Indeed in elderly patients with RA, prednisolone has been shown to have a dose-dependent risk of infection, with current/recent glucocorticoid therapy demonstrating the greatest impact on infection risk [149]. Therefore use of glucocorticoids specifically for ILD in RA is best performed after liaison with respiratory colleagues, with use of the lowest possible dose prescribed for the shortest duration.

Anti-Fibrotic Treatments

Pirfenidone is an anti-fibrotic drug that inhibits transforming growth factor beta (TGF-β)-stimulated collagen synthesis, decreases the extracellular matrix and blocks fibroblast proliferation. It has demonstrated efficacy in IPF [150–152] and has been approved by the National Institute of Health and Care Excellence in the UK and the FDA in the USA for use in patients with mild or moderate IPF. In CTD-ILD, specifically secondary to systemic sclerosis, case reports and small

retrospective studies have suggested modest benefit [153–156], whilst a recent open-label study in systemic sclerosis demonstrated acceptable tolerability of pirfenidone, especially important since 63.5% of patients were on concomitant mycophenolate mofetil [157]. Currently there is no evidence for its use in RA-ILD. Theoretically, however, given its action on TGF-β and fibroblast proliferation, there may be justification of its use in the fibrotic NSIP pattern and fibrotic stages of other RA-ILD subtypes [158, 159]. Currently there is a phase II trial underway to assess the safety and tolerability of pirfenidone 2403 mg/day for the treatment of RA-ILD [160], with a need for more RCTs the effect on respiratory function in this setting. Other anti-fibrotic agents such as nintedanib, a tyrosine kinase inhibitor that targets multiple tyrosine kinases, including vascular endothelial growth factor, fibroblast growth factor and platelet-derived growth factor receptors, have been recommended by the international thoracic guidelines for its use in IPF [144]. It was recently found in various murine systemic sclerosis models to effectively inhibit the endogenous as well as cytokine-induced activation of fibroblasts and exert potent anti-fibrotic effects [161]. Whilst there is currently no clinical evidence to date in CTD/RA-ILD, there may be potential for future clinical trials with this drug.

Other Agents with Limited Evidence in RA-ILD

Cyclophosphamide has been commonly used to treat ILD unresponsive to glucocorticoids. However evidence of its use in IPF is lacking [162]. Conflicting data exist regarding its use in scleroderma-related ILD [163], with additional concerns regarding its toxicity profile. RCTs using cyclophosphamide suggest moderate benefit in scleroderma-ILD patients with early disease [164–166], although a previous meta-analysis concluded no improvement in pulmonary function following 12 months of treatment [167]. No RCTs have been performed assessing the use of cyclophosphamide in RA-ILD. Limited evidence suggests that there may be some role in rapidly progressing patients with restricted therapeutic options in the acute or subacute setting [168] or in refractory drug-induced pneumonitis unresponsive to glucocorticoids [169]. The use of this agent is not recommended for mild/moderate stable RA-ILD disease.

Experience of using cyclosporine in the treatment of RA-ILD is limited and not recommended currently due to its poor safety profile and absence of proven benefit on pulmonary or joint disease. Few publications in IPF have been less than encouraging [170, 171]; however, it appears to yield some benefits according to anecdotal reports in myositis-related ILD particularly anti-synthetase syndrome [172–174]. Mycophenolate mofetil often used in the treatment of scleroderma-ILD is an inhibitor of lymphocyte proliferation and additionally targets nonimmune cells such as fibroblasts and smooth muscle cells. The majority of the evidence for use has been derived from small prospective case series and retrospective reviews and has been shown to stabilise scleroderma-ILD [175–177] and CTD-ILD [178]. In the latter

series, 18 patients with RA-ILD were included; mycophenolate was associated with modest improvements in forced vital capacity (FVC), diffusing capacity and reductions in the prednisone dose [178]. A head-to-head RCT assessing the use of a two-year course of mycophenolate compared to oral cyclophosphamide for 12 months in SSc-ILD has recently been published, demonstrating a more favourable safety profile with mycophenolate; however, both treatment arms demonstrate similar efficacy on lung function [179]. In the treatment of RA-ILD, mycophenolate has been prescribed at doses of 1–2 g per day in patients with RA who have limited pulmonary disease with some benefit [175, 180]. However it is not effective in the treatment of active articular disease on RA, requiring the use of concomitant nbDMARDs, which may have additional consequences on tolerability. Whilst studies supporting the use of mycophenolate in RA-ILD represent a relatively small number of patients, further work on tolerability and safety in the context of active RA is required, and if promising well-designed trials may be helpful before advocating its use in this area.

Of the biologics having potential utility for treatment of RA and other connective tissue disease-related ILD, perhaps rituximab has had the most interest and shown some promising results in published case reports and case series, not inclusive of RA [181–184]. A recent retrospective review of CTD-ILD cases treated with rituximab, which included anti-synthetase syndrome ($n = 10$), dermatomyositis ($n = 3$), systemic sclerosis ($n = 3$), systemic lupus erythematosus ($n = 2$) and unclassifiable CTD-ILD ($n = 4$), suggested stabilisation of lung disease in 11 patients and worsening in nine patients. Four patients with myositis had a reported clinically significant improvement with an FVC of >10% post treatment. Whilst encouraging in a CTD-ILD setting, most published work is in the form of case reports, subject to reporting bias, or retrospective case series.

Evidence of rituximab use for the treatment of RA-ILD has not been encouraging and studies to date have been small or inconclusive. In an open-label pilot study of rituximab in RA-ILD [185] of seven patients who completed a 48-week follow-up, one showed improvement in respiratory function, five were stable and one deteriorated. The study initially recruited ten patients, and of the three who did not complete the study, one patient died of ARDS/possible pneumonia, 6 weeks post treatment (no infective source identified). Four small retrospective observational studies assessing the use of rituximab in RA-ILD have been inconclusive (all still in abstract form, full papers not published). Dass and colleagues in 2011 [186] presented data from 48 patients with baseline RA-ILD; three deaths were reported in patients with RA-ILD following rituximab treatment, one due to pneumonia and possible acute progression of ILD, 4 weeks after the first cycle of rituximab therapy. Furthermore, five patients had a decline in transfer factor of >10% over an unspecified time in the presented results of this study. The same group reported their rituximab experience in RA-ILD over 10 years (January 2004–July 2014) in 2015 [187]. Of the 53 patients with RA-ILD on rituximab with a total of 171 patient-years, the authors concluded there was no significant improvement or deterioration in the majority (as measured using FVC/ DLCO; actual data not available in abstract). However there were 12 deaths reported, nine of which were attributed to progressive ILD (median DLCO of 41% [range

35–64%] pre-rituximab). Other reasons for death were lung cancer, colon cancer and infection post surgery ($n = 1$ each).

Becerra et al. [188] reported on a single-centre retrospective review of 38 patients with RA and known lung involvement who were undergoing therapy with rituximab, of whom 19 had established RA-ILD. Progression of ILD over 4 years was described in one patient with severe UIP at baseline. Improvement in lung function was observed in none of the patients, 66% ($n = 25$) reporting respiratory infections, two of which required hospitalisation. Recent work from the BSRBR-RA compared mortality of 353 patients with physician-reported RA-ILD, of whom 310 were treated with TNFi and 43 on rituximab [189]. The differences in mortality between the two groups were not statistically significant, and adjustment for baseline confounders made little difference to the estimates (HR_{adj} 0.51, 95% CI 0.25–1.06). However, methodological issues included inherent differences in the two treated groups (the TNFi group being a more historic cohort, therefore likely to have more severe disease), low numbers of deaths and no information on baseline RA-ILD severity. The results of all four of these studies are difficult to interpret often due to a lack of well-matched comparator groups and uncertainty about the natural history of RA-ILD.

Therefore, currently, few data exists that suggest that rituximab can markedly improve RA-ILD. In comparison to other biologics, there did not seem to be a significantly lower risk of complications related to ILD in the Curtis et al. study [81], although channelling bias may exist. Furthermore rituximab is known to reduce IgG levels, which in turn may be associated with an increased infection risk, which bears consideration whilst making such treatment decisions [190]. In the context of RA overlap with another CTD, however, RTX may have a role in stabilising ILD, especially with other extra-pulmonary manifestations of CTD which exist that may benefit from B-cell depletion. A clinical trial is currently underway comparing rituximab versus cyclophosphamide in patients with systemic sclerosis, myositis and mixed connective tissue disease (RECITAL, ClinicalTrials.gov Identifier: NCT01862926). Currently, therefore, the evidence does not support preferentially switching to rituximab in all patients with RA-ILD who have active joint disease, regardless of the severity of lung disease.

Lung Transplant

In end-stage refractory RA-ILD, single lung transplantation may be considered. However there are limited data on long-term outcomes for lung transplant in RA-ILD. Amongst ten patients with RA-ILD who underwent transplantation, survival at 1 year was similar to IPF lung transplant recipients (67 and 69%, respectively), although higher for scleroderma-ILD at 82% [191]. Eligibility for lung transplantation may be restricted due to age (typically <65 years), contraindicated with certain comorbidities common in RA including osteoporosis, whilst other extra-articular manifestations of RA may in turn complicate transplantation.

Nonetheless, comparable survival outcomes of RA-ILD with IPF are somewhat reassuring.

In summary at present, there are no current treatments available that have appeared to consistently stabilise RA-ILD as well as adequately treat joint symptoms. The risks and limited benefits of such medications bear consideration, especially since most evidence for efficacy has been demonstrated in IPF and CTD-ILD. Glucocorticoids may be used in RA-ILD, however, with the lowest effective dose for the shortest possible duration to minimise risk of infection amongst others. Robust RCTs are required to support the use of novel antfibrotic agents or immunosuppressive therapies directed towards treatment of RA-ILD. However, at present there is a paucity of evidence to support the routine use of these strategiest.

Patient Assessment and Management

Evidence to guide management and treatment of RA-ILD is of low quality or absent, hence extrapolated from systemic sclerosis-ILD or IPF. However, despite the lack of robust data, clinicians are required to advise patients on the comparative safety of treatment and strategies to minimise complications of RA-ILD such as infection and reduce the overall burden of morbidity to prolong survival. In addition RA management has become increasingly complex over the last decade. Several effective DMARDs are available, and treat-to-target strategies support the use of early, rapidly escalating treatment often in combination with each other. As discussed earlier, there are no treatments that conclusively improve both joint and pulmonary disease in all patients; therefore, careful baseline assessment, adequate risk assessment for adverse outcomes and regular monitoring and vigilance whilst using the majority of DMARD strategies are essential.

Baseline Assessment of Pre-Existing RA-ILD

To enable guidance of management strategies, a recent approach in idiopathic interstitial pneumonias (IIP) has been to classify pulmonary disease as self-limiting, reversible, stable, progressive or irreversible [143, 192, 193]. A thorough assessment of baseline RA-ILD severity should consider clinical features, PFTs and imaging pattern/extent on HRCT, low DLCO and a high radiological fibrosis score on HRCT being predictors of poor survival [194–196]. Such information in combination with monitoring disease progression over time allows mapping of the disease trajectory and may better inform management decisions in the face of poor evidence.

Clinical assessment including quantification of exercise tolerance using instruments such as the five-point Medical Research Council (MRC) breathlessness scale

[197] can help aid serial assessment of the symptoms of RA-ILD (Table 9.3). Bibasilar crepitations are an associated feature that may help trigger detection of asymptomatic ILD, but have limited value in assessing severity or monitoring progression. The 6-min walk test is a commonly used instrument for assessing IPF and can be performed easily. Reduced walk distance and oxygen desaturation below 88% are poor prognostic factors in IPF [144, 198]; however, practically this may be challenging to perform in RA patients with poor mobility. PFTs provide objective measures of lung function and should be performed in all patients with respiratory clinical features, or confirmed RA-ILD, prior to decisions about therapy. ILDs share a restrictive pattern, with reductions in lung volumes and a reduced DLCO [199]. Low baseline FVC and DLCO (FVC <60% and DLCO <40% of predicted values) are independent predictors of early death in patients with IPF [195, 196]. Importantly, a 6–12-month decline in FVC of ≥10%, or a decline in DLCO of ≥15%, is associated with increased mortality in IPF [200]; this association might also exist in patients with idiopathic fibrotic NSIP.

Table 9.3 Baseline assessment of patients with rheumatoid arthritis-related interstitial lung disease prior to treatment with nbDMARDS and bDMARDs

Initial baseline assessment	Measure	Factors associated with poor prognosis
Clinical assessment	MRC breathlessness score	
	Chest auscultation	
	6-min walk test	Oxygen saturations <88% poor prognosis
	Smoking status	
Respiratory physiology	PFTS	FVC <60%
		DLCO <54%
Chest radiograph and HRCT assessment	Extent of fibrosis	>20% lung involvement
	Subtype of ILD	UIP
Pre-non-biologic DMARDs		
Vaccinations	Ensure annual flu vaccination and one off pneumococcal vaccine administered (review 5 yearly)	
Pre-biologic DMARDs		
Vaccinations	Ensure annual flu vaccination and one off pneumococcal vaccine administered (review 5 yearly)	
Tuberculosis screening	Obtain history of TB exposure	
	Perform Mantoux and/or QuantiFERON gold	
Pre-rituximab (in addition to the above)	Immunoglobulin levels (IgG levels)	

bDMARDs biologic disease-modifying antirheumatic drugs, *DLCO* diffusing capacity of the lungs for carbon monoxide, *FVC* forced vital capacity, *ILD* interstitial lung disease, *HRCT* high-resolution computed tomography, *nbDMARDs* non-biologic disease-modifying antirheumatic drugs, *PFTs* pulmonary function tests, *TB* tuberculosis, *UIP* usual interstitial pneumonia

HRCT imaging is indicated in patients with RA-ILD clinical features or in asymptomatic patients with a DLCO of <70% of predicted [201]. Individuals with HRCT findings consistent with UIP, such as basally dominant honeycomb cysts with little or no ground-glass change, have poorer prognosis than those with HRCT-detected features indicative of other types of IIP [142, 202]. In SSc-ILD, an HRCT-based prognostic staging system has been developed, categorising patients as having limited (<20% lung involvement) or extensive (>20% lung involvement) SSc-ILD, with extensive disease found to be a strong predictor of mortality [203]. Similarly quantifying the extent of fibrosis and disease on HRCT has been shown to predict disease progression in IPF [204]. No comparable studies have assessed the use of similar HRCT-based scoring in RA-ILD, although a small study suggested that the degree of interstitial changes detected using HRCT imaging was predictive of prognosis [205]. On the basis of these factors, the authors have previously proposed a framework for assessment of RA-ILD, risk assessment before initiation of biologic therapy and post-treatment monitoring [206] (Fig. 9.1). The proposed approach is designed to help predict short-term progression of ILD irrespective of biologic therapy. In patients at higher risk of progression, even in patients who appear to have stable lung disease over a one- or two-year period, treatment decisions should involve a multidisciplinary approach including a respiratory physician as well as a careful discussion with the patient regarding the benefits and risks of treatment options available.

Considerations of Post-Treatment

In all patients, including those with self-limiting and stable RA-ILD on treatment for their joint disease, rheumatologists should prompt questioning of new or evolving respiratory symptoms at follow-up, as patients may not spontaneously disclose such information. All patients who smoke should be educated about the important associated risks. Whilst being implicated in the pathogenesis of RA-ILD, it may also lead to deterioration of lung disease and is associated with higher joint disease activity and reduction in the effectiveness of medications such as MTX and TNFi drugs [207]. Smoking cessation advice and further support such as nicotine replacement therapy should be made available for all patients with RA-ILD [159]. Following an adequate period of monitored observation, classification of the trajectory of RA-ILD may be possible in the individual patient. In patients in whom a 12–24-month period of stability is observed, PFT follow-up intervals can be extended to 12 monthly.

Responses to Decreasing Lung Function

Routine monitoring of PFTs is suggested every 3–6 months in individuals at high risk of progression of RA-ILD or on any biologic drug [206]. An observed decline following serial PFTs could be due to progression of RA-ILD, either its natural

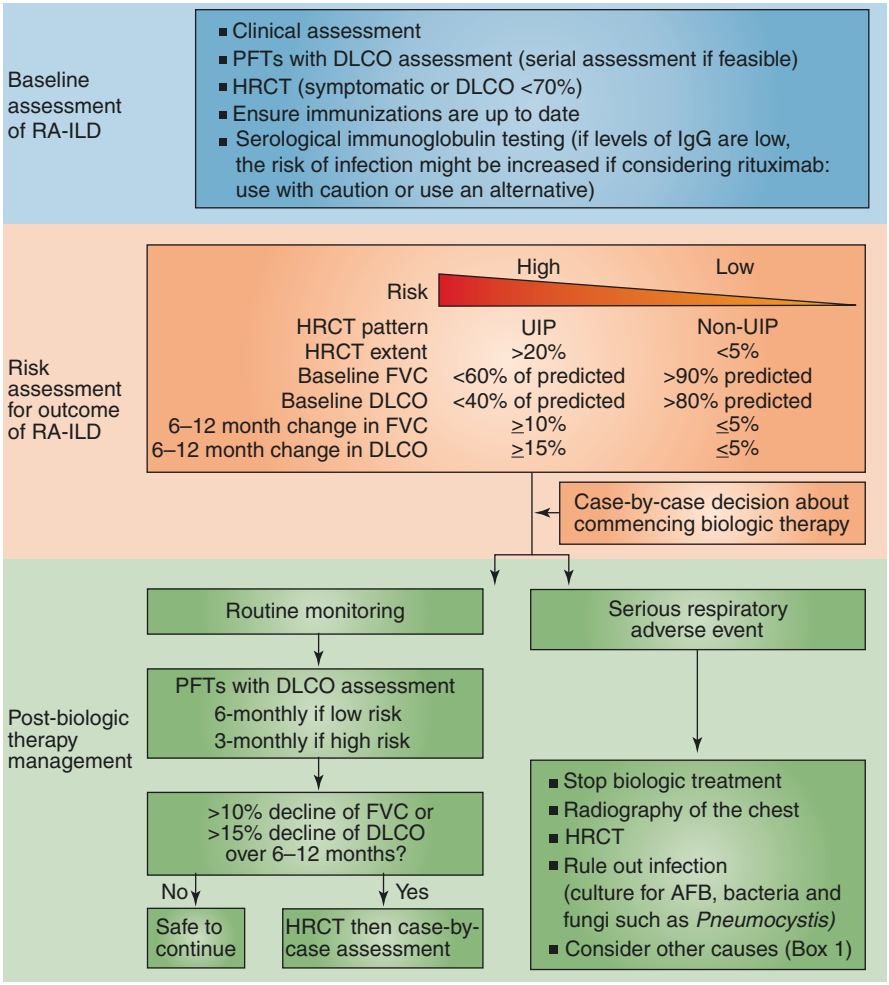

Fig. 9.1 Suggested algorithm for assessment, monitoring and management of patients with RA-ILD on biologic therapy. Case-by-case decisions about commencing biologic therapy are required, informed by baseline assessments. For example, a patient with HRCT-detected UIP affecting 30% of lung fields and with a DLCO 40% of predicted is likely to experience disease progression and to have limited capacity to withstand a respiratory insult. Conversely, a clinician might be more reassured if their patient has 5% of lung fields involved, with NSIP detected using HRCT, and a 12-month decline in DLCO of only 5%. Abbreviations: *AFB* acid-fast bacilli; *DLCO* diffusion capacity of the lung for carbon monoxide; *FVC* forced vital capacity; *HRCT* high-resolution CT; *NSIP* nonspecific interstitial pneumonia; *PFTs* pulmonary function tests; *RA-ILD* rheumatoid arthritis-associated interstitial lung disease; *UIP* usual interstitial pneumonia. Initially published in Nature Reviews Rheumatology 2014. Jani M, Hirani N, Matteson EL, Dixon WG. The safety of biologic therapies in RA-associated interstitial lung disease. Nat Rev Rheumatol. 2014;10(5):284–94 [206]

history or accelerated by therapy or attributable to other causes that may or may not have an association with the DMARD prescribed. 'Reversible' decline has been categorised into potentially reversible with risk of irreversible disease (e.g. cases of drug-induced lung disease) or reversible disease with risk of progression (e.g. RA-cellular NSIP, some RA-fibrotic NSIP, RA-organising pneumonia) [143]. Management strategy for the former would involve cessation of the putative drug with or without further treatment with glucocorticoids if required, whilst the latter may require more prolonged therapy and monitoring. In practice, the two are difficult to delineate given their similar presentations, and therefore rheumatologists faced with such patients demonstrating worsening respiratory symptoms or lung function should consult with respiratory colleagues early. If the deterioration in clinical picture is found to be due to progression of RA-ILD, the decision to continue any DMARD, but especially bDMARDs or tsDMARDs, necessitates clinical decisions on a case-to-case basis. The choice of whether to continue with effective DMARD therapy for joint disease or the risk of potential pulmonary toxicity may be based on the perceived likelihood that the DMARD in question is driving deterioration (e.g. temporal relationship of starting the drug with the clinical scenario). Currently there is no observational evidence that preferentially switching between biologics, for instance, helps prolong survival or stabilises the disease; however, this may be tried in individuals that require management of their articular disease following careful discussion. In patients deemed to have progressive, irreversible disease, management of patients with RA-ILD in a joint pulmonary and rheumatology clinic should be especially considered where possible, with attempts made at stabilisation. In all patients, and especially in those with multimorbidity, conservative and nonpharmacological options that may be worth exploring include education, psychological support, pulmonary rehabilitation and supplemental oxygen if appropriate [143, 159, 208].

Serious Respiratory Adverse Events Following Treatment

SRAEs following treatments for RA may be due to incidence/exacerbation of RA-ILD or due to other reported pulmonary complications summarised in Table 9.4. Careful consideration of the underlying aetiology of SRAEs is essential, as deterioration in chest symptoms may not be due to pneumonitis or progression of ILD, which has been the focus of review in this chapter. A thorough investigation of common and opportunistic infections is imperative in patients with RA, especially on high glucocorticoid doses, certain nbDMARDs, bDMARDs and tsDMARDs. A full review of infection risk and biologics is beyond the scope of this chapter, as has been extensively reviewed recently [209, 210]. Rare reports of pulmonary manifestations of certain drugs have also been reported in the literature and are summarised in Table 9.4. For instance, lymphoproliferative disease (including non-Hodgkin lymphoma) have been described during treatment with MTX and may regress following cessation [211, 212]. TNFis have been associated with paradoxical AEs (associated with the

Table 9.4 Possible reported serious respiratory adverse events to drugs used in the treatment of rheumatoid arthritis

Drug group	Reported adverse event	Details
Glucocorticoids	Infection	– Dose and duration of treatment related to infection risk – Co-prescription of bDMARDs may increase risk
NSAIDs	Eosinophilic pneumonia	– Idiosyncratic reactions, sometimes reported in patients on high doses
nbDMARDs		
Methotrexate	– Pneumonitis – Possible increase in infections including reports of opportunistic infections (e.g. *Pneumocystis jirovecii*, cytomegalovirus, varicella-zoster virus, *Nocardia*, mycobacteria or other fungi) – Pulmonary lymphoproliferative disease	– Co-prescription of bDMARDs may increase risk of chest/ opportunistic infections
Leflunomide	– Pneumonitis (especially Japanese/Korean patients) – Progression of pulmonary nodules +/− pneumothorax	– Co-prescription of bDMARDs may increase risk of chest/ opportunistic infections
Sulphasalazine	– Pneumonitis – Eosinophilic pneumonias most commonly reported	– Reported sometimes with DRESS
Hydroxychloroquine	– Rare cases of pneumonitis	– Reported sometimes with DRESS
bDMARDs		
TNFis	– Infection such as *Streptococcus pneumoniae*, *Haemophilus influenzae* and opportunistic infections (*Mycobacterium tuberculosis*, *mycobacteria* other than *M. tuberculosis*, *Mycoplasma*, *Legionella*, *Pneumocystis jirovecii*) – Pneumonitis – Congestive heart failure – Non-infectious granulomatous disease, e.g. sarcoidosis – Pulmonary vasculitis (rare) – New lung nodules (rare)	– Co-prescription of glucocorticoids (in patients with high disease activity) further increases infection risk

(continued)

Table 9.4 (continued)

Drug group	Reported adverse event	Details
Rituximab	– Rapidly progressive pneumonitis Reported, especially in haematology Ratients with few in RA – Infection (including opportunistic)	– Low IgG levels may help predict infection risk
Abatacept	– Rare reports of pneumonitis – Infection (including opportunistic)	– In patients with a history of serious infections, abatacept may have a better safety profile compared to other biologics
Tocilizumab	– Pneumonitis – Infection (including opportunistic)	
Anakinra	– Infection	One report of new ILD from spontaneous pharmacovigilance
tsDMARDs		
Tofacitinib	– Ifection (including opportunistic)	No conclusive data on pneumonitis risk

bDMARDs biologic disease-modifying antirheumatic drugs, *DRESS* drug reaction with eosinophilia and systemic symptoms, *ILD* interstitial lung disease, *nbDMARDs* non-biologic biologic disease-modifying antirheumatic drugs, *tsDMARDs* targeted synthetic disease-modifying antirheumatic drugs

treatment and possible induction of the same event) such as sarcoidosis and vasculitis [48]. The authors recommend a low threshold for withholding treatment with such cases, close liaison with respiratory and infectious disease physicians and imaging using HRCT, which in turn may help determine the cause of the deterioration.

Conclusions

The respiratory safety of RA therapy is an important consideration whilst deciding on the best treatment for patients with RA with active joint disease and coexisting ILD. This chapter summarises the current evidence available of the use of DMARDs in the context of pulmonary toxicity. However several limitations of the existing literature exist. Whilst RA-ILD is increasingly recognised, its natural history is still poorly understood. With newer treatments, case reports are helpful to identify a signal for concern, although such case reports are insufficient alone to provide a clear picture of drug toxicity. Where observational evidence is available, confounding by indication and channelling to certain treatments may limit robust conclusions. The lack of adequate comparator groups in several retrospective studies may

further limit inferences drawn from the evidence. It appears that legitimate concerns are associated with several therapies; therefore, involving patients and multidisciplinary teams in such decisions is important. Careful discussion of the benefits and harms of treatments is encouraged, although this is made more challenging by the uncertainty of the current safety profile.

Systematic pre- and post-treatment assessment can help identify the trajectory of patients with RA-ILD and enable more effective risk stratification, enabling clinicians and patients to make better-informed decisions. Unfortunately at present, there are limited therapeutic options for additional treatment for specifically stabilising or reversing established fibrosis; however, emerging treatments such as novel anti-fibrotics may hold promise. Given the current evidence base, the decision to start an DMARD in patients with RA who have ILD should be based on its potential for improving joint disease, individual patient characteristics, patient education about the known risks and benefits of treatment and multidisciplinary team input.

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Chapter 10
The Non-ILD Pulmonary Manifestations of RA

Misbah Baqir and Jay H. Ryu

Introduction

A broad spectrum of pulmonary manifestations may be encountered in patients with rheumatoid arthritis (RA) and can involve any of the intrathoracic compartments including the lung parenchyma, pleura, airways, and the pulmonary vasculature (Table 10.1). Parenchymal lung disease consists of various patterns of interstitial lung disease (ILD) (discussed elsewhere) and rheumatoid lung nodules. Rheumatoid lung nodules can be confused for malignancy. Airway diseases include cricoarytenoiditis, bronchiectasis, and small airway disease including constrictive bronchiolitis which can cause progressive airflow obstruction. Other forms of intrathoracic involvement include pleuritis, pleural effusion, and pulmonary vasculitis. Lastly, possibility of drug-induced lung disease and pulmonary infections must always be considered in RA patients presenting with respiratory symptoms.

Pulmonary manifestation can be the presenting feature of RA, preceding articular manifestations in 10–20% of RA patients [1, 2]. 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. This chapter will focus on non-ILD pulmonary manifestations of RA.

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Table 10.1 Spectrum of pulmonary manifestations in rheumatoid arthritis

Parenchymal
Interstitial lung disease, various patterns
Rheumatoid lung nodule
Caplan's syndrome
Airways
Cricoarytenoiditis (upper airway obstruction)
Bronchiectasis
Constrictive bronchiolitis
Follicular bronchiolitis
Pulmonary vascular
Vasculitis
Pulmonary hypertension
Pleural
Pleuritis/pleural fibrosis
Pleural effusion
Empyema
Pneumothorax
Bronchopleural fistula
Others
Drug-induced lung disease
Infections

Rheumatoid Lung Nodules and Caplan's Syndrome

Rheumatoid lung nodules are detected by chest radiography in 1% of patients with RA, whereas high-resolution computed tomography (HRCT) can detect lung nodules in up to 22% [3–5]. The rheumatoid lung nodules are usually multiple and well-circumscribed, ranging in size from few millimeters to several centimeters (Fig. 10.1a, b). They are more commonly seen in males, smokers, and those with active RA, subcutaneous nodules, and high titers of rheumatoid factor [4].

Pathologically, rheumatoid lung nodules appear granulomatous with collections of macrophages, lymphocytes, plasma cells, and palisading epithelioid cells around a necrotic core [6–8]. Rheumatoid lung nodules are pathologically identical to subcutaneous nodules and are the only pulmonary manifestation that is specific for RA [6].

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 variable fluorodeoxyglucose (FDG) uptake on positron emission tomography (PET) scanning. This means increased FGD uptake does not necessarily translate into the diagnosis of malignancy [9]. Transthoracic needle biopsy or bronchoscopic biopsy and sometimes surgical lung biopsy may be needed to clarify the diagnosis in cases where evolution of the lung lesion(s) causes suspicion regarding the underlying nature.

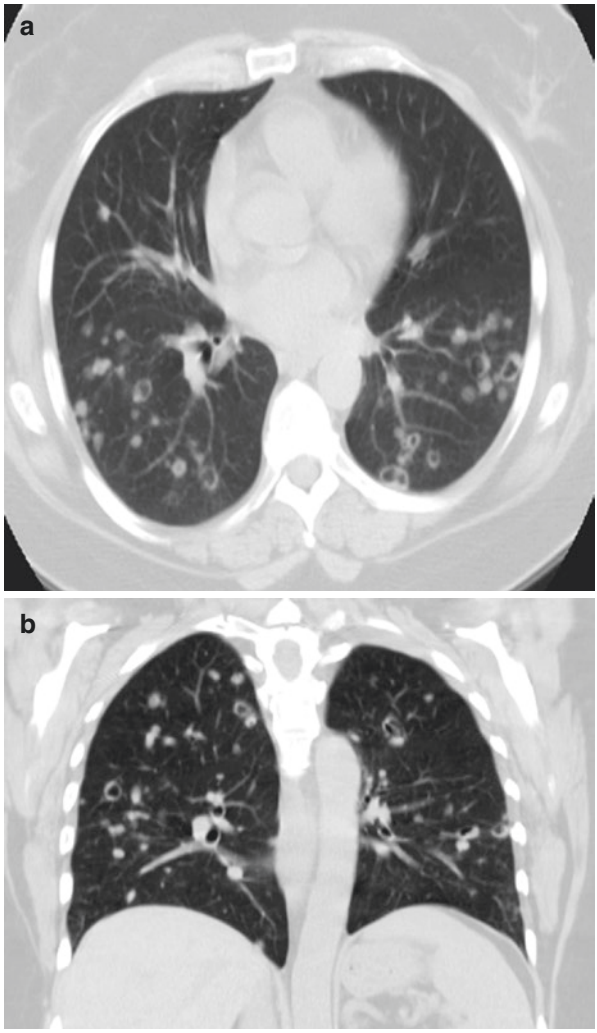

Fig. 10.1 High-resolution computed tomography scan of the chest on a 50-year-old woman with a long history of rheumatoid arthritis dating back to childhood. Multiple rheumatoid pulmonary nodules (confirmed by transthoracic needle biopsy), some cavitated, are seen in both lungs on transverse (**a**) and coronal (**b**) views

Rheumatoid lung nodules generally have a benign course. However, these lung nodules are commonly subpleural in location and can cavitate causing pneumothorax and sometimes a bronchopleural fistula or empyema [4, 8, 10–12].

Caplan's syndrome refers to multiple lung nodules seen in patients with both RA and pneumoconiosis as originally described by Caplan in 1953 [13–17]. It has sometimes been called "rheumatoid pneumoconiosis" [13, 15]. Pneumoconiosis may be related to coal, silica, asbestos, or other inorganic dust exposure. Silicotic nodules are important to distinguish and appear as fibrous nodules composed of whorled collagen fibers with hyalinized centers, whereas in Caplan's syndrome, findings of necrobiotic nodules are seen with the additional presence of inorganic dust particles [6, 13, 18]. In this setting, these nodules can appear relatively rapidly over a course of weeks to a few

months ("in crops") and often cavitate, resembling tuberculomas [13, 14]. However, most patients with Caplan's syndrome are asymptomatic.

Upper Airway Disease

Airway involvement in RA can manifest abnormalities at various levels along the laryngotracheobronchial tree. Upper airway obstruction resulting from cricoarytenoiditis can be life-threatening [19, 20]. Cricoarytenoiditis results from synovitis of the cricoarytenoid (CA) joint and generally occurs in patients with long-standing RA and severe articular disease [21]. The CA joints are diarthrotic joints composed of two triangular cartilages resting on the signet of the cricoid cartilage. They have two types of movements: rotatory on the anteroposterior direction and gliding in a mediolateral direction. These joints work closely with vocal cords; they rotate with the vocal cords as they abduct and adduct to the pitch and tone of the voice [22]. Patients with cricoarytenoiditis present with dysphagia, odynophagia, laryngeal tenderness, hoarseness, progressive dyspnea, and stridor. Dyspnea and stridor are usually late manifestations of the disease and may eventuate in hypoxia and cardiovascular collapse [23].

The prevalence of cricoarytenoiditis in RA is estimated to be 13–75% [22, 24]. The broad range of this estimate relates to the methods used to detect cricoarytenoiditis including symptom survey, laryngoscopy, and radiologic imaging [19, 20, 25]. For example, the diagnostic yield of laryngoscopy partly depends on the stage of disease evolution since inflammatory signs may be absent in chronic cricoarytenoiditis. In late stages, difficulties in abduction of the vocal cords and reduced glottic rims are seen [26]. If indirect laryngoscopy is combined with direct laryngoscopy, the diagnostic yield can be increased to 69% [19]. When cricoarytenoiditis is bilateral and severe causing fixed airflow obstruction, flattening (plateauing) is seen in the inspiratory and expiratory limbs of the flow-volume loop on pulmonary function testing [25]. HRCT can also be informative, and its diagnostic yield is reported to range from 55 to 66% [20, 22, 25]. Clinical history taking, laryngoscopic examination, and radiologic investigations complement each other in making the diagnosis of cricoarytenoiditis.

Management of cricoarytenoiditis may require surgical intervention with mobilization of the cricoarytenoid joints. Local and systemic corticosteroid therapy can be utilized to ameliorate cricoarytenoid inflammation. In those patients presenting with acute stridor, emergency tracheostomy may be needed [27].

Lower Airway Disease

Lower airway disease seen in patients with RA includes bronchiectasis and bronchiolar disorders (small airways disease). Bronchiectasis (permanently dilated bronchi) has been reported in up to 30% in patients with RA [4, 28, 29]. In many of these patients, bronchiectasis is not associated with typical respiratory symptoms and 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 progress resulting in gradually worsening airflow obstruction and eventually respiratory failure [30–35]. Usual presenting symptoms are persistent exertional dyspnea and cough. Lungs sound clear to auscultation with no crackles or wheezes [31, 32]. Pulmonary function testing reveals evidence of airflow obstruction with air trapping and hyperinflation. Airflow obstruction is irreversible with no or minimal response to inhaled bronchodilator. Diffusing capacity measurement, however, is normal or only mildly reduced. HRCT scan of the chest typically demonstrates a mosaic pattern with patchy regions of air trapping (areas of hypoattenuation) which becomes more pronounced on expiratory views (Fig. 10.2a, b)

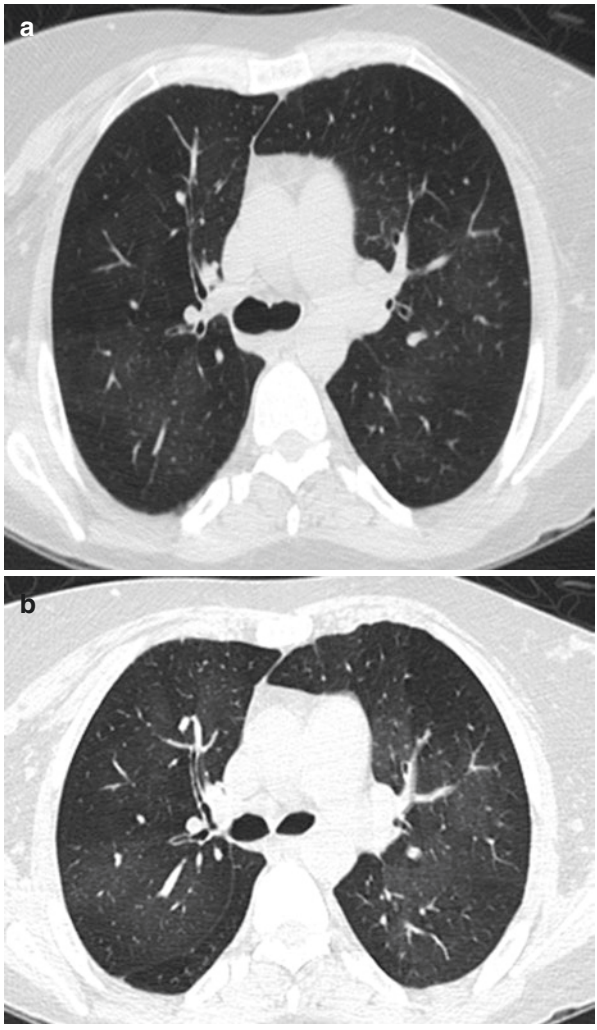

Fig. 10.2 High-resolution computed tomography scan of the chest on a 33-year-old woman, nonsmoker, with a 12-year history of rheumatoid arthritis and progressive obstructive lung disease from constrictive bronchiolitis. Mosaic pattern due to patchy air trapping seen on inspiratory view is accentuated on expiratory view. Her total lung capacity measured was 115% predicted, residual volume 210% predicted, forced vital capacity (FVC) 79% predicted, forced expiratory volume in 1 s (FEV1) 35% predicted, FEV1/FVC ratio 37%, and diffusing capacity 89% predicted

[31, 36]. 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. [30, 31, 37].

Follicular bronchiolitis is another form of bronchiolar disease that can be seen in patients with RA [32, 38, 39]. Follicular bronchiolitis is associated with small nodular opacities in the lung on HRCT and variable abnormalities on pulmonary function testing [38–40]. In contrast to constrictive bronchiolitis, prognosis is relatively good for patients with follicular bronchiolitis [38–40].

Pulmonary Vascular Disease

Systemic vasculitis can rarely be seen in patients with RA and can involve the pulmonary vasculature [6, 41]. This vascular involvement can result in alveolar hemorrhage [42]. Pulmonary hypertension in patients with RA is usually associated with advanced ILD but can sometime be seen with pulmonary vasculitis in the absence of parenchymal fibrosis [21, 43, 44].

Pleural Disease

Pleural disease is common in patients with RA although it is frequently subclinical. The incidence of symptomatic pleural effusion is 3–5%, but pleural effusion can be detected by imaging in 24% in men and 16% in women [45]. On autopsy, pleural abnormalities can be identified in 38–73% of patients [6, 21, 45, 46]. The spectrum of pleural involvement in RA includes pleuritis, pleural effusion, empyema, pneumothorax, and bronchopleural fistula (Fig. 10.3).

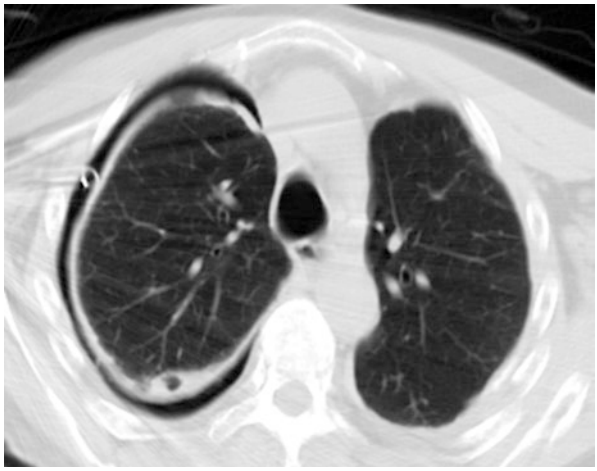

Fig. 10.3 High-resolution computed tomography scan of the chest on a 45-year-old man with rheumatoid arthritis and spontaneous right pneumothorax. Right-sided pneumothorax with a chest tube is present along with extensive pleural thickening bilaterally. A cavitated rheumatoid pulmonary nodule is present posteriorly in the right lung

Pleural effusion is more commonly seen in men with long-standing joint disease and subcutaneous nodules [21, 47, 48]. Most rheumatoid pleural effusions are small, unilateral, and asymptomatic [21, 47–49]. The pleural fluid is exudative by biochemical parameters with a low glucose level (usually <30 mg/dL) and a high rheumatoid factor titer [21, 48, 49]. For persistently symptomatic pleural effusions, treatment with corticosteroids (e.g., prednisone 10–20 mg per day), other immunosuppressive therapies, as well as nonsteroidal anti-inflammatory agents has been reported to be effective [21, 49, 50]. Pleurodesis is rarely needed in patients with rheumatoid pleural effusion [11, 49].

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) [48, 49, 51]. This is seen in the setting of a chronic pleural effusion associated with thickened pleura. Sometimes, sterile empyema-like pleural effusion due to rupture of necrobiotic nodules can be seen [52]. Pleural biopsy, when performed, reveals thickened pleura, replacement of normal mesothelial cells by epithelioid cells, and the presence of nodules [53].

More severe forms of pleural disease are rarely encountered and include spontaneous pneumothorax, empyema, fibrothorax, and bronchopleural fistula [11, 21, 48, 49]. Not uncommonly, management of these complications involves surgical maneuvers.

Miscellaneous Manifestations

Apical Fibrobullous Disease

A few cases of apical fibrocavitary lesions resembling those of ankylosing spondylitis have been described. This raises the possibility of some shared pathogenic mechanism in these two disorders [21]. These lesions may form as a result of cavitation of necrobiotic nodules. On histopathology, extensive pleural adhesions are seen associated with large necrotic cavitary lesions, the walls of which are composed of palisading histiocytes with infiltrating mononuclear cells. Situated between these cavitary lesions are numerous necrobiotic nodules. There may also be areas of interstitial fibrosis. The characteristic manifestations of these fibrocavitary lesions are their location and the absence of antecedent pulmonary nodules [54].

Pulmonary Amyloidosis

The presence of localized pulmonary amyloidosis both in the form of perivascular and alveolar amyloid and parenchymal nodular lesions has occasionally been described in patients with RA. In these cases amyloid deposition appeared to be limited to the lung with the absence of amyloid deposits in extrapulmonary organs [55, 56].

Intrathoracic Lymphadenopathy

Mediastinal and hilar lymphadenopathy has been associated with RA and is mainly described in autopsy series. In most of these cases, histopathologic analysis of lymph nodes showed chronic inflammation, fibrosis, and granulomas [57]. Plasma cells can be seen situated in between lymphoid follicles. In most cases the lymphadenopathy is likely reactive in conjunction with progression of the pulmonary disease [58]. In some cases biopsy of the lymph nodes may be needed to exclude lymphoma.

Thoracic Cage Disorder

RA is one of the systemic disorders that affect the chest cage. There are a number of ways RA can deform chest cage including erosions of the superior margins of the ribs, resorption of the outer and undersurface of the clavicles, and rotator cuff tears resulting in subluxation of the humeral head [59]. Thoracic cage stiffness and restriction of expansion can also occur related to joint involvement.

Conclusions

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

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