Chapter

57 Rheumatoid Arthritis

Rheumatoid arthritis (RA) is an inflammatory arthritis characterized by lymphocytic infiltration of the synovial joints and granulomatous extra-articular nodules. RA affects 1% of the adult population, with a peak onset most often between the ages of 40 and 50. Women are more affected than men (3 : 1).

There appears to be a genetic predisposition to RA, with a strong linkage to certain HLA-DR alleles. First-degree relatives of RA patients have a fourfold higher risk of developing the disease. Theories about infectious agents precipitating RA have not been proved.

Analysis of synovial tissue in RA reveals an inflamed synovium with high levels of tumor necrosis factor alpha (TNF-α) and interleukin-1 (IL-1). These factors upregulate production of metalloproteinases, which are believed to be responsible for joint destruction. Blockade of the effects of TNF-α and IL-1 has an important role in RA treatment.

CLINICAL MANIFESTATIONS

History

Patients often present with **pain** and **swelling** in joints, usually a polyarticular symmetric arthritis. **Morning stiffness** (>1 hour) is a key feature. Constitutional symptoms such as weight loss, fatigue, and anorexia may also occur and even precede onset of joint symptoms.

Physical Examination

Most often involved are the proximal interphalangeal, metacarpophalangeal, and wrist joints. Examination of the joints reveals an inflammatory synovitis (warmth, tenderness, swelling). Late presentations include joint deformities such as ulnar deviation of the phalanges, swan neck, or boutonnière deformities (Figure 57-1).

Subcutaneous **rheumatoid nodules** may be found on the extensor surfaces of the forearm and elbow or Achilles tendon. Splenomegaly may be found in RA, and, when associated with leukopenia, the triad is known as **Felty's syndrome**. Baker's cysts, located in the popliteal fossa, may develop and mimic deep venous thrombosis by causing pain and swelling when they rupture.

RA may also be associated with a severe **vasculitis**, presenting with digital infarcts, palpable purpura, and mononeuritis multiplex.

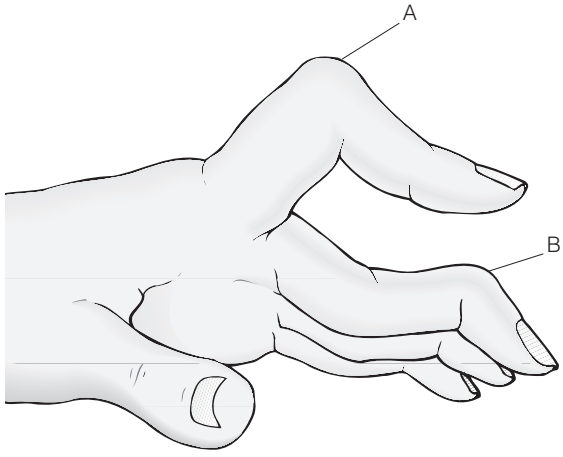

Figure 57-1 • (a) Boutonnière deformity. (b) Swan neck deformity.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis involves other etiologies of arthritis or joint pain, including:

- Osteoarthritis
- Psoriatic arthritis
- Gout or pseudogout
- Connective tissue diseases (lupus)
- Septic arthritis
- Lyme disease

DIAGNOSTIC EVALUATION

Table 57-1 shows the diagnostic criterion for RA. Most criteria are achieved through clinical examination and history. The two additional criteria are **rheumatoid factor** (RF) and **plain films**. RF is an autoimmune antibody to IgG and is positive in 70% to 80% of patients with RA. However, it is not specific for RA and by itself does not confirm the diagnosis. The following conditions may have a positive RF in the absence of RA:

- Older age
- Other autoimmune diseases (systemic lupus erythematosus, sarcoid, etc.)
- Infective endocarditis
- Liver disease (especially hepatitis C)
- Chronic infections (syphilis, leprosy, parasites)
- Hyperglobulinemic states

Plain films of the hands may demonstrate periarticular osteopenia or erosions, usually in more advanced disease.

Other laboratory findings measure the inflammatory nature of the disease, such as an increased erythrocyte sedimentation rate (ESR) or C-reactive protein. Joint aspiration is usually performed to rule out other causes, such as infection or gout. See Chapter 55 for discussion of joint fluid examination.

Chest x-ray may reveal extra-articular disease such as rheumatoid nodules, interstitial lung disease, or pleural effusions. Pulmonary nodules should be tested in the usual manner (see Chapter 19). Effusions that are tapped will show an exudative pattern, usually with a low fluid glucose level.

Patients with RA may also have atlantoaxial subluxation discovered on cervical spine films. This must be ruled out before manipulation of the patient's neck, as in endotracheal intubation.

TABLE 57-1

Criteria for Diagnosis of Rheumatoid Arthritis*

Morning stiffness of joints >1 hr
Arthritis (soft tissue swelling) of three or more joints
Arthritis of wrist, metacarpophalangeal, or proximal intraphalangeal joints
Symmetric arthritis
Rheumatoid nodules
Elevated rheumatoid factor
Hand or wrist films showing erosions or periarticular osteopenia

* Four or more criteria are necessary for definite diagnosis.

TREATMENT

The primary goal of treatment in RA is to achieve a complete remission, defined as absence of symptoms or objective synovitis, no radiographic progression, and a normal ESR. For most patients, early administration of **disease-modifying antirheumatic drugs** (DMARDs) is advocated to accomplish this goal. When remission is unable to be achieved, management focuses on pain control, maintenance of function, and slowing irreversible joint destruction. Patients with positive RF, erosions on hand films, or extra-articular manifestations tend to have a more severe disease course; however, there is no reliable way to predict poor prognosis.

Symptom relief in RA may initially rely on **nonsteroidal anti-inflammatory drugs**. Examples include ibuprofen, ketoprofen, and naproxen. NSAIDs do not significantly influence synovial inflammation or joint destruction. **Side effects of NSAIDs** are numerous and include:

- Peptic ulcers/gastritis
- Renal dysfunction
- Increased liver enzymes
- Rash

Cox-2 inhibitors (celecoxib, rofecoxib, valdecoxib) are NSAIDs that selectively inhibit the cyclooxygenase-2 enzyme (involved in inflammation) and not the cyclooxygenase-1 enzyme (involved in gastric mucosa protection). This theoretically should translate into an anti-inflammatory effect with lower gastrointestinal side effects. A few studies show a decreased risk of symptomatic peptic ulcers with long-term use of these agents.

DMARDs have the added benefit of slowing disease progression in RA. DMARDs should be started early (within 3 months) in almost all patients with RA to prevent further joint destruction. Typical DMARDs and their common side effects are:

- Methotrexate (bone marrow toxicity, hepatic fibrosis, pneumonitis, stomatitis)
- Sulfasalazine (rash)
- Antimalarials, such as hydroxychloroquine (retinopathy)
- Leflunomide (diarrhea, rash)
- Minocycline (hyperpigmentation)
- Gold (bone marrow toxicity, proteinuria, rash)
- Penicillamine (same side effects as gold)
- Azathioprine (immunosuppression)

Methotrexate is used as a first-line DMARD in many patients with RA. Methotrexate has a high clinical response rate and an acceptable treatment adherence rate. It is given in low dose (7.5–15 mg) in weekly intervals. The dose should be increased up to 25 mg weekly when patients fail to respond. A unique feature of methotrexate is that rheumatoid nodules may increase with initiation of treatment. Liver biopsy for cirrhosis was once recommended for all patients on treatment but now is reserved for persistent liver function abnormalities. Alcohol should certainly be avoided because it greatly increases risk of liver damage. Gastrointestinal symptoms may be decreased with oral folate supplements. An alternative to methotrexate therapy is leflunomide, a pyrimidine synthesis inhibitor. The dosage is 10 to 20 mg daily, and its efficacy is similar to methotrexate.

Corticosteroids remain controversial in RA. Low-dose prednisone may be effective, but the numerous side effects (osteoporosis, immunosuppression, hyperglycemia) make this choice less desirable.

In patients with uncontrolled disease on the above agents, **biologic agents** are newer DMARDs with promising results. Monoclonal antibodies against TNF-α (infliximab) and soluble TNF receptors (etanercept) have been effective in decreasing disease activity for up to 12 months in trials. Case reports of uncommon infections, such as mycobacterial infection, in treated patients have raised concerns about the safety of anti-TNF therapy. Additional trials have targeted IL-1 with a receptor antagonist (anakinra).

Monitoring in RA consists of following the patient's symptoms and examining joints for improvement. Other monitoring includes hand and/or foot films for disease progression, ESR, liver and renal function tests (especially for patients on NSAIDs or methotrexate), and regular retinal evaluation (if on hydroxychloroquine).

KEY POINTS

1. Rheumatoid arthritis is an inflammatory disease characterized by symmetric arthritis, most commonly affecting the wrist and the metacarpophalangeal and proximal interphalangeal joints. Morning stiffness is a key feature.
2. Rheumatoid factor is positive in 70% to 80% of patients with RA. This is not a specific test, however, and false positives occur in the elderly and in patients with other autoimmune diseases, liver diseases, and chronic infections.
3. Extra-articular manifestations of RA include rheumatoid nodules, pleural effusions, vasculitis, and Felty's syndrome (associated splenomegaly and leukopenia). Associated conditions include atlantoaxial subluxation and Baker's cysts.
4. Treatment consists of early institution of disease-modifying antirheumatic agents such as methotrexate, leflunomide, sulfasalazine, or hydroxychloroquine. Biologic agents against TNF-α are useful adjuncts for refractory cases.