

Rheumatoid arthritis (RA)

Tarlaan Hassanaghahi

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Rheumatoid arthritis

Epidemiology

- ▶ RA affects approximately 0.5-1% of the adult population worldwide.
- ▶ **incidence** : decreasing in recent decades
- ▶ **prevalence** : has remained the same because individuals with RA are living longer.
- ▶ more commonly in **females** than in males
- ▶ **2-3 : 1 ratio**
- ▶ Incidence increases between **25 and 55** years of age
it plateaus until the age of 75
then decreases

Rheumatoid arthritis

Definition

- ▶ chronic inflammatory disease
- ▶ unknown etiology
- ▶ symmetric , peripheral polyarthritis
- ▶ most common form of chronic inflammatory arthritis
- ▶ joint damage and physical disability

Rheumatoid arthritis

Definition

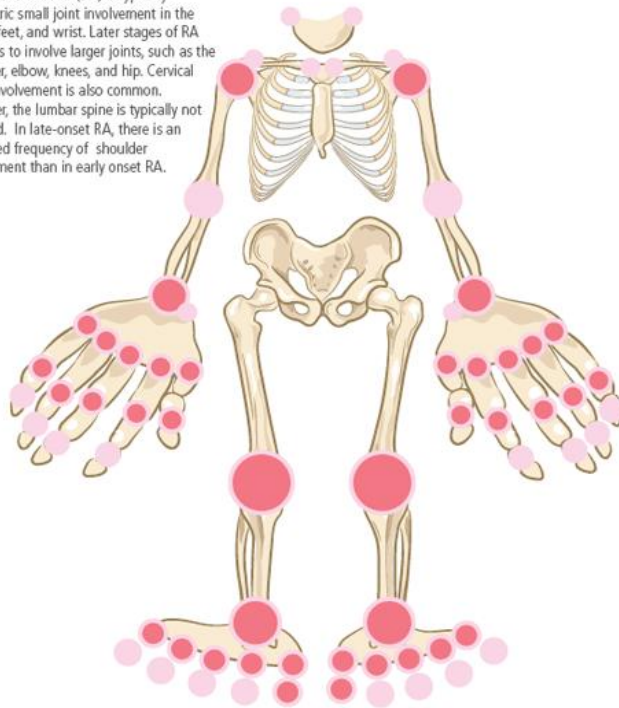
- ▶ early morning joint stiffness
- ▶ lasting more than 1 hour
- ▶ easing with physical activity.
- ▶ The earliest involved joints are typically the small joints of the hands and feet.
- ▶ chronic, irreversible deformities

The initial pattern of joint involvement may be

- ▶ monoarticular,
 - ▶ oligoarticular (4 joints)
 - ▶ polyarticular (>5 joints)
-
- ▶ usually in a symmetric distribution

clinical signs

The pattern of affected joints early in rheumatoid arthritis (RA) is typically symmetric small joint involvement in the hands, feet, and wrist. Later stages of RA progress to involve larger joints, such as the shoulder, elbow, knees, and hip. Cervical spine involvement is also common. However, the lumbar spine is typically not involved. In late-onset RA, there is an increased frequency of shoulder involvement than in early onset RA.



the most frequently involved joints

- ▶ wrists
- ▶ metacarpophalangeal (MCP)
- ▶ proximal interphalangeal (PIP)

Flexor tendon tenosynovitis

- ▶ hallmark of RA
- ▶ leads to decreased range of motion
- ▶ reduced grip strength,
- ▶ "trigger" fingers.

swan-neck deformity

Hyperextension of the PIP joint with flexion of the DIP joint



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boutonnière deformity

flexion of the PIP joint with
hyperextension of the DIP joint

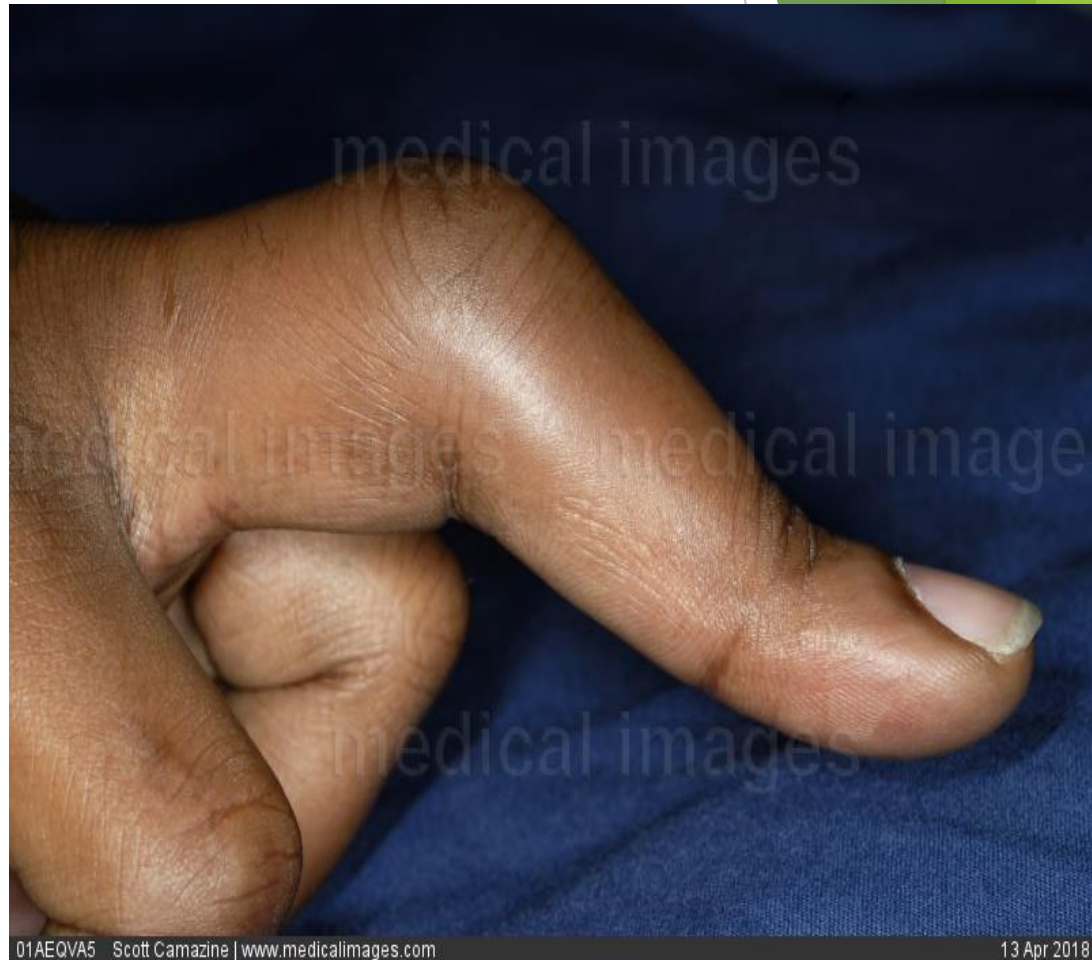




FIGURE 243-3. Severe advanced rheumatoid arthritis of the hands. There is massive tendon swelling over the dorsal surface of both wrists, severe muscle wasting, ulnar deviation of the metacarpophalangeal joints, and swan-neck deformity of the fingers. (From Forbes CD, Jackson WF. *Color Atlas and Text of Clinical Medicine*, 3rd ed. London: Mosby; 2003.)

Atlantoaxial involvement of the cervical spine

compressive myelopathy and
neurologic dysfunction



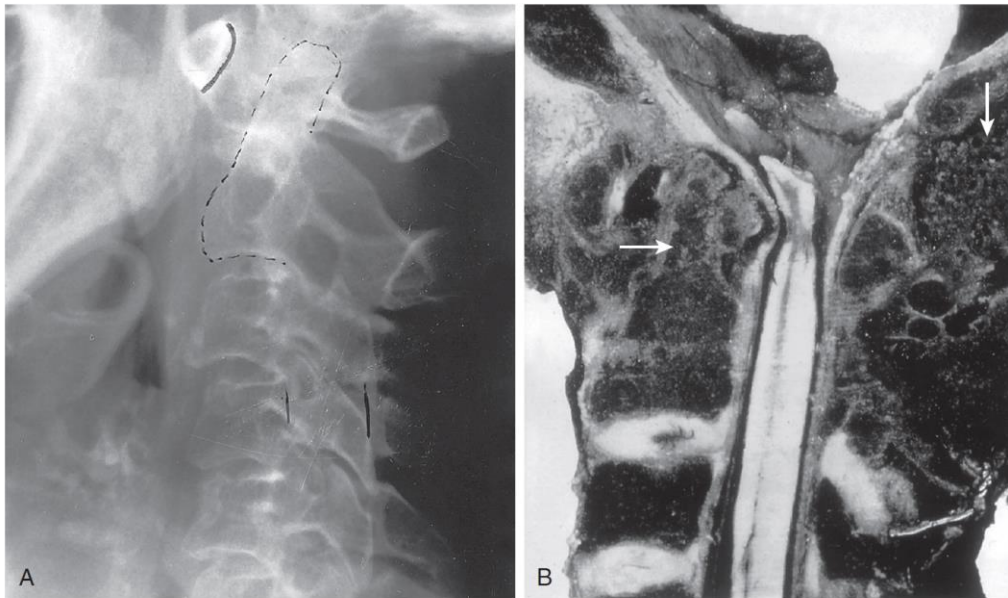


FIGURE 243-2. Subluxation of the cervical spine in patients with rheumatoid arthritis. A, In a lateral radiograph of the cervical spine, the body of C2 and its odontoid process are outlined by the *broken lines* and the posterior aspect of the anterior segment of C1 is indicated by a *solid line*. Normally, a space of only 2 to 3 mm separates C1 from C2. The space between C1 and the odontoid of C2 is markedly increased, indicative of subluxation of C1 and C2. B, Lateral view of a pathologic specimen from a patient who died of C1-C2 subluxation. The *horizontal arrow* shows the odontoid process that subluxed posteriorly, severely compressing and almost severing the cord. The *vertical arrow* shows a bone graft that had been put in place posteriorly in an attempt to prevent subluxation. Below the *arrow*, a nonhealing area is present through the bone graft, and inferior to that a wire fixation suture is still in place.

Extraarticular manifestations

- ▶ fatigue
- ▶ subcutaneous nodules
- ▶ lung involvement
- ▶ pericarditis
- ▶ peripheral neuropathy
- ▶ vasculitis
- ▶ hematologic abnormalities

Extraarticular manifestations

Patients most likely to develop extraarticular disease have:

- ▶ history of smoking
- ▶ Early onset of significant physical disability
- ▶ Positive for serum RF

the most frequently observed extraarticular manifestations:

- ▶ Subcutaneous nodules, secondary Sjögren's syndrome, pulmonary nodules, anemia

Extraarticular manifestations

Constitutional

These signs and symptoms include **weight loss, fever, fatigue, malaise, depression**, and in the most severe cases, **cachexia**.

In general, the presence of a fever of **>38.3°C** at any time during the clinical course should raise suspicion of systemic vasculitis or infection.

Subcutaneous nodules

- Firm
- Nontender
- Adherent to periosteum, tendons, or bursae
- Forearm, sacral prominences, and the Achilles tendon
- Benign





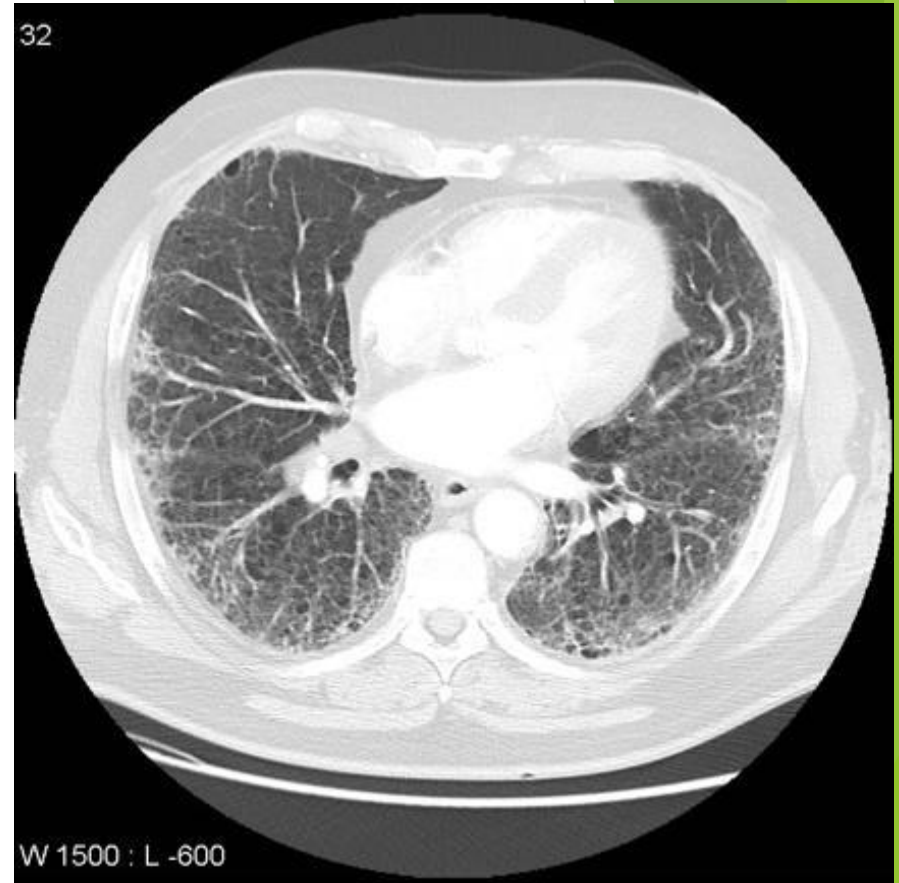
Extraarticular manifestations

Pulmonary

- ▶ **Pleural disease**, the most common pulmonary manifestation
- ▶ pleuritic chest pain and dyspnea, as well as a pleural friction rub and effusion.
- ▶ **Pleural effusions** tend to be exudative

Interstitial lung disease (ILD) :

- dry cough and progressive shortness of breath
- Restrictive
- decrease DLCO
- poor prognosis



Extraarticular manifestations

Cardiac

- ▶ The most frequent site of cardiac involvement in RA is the **pericardium**.
- ▶ **Cardiomyopathy**
- ▶ **Mitral regurgitation** is the most common valvular abnormality in RA

Extraarticular manifestations

Vasculitis

Rheumatoid vasculitis is seen most commonly in

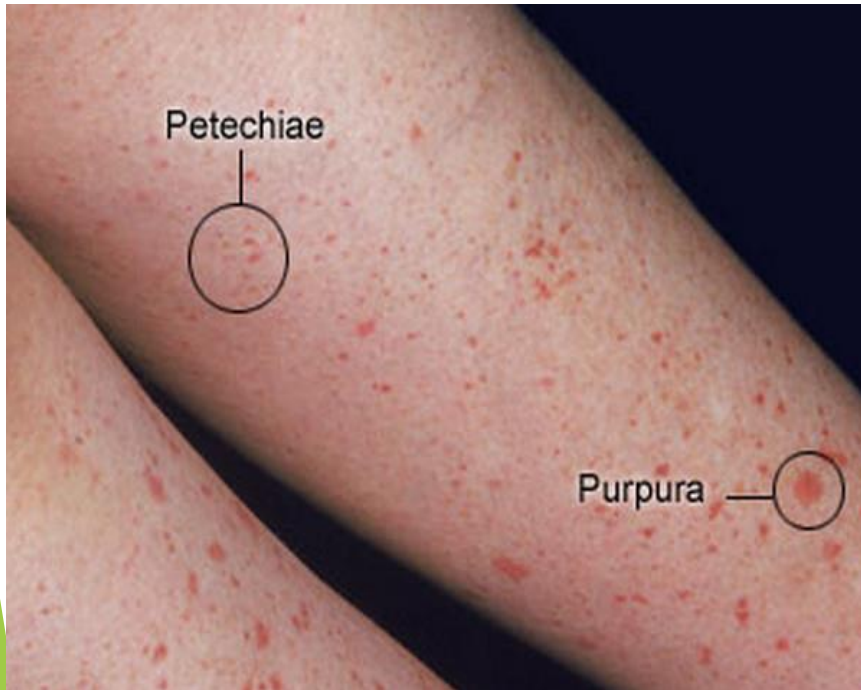
- ▶ patients with long-standing disease
- ▶ positive test for serum RF
- ▶ hypocomplementemia

- ▶ the overall incidence is quite rare, occurring in no more than **1%** of cases.

The cutaneous signs

- ▶ petechiae, purpura, digital infarcts, gangrene, livedo reticularis, and in severe cases large, painful lower extremity ulcerations.

Petechiae & purpura livedo reticularis





Extraarticular manifestations

Hematologic

- ▶ most common hematologic abnormality :
normochromic, normocytic anemia
- ▶ The degree of anemia parallels the degree of inflammation, correlating with the levels of serum C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR).
- ▶ **Platelet counts** may also be elevated in RA as an acute-phase reactant.

Extraarticular manifestations

Felty's syndrome

defined by the clinical triad of

- ▶ neutropenia
 - ▶ Splenomegaly
 - ▶ nodular RA
-
- ▶ less than 1% of patients.
-
- ▶ It typically occurs in white patients in the late stages of severe RA.

Extraarticular manifestations

Lymphoma

- ▶ **two- to four fold** increased risk of lymphoma
- ▶ The most common histopathologic type of lymphoma is a **diffuse large B-cell lymphoma**.
- ▶ The risk of developing lymphoma increases if the patient has **high levels of disease activity** or **Felty's syndrome**.

TABLE 243-1 EXTRA-ARTICULAR MANIFESTATIONS OF RHEUMATOID ARTHRITIS

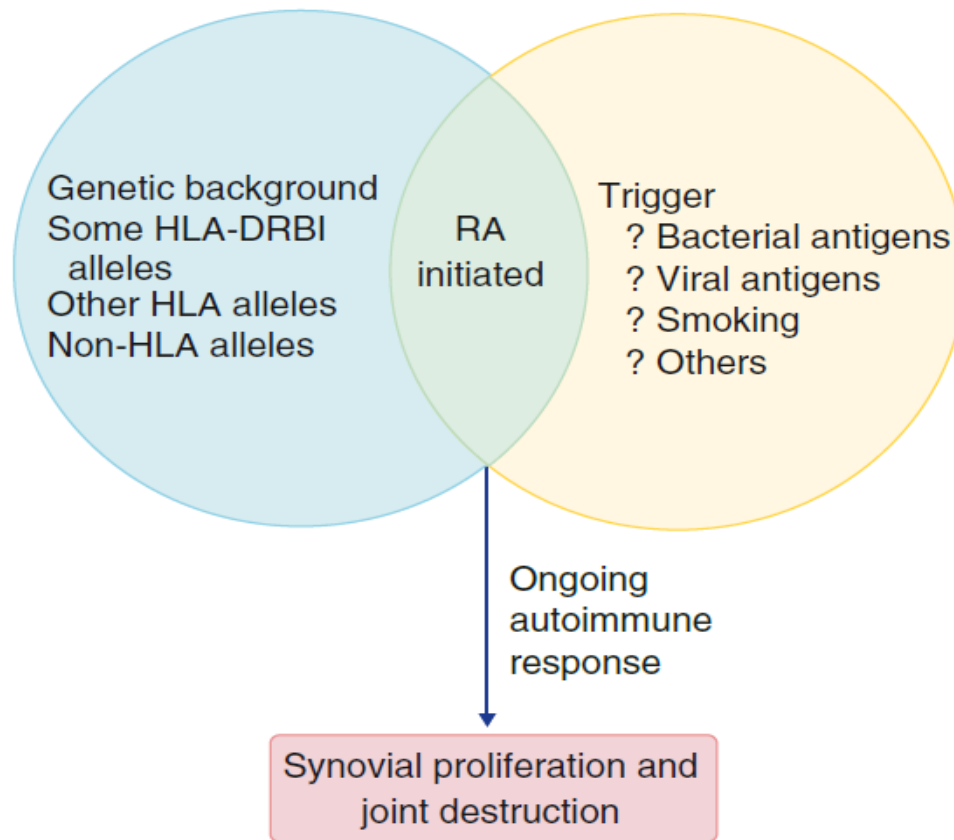
Skin	Nodules, fragility, vasculitis, pyoderma gangrenosum
Heart	Pericarditis, premature atherosclerosis, vasculitis, valve disease, and valve ring nodules
Lung	Pleural effusions, interstitial lung disease, bronchiolitis obliterans, rheumatoid nodules, vasculitis
Eye	Keratoconjunctivitis sicca, episcleritis, scleritis, scleromalacia perforans, peripheral ulcerative keratopathy
Neurologic	Entrapment neuropathy, cervical myelopathy, mononeuritis multiplex (vasculitis), peripheral neuropathy
Hematopoietic	Anemia, thrombocytosis, lymphadenopathy, Felty syndrome, large granular lymphocyte syndrome
Kidney	Amyloidosis, vasculitis
Bone	Osteopenia

Pathology

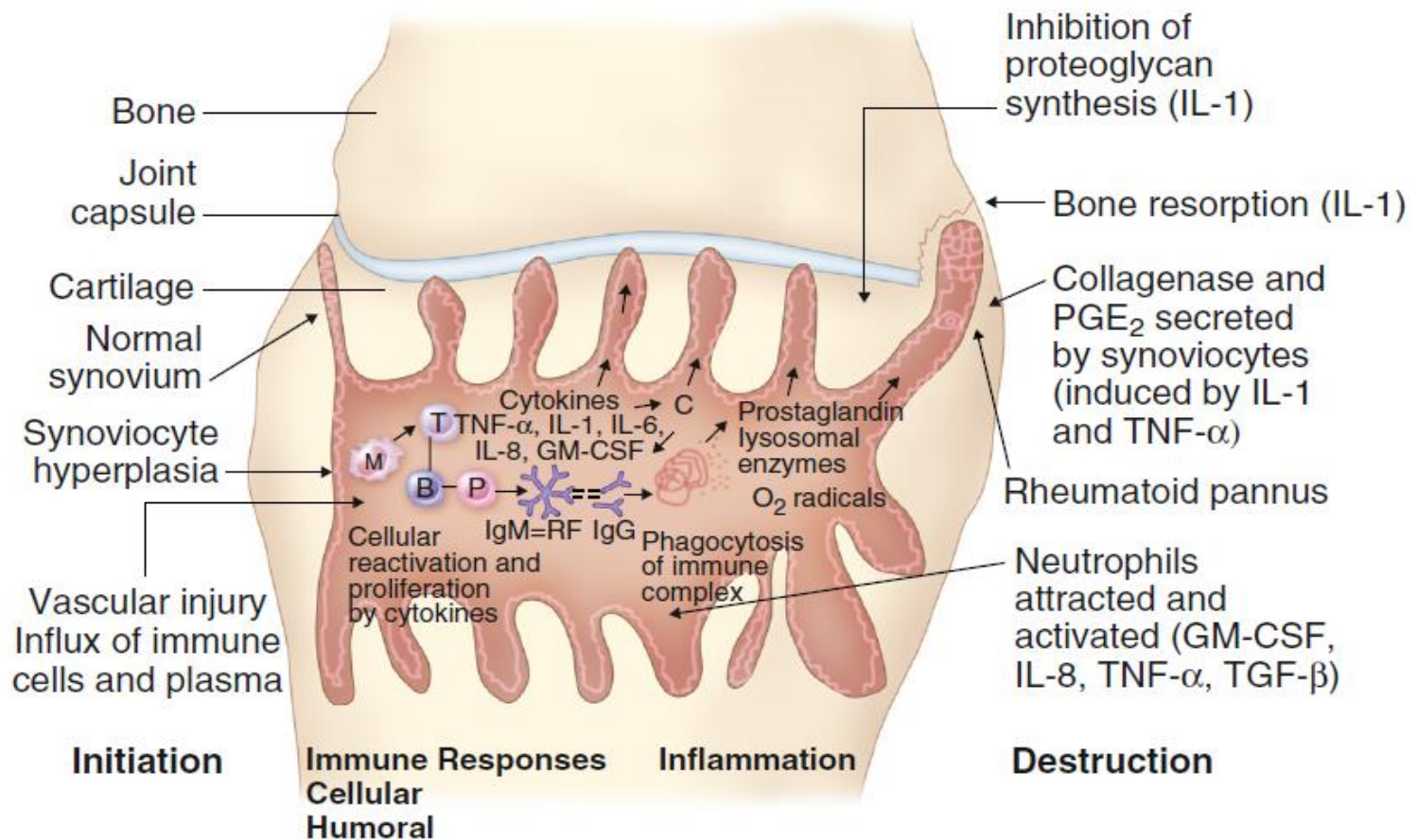
- ▶ RA affects the synovial tissue and underlying cartilage and bone.
- ▶ **The synovial membrane**, which covers most articular surfaces, tendon sheaths, and bursae, normally is a thin layer of connective tissue

The pathologic hallmarks :

- ▶ synovial inflammation and proliferation
- ▶ focal bone erosions
- ▶ thinning of articular cartilage

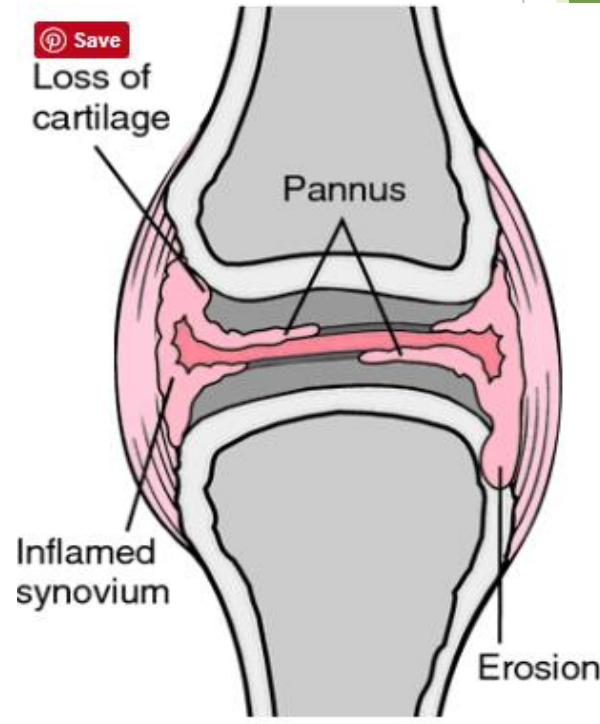


E-FIGURE 243-1. Initiation of rheumatoid arthritis (RA). HLA = human leukocyte antigen.



Pathology

- ▶ Chronic inflammation leads to synovial lining hyperplasia and the formation of **pannus**, a thickened cellular membrane of granulation-reactive fibrovascular tissue that invades the underlying cartilage and bone.



- ▶ The pathogenic mechanisms of synovial inflammation are likely to result from a complex interplay of :

genetic

environmental

immunologic factors that produces dysregulation of the immune system and a breakdown in self-tolerance

- ▶ **Smoking**
- ▶ **EBV**

► CD4+ T-cell

IL-17

- promoting joint inflammation
- destroying cartilage and subchondral bone

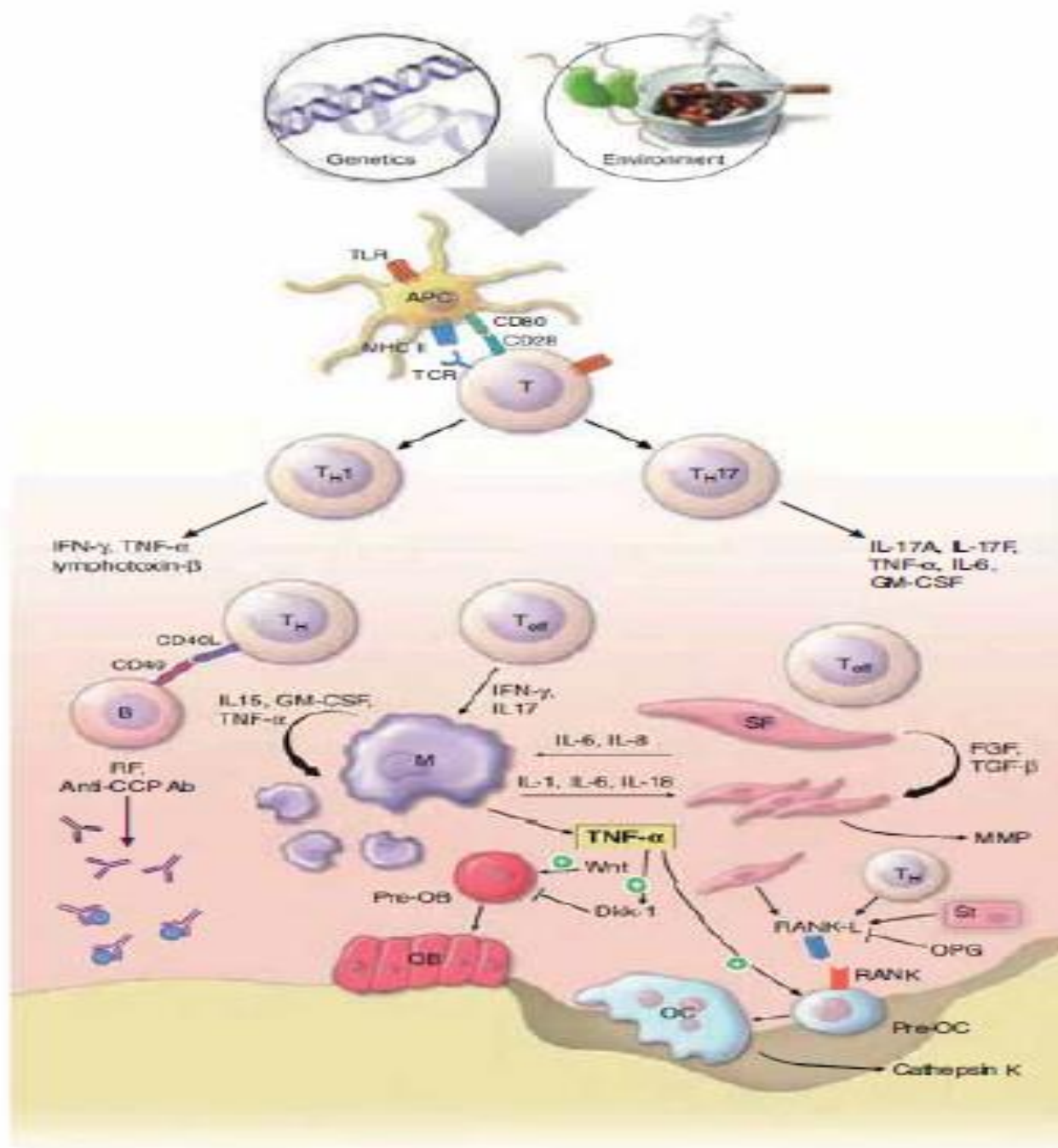
Activated B cells

- chronic inflammatory response.
- B cells give rise to plasma cells, which in turn, produce antibodies, including RF and anti-CCP antibodies.

TNF-a

- ▶ upregulates adhesion molecules on endothelial cells,
- ▶ promoting the influx of leukocytes into the synovial microenvironment.
- ▶ activates synovial fibroblasts
- ▶ stimulates angiogenesis
- ▶ promotes pain receptor sensitizing pathways
- ▶ drives osteoclastogenesis.

Fibroblasts secrete matrix metalloproteinases (MMPs) as well as other proteases that are chiefly responsible for the breakdown of articular cartilage



Diagnosis

- ▶ signs and symptoms of a chronic inflammatory arthritis,
 - ▶ Laboratory tests
 - ▶ radiographic results.
-
- ▶ Application of the newly revised **criteria** yields a **score of 0-10**, with a **score of 6** fulfilling the requirements for definite RA.

Diagnosis

Joint involvement

- ▶ 1 large joint (shoulder, elbow, hip, knee, ankle) 0
- ▶ 2-10 large joint 1
- ▶ 1-3 small joints (MCP, PIP, Thumb IP, MTP, wrists) 2
- ▶ 4-10 small joints 3
- ▶ >10 joints (at least 1 small joint) 5

Diagnosis

Serology

- ▶ Negative RF and negative ACPA 0
- ▶ Low-positive RF or low-positive anti-CCP antibodies (3 times ULN) 2
- ▶ High-positive RF or high-positive anti-CCP antibodies (>3 times ULN) 3

Acute-phase reactants

- ▶ Normal CRP and normal ESR 0
- ▶ Abnormal CRP or abnormal ESR 1

Diagnosis

Duration of symptoms

- ▶ <6 weeks 0
- ▶ 6 weeks 1

Joint Involvement (0-5)	
1 medium-large joint	0
2-10 medium-large joints	1
1-3 small joints	2
4-10 small joints	3
>10 joints (at least one small joint)	5
Serology (0-3)	
Neither RF or ACPA positive	0
At least one test low positive titre	2
At least one test high positive titre	3
Duration of Synovitis (0-1)	
<6 weeks	0
≥6 weeks	1
Acute Phase Reactants (0-1)	
Neither CRP or ESR abnormal	0
Abnormal CRP or abnormal ESR	1

Score ≥ 6 indicates
'Definite RA'

Low +: >1 & $\leq 3 \times$ ULN
High +: $>3 \times$ ULN

Medium/Large joints
Knee, hip, shoulders,
elbow and ankle

Small joints
PIPs, MCPs, wrists
and MTPs

Laboratory Features

- ▶ Serum IgM RF has been found in 75-80% of patients with RA; therefore, a negative result does not exclude the presence of this disease.
- ▶ The presence of serum anti-CCP antibodies has about the same sensitivity as serum RF for the diagnosis of RA. However, its diagnostic specificity approaches 95%
- ▶ The presence of RF or anti-CCP antibodies also has **prognostic significance**, with anti-CCP antibodies showing the most value for predicting worse outcomes.

Laboratory Features

Synovial Fluid Analysis

- ▶ between 5000 and 50,000 WBC / 3
- ▶ the overwhelming cell type in the synovial fluid is the neutrophil.

analysis of synovial fluid

- ▶ most useful for confirming an inflammatory arthritis
- ▶ while at the same time excluding infection or a crystal-induced arthritis such as gout or pseudogout

Plain Radiography

- ▶ the initial radiographic finding is **juxtaarticular osteopenia**.
- ▶ Other findings on plain radiographs include **soft tissue swelling**, **symmetric joint space loss**, and **subchondral erosions**, most frequently in the wrists and hands (MCPs and PIPs) and the feet (MTPs).
- ▶ **severe destruction**, including **joint subluxation and collapse**



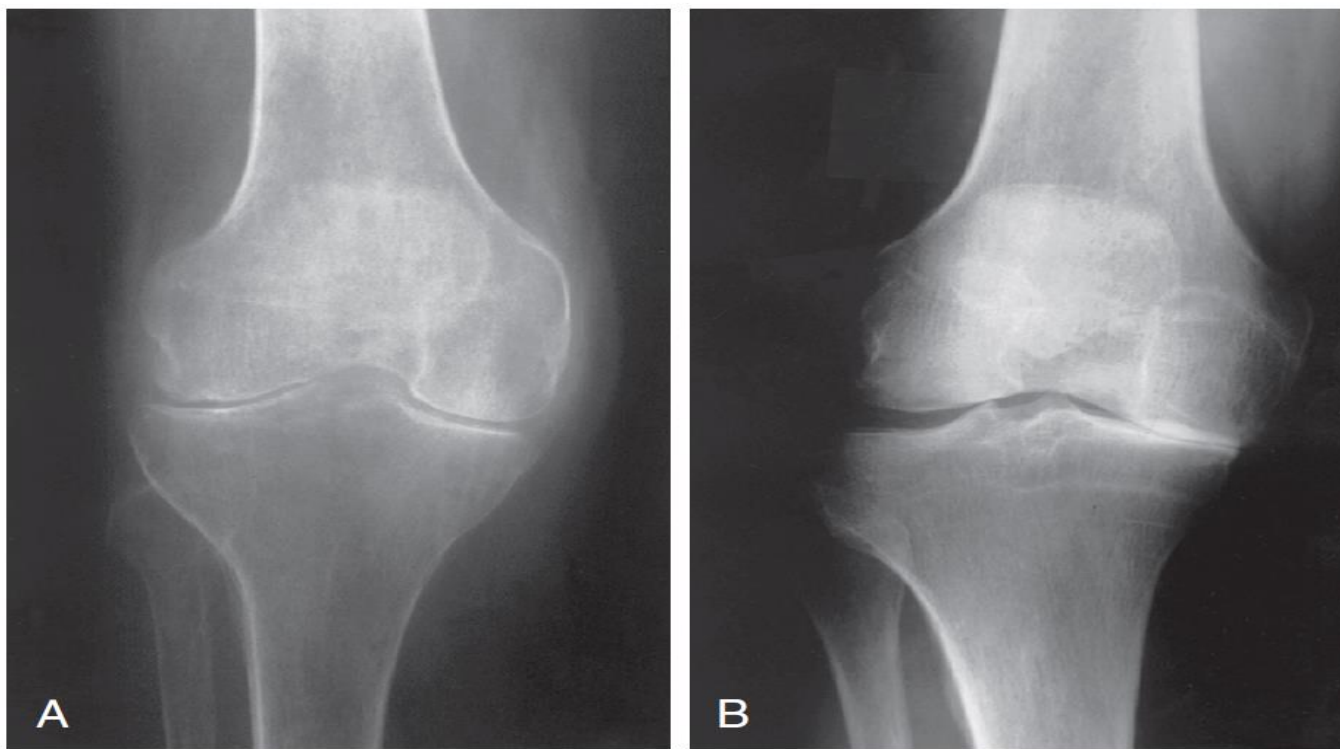


FIGURE 243-5. Radiographs of the knees in the two most common forms of arthritis: rheumatoid arthritis and osteoarthritis. **A**, Severe involvement in rheumatoid arthritis, with almost complete symmetrical loss of joint space in both the medial and the lateral compartments, but with little subchondral sclerosis or osteophyte formation. **B**, Typical osteoarthritis, with severe, near-total loss of joint space of one compartment and a normal or actually increased joint space of the other compartment. Note also the significant subchondral sclerosis in the involved area, typical of osteoarthritis.



Treatment

NSAIDs

analgesic and anti-inflammatory

NSAIDs are roughly equivalent in their efficacy, experience suggests that some individuals may preferentially respond to a particular NSAID

-

Treatment

- ▶ **Glucocorticoids** may serve in several ways to control disease activity in RA.
- ▶ First, they may be administered in low-to-moderate doses to achieve **rapid disease control** before the onset of fully effective DMARD therapy, which often takes several weeks or even months.
- ▶ Second, a 1-2 week burst of glucocorticoids may be prescribed for the management of **acute disease flares**, with dose and duration guided by the severity of the exacerbation

Treatment

DMARDs (Disease-Modifying Antirheumatic Drugs)

DMARDs are so named because of their ability to slow or prevent structural progression of RA.

The conventional DMARDs include hydroxychloroquine, sulfasalazine, methotrexate, and leflunomide;

they exhibit a delayed onset of action of approximately 6-12 weeks.

Methotrexate is the **DMARD of choice** for the treatment of RA and is the anchor drug for most combination therapies.

Treatment

Anti-TNF Agents

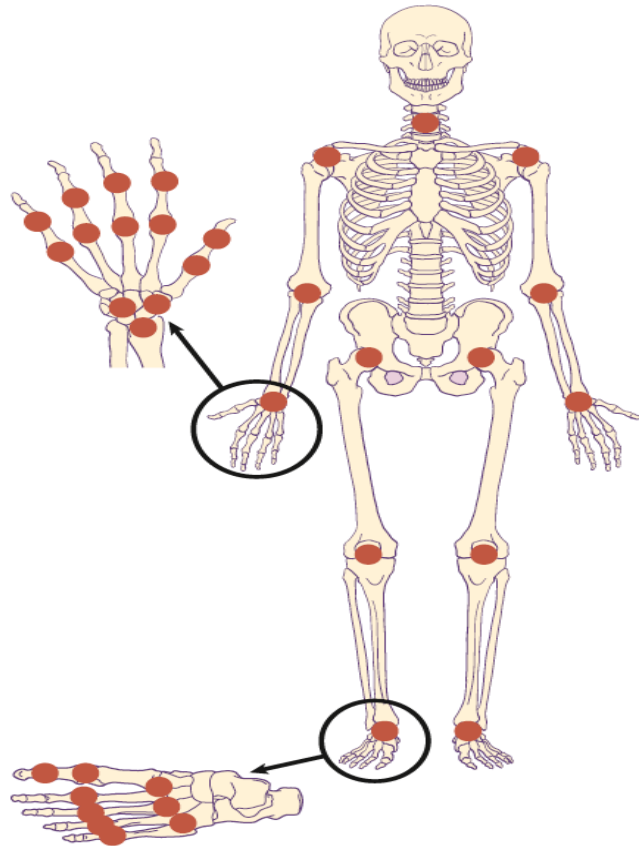
(Infliximab , Etanercept , adalimumab)

Reduce the signs and symptoms of RA, **slow** radiographic progression of joint damage, and **improve** physical function and quality of life.

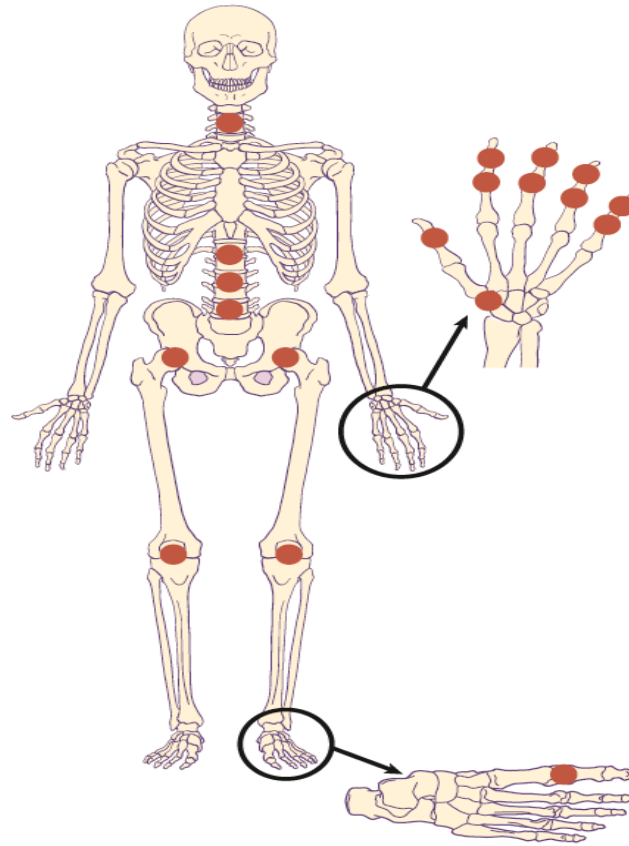
Anti-TNF drugs are typically used in combination with background methotrexate therapy.

the next step for treatment of patients with an inadequate response to methotrexate therapy.

Rheumatoid Arthritis



Osteoarthritis



RA and Pregnancy

- ▶ 75% improvement
- ▶ Often have flare up after delivery
- ▶ Flare up during pregnancy : low dose Prednisolon
- ▶ The Most safe DMARDs during Pregnancy: SSZ,HCQ
- ▶ MTX , LEF : teratogen