Chapter 1
Clinical Overview of Rheumatoid Arthritis

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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

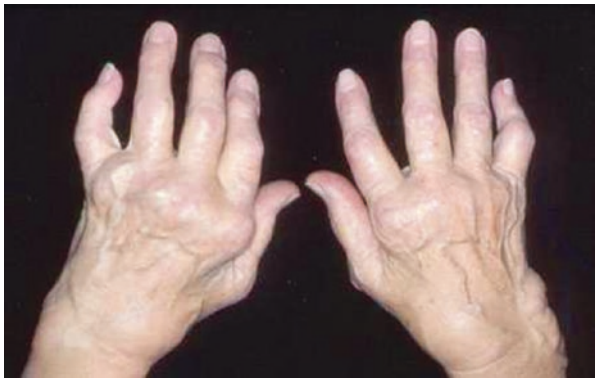

Fig. 1.1 Rheumatoid arthritis involving the hands and wrists

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.

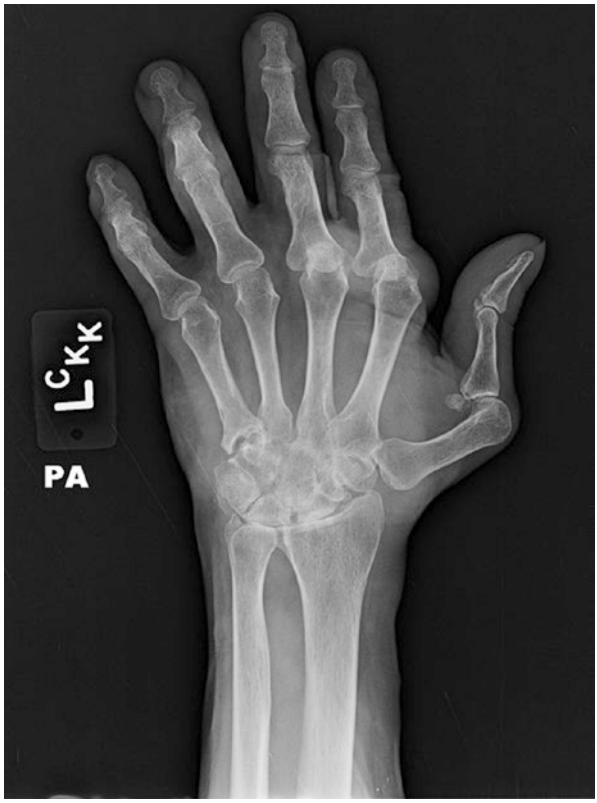

Fig. 1.2 Hand radiographs of a rheumatoid arthritis patient showing swelling, erosions, and joint space narrowing of the second and third metacarpophalangeal joints and wrist

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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