# MSS

## PATHOLOGY

**# 7**

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# RHEUMATOID ARTHRITIS

## *Important concepts about rheumatoid arthritis (RA):*

- Less common than osteoarthritis (DJD).
- **Chronic inflammatory disease (true inflammation).**
- **Autoimmune in nature** (failure of immune tolerance & abnormal activation of T lymphocytes - your own body is creating antibodies against your own tissue).
- **Attacks joints with nonsuppurative** (no bacteria included, no pus formation) **proliferative and inflammatory synovitis, leading to destruction of joints and ankylosis (adhesion,** fusion and rigidity of the bones of the joint and it's a common complication of RA).
- **Systemic disease which means it can affect (skin, heart, vessels & lungs) but the main target is the synovium and surrounding ligaments.**
- **1% prevalence in USA; F:M = 3:1 (important ratio); 4th-5th decade.**
- **Genetic predisposition + environmental factors play a role in the development, progression and chronicity of the disease (multifactorial; not easy to manage).**

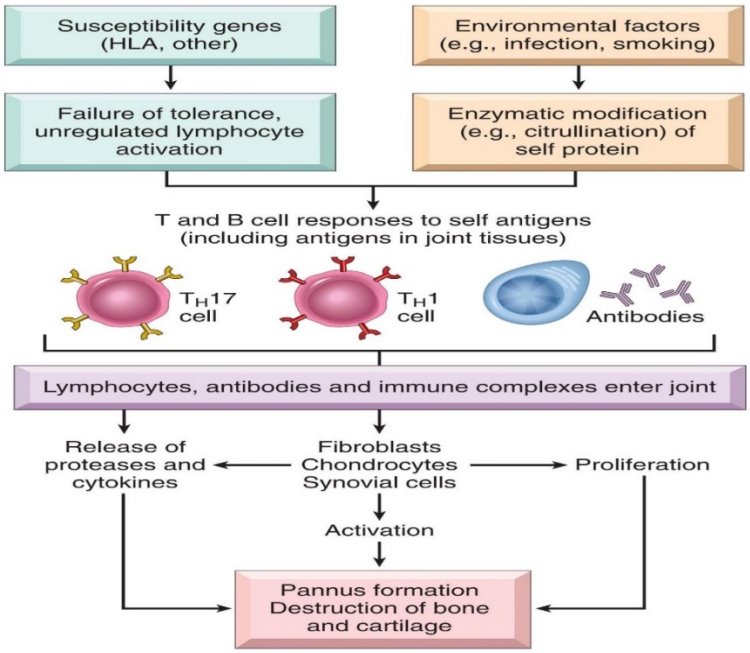
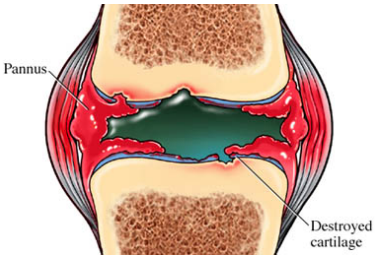



Fig. 21.36 Major processes involved in the pathogenesis of rheumatoid arthritis.

**Bone destruction is secondary to the primary pathogenesis which is proliferative autoimmune synovitis.*

Note: pannus formation means severe proliferation of the synovium & surrounding ligaments.



# PATHOGENESIS:

| Mediator | Function |
|---|---|
| IFN-γ from TH1 (one of the mediators that are triggered &released initially) | **Activates macrophages & synovial cells** |
| IL-17 from TH17 | **Recruits neutrophils and monocytes** |
| RANKL from T cells | **Stimulates osteoclasts & bone resorption** |
| **TNF** & IL-1 from macrophages<br>(Targeted therapy is possible here by giving anti-TNF) | **Stimulates residents synoviocytes to secrete proteases that destroy hyaline cartilage** |

- **80% of patients with RA have autoantibodies IgG & IgM against the Fc portion of their own IgG [Rheumatoid factor] → one of the main serum tests used to diagnose RA & it is more sensitive.**

  Note: not all cases of RA are rheumatoid factor positive, such cases are called seronegative RA.

  Seronegative: - Rheumatoid factor

  Seropositve: + Rheumatoid factor

- **70% of patients with RA have Anti-Citrulliniated Protein Antibodies (ACPA) → a newer test & it is more specific.**

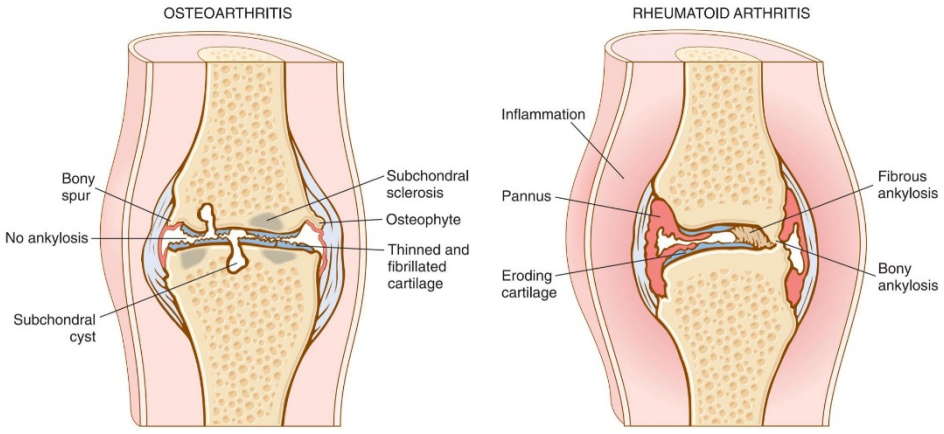



Fig. 21.35 Comparison of the morphologic features of rheumatoid arthritis and osteoarthritis.

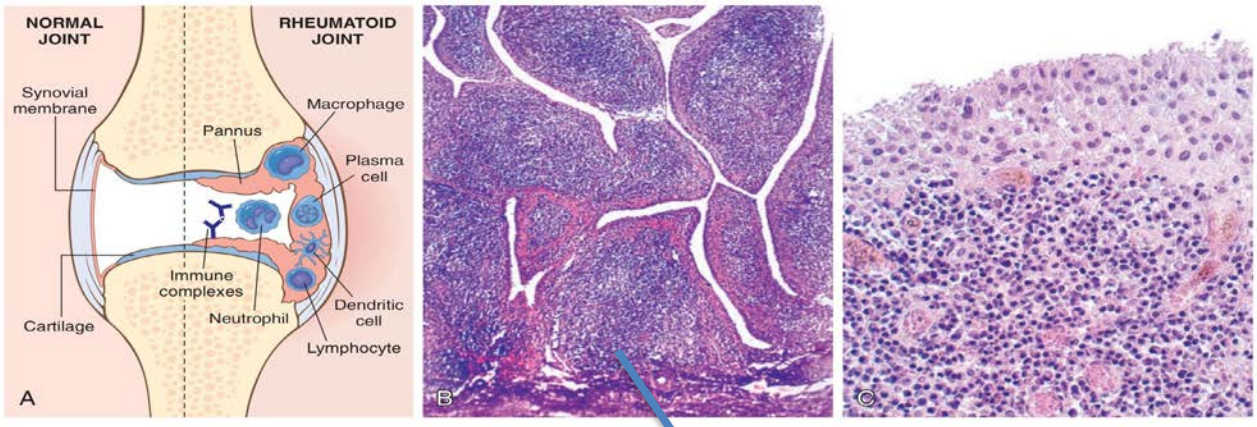



Fig. 21.37 Rheumatoid arthritis. (A) Schematic view of the joint lesion. (B) Low magnification shows marked synovial hypertrophy with formation of villi. (C) At higher magnification, subsynovial tissue containing a dense lymphoid aggregate. (A, *Modified from Feldmann M: Development of anti-TNF therapy for rheumatoid arthritis.* Nat Rev Immunol *2:364, 2002.*)

Proliferative synovitis (chronic inflammatory cells-lymphocytes)

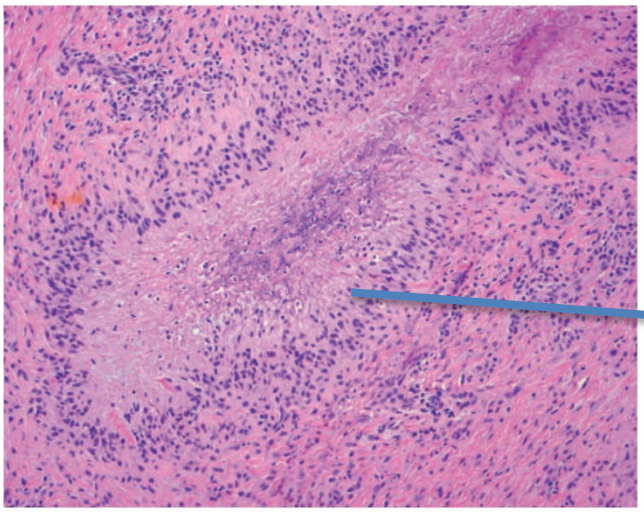
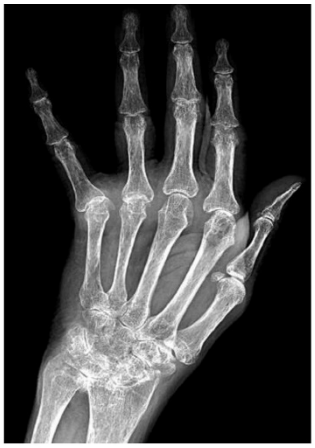


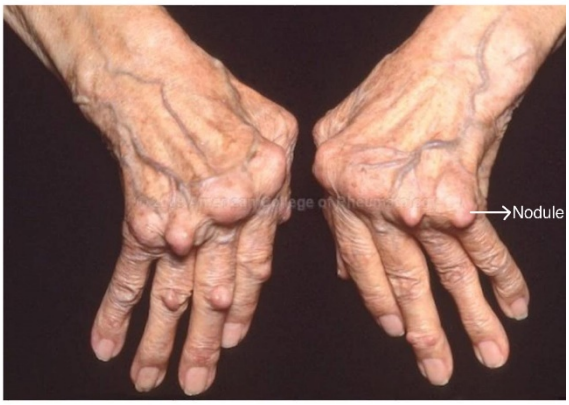
Fig. 21.38 Rheumatoid nodule composed of central necrosis rimmed by palisaded histiocytes.

Severe forms of RA include rheumatoid granulomas (with central necrosis), found mainly within rheumatoid nodules in the skin of extensor surfaces around elbows and small joints of the hand.

# CLINICAL COURSE OF RA:

- **Begins slowly and insidiously, polyarthritis.**
- **Symmetrical joints: hands, feet, wrists, ankle, MCP "metacarpophalangeal" and proximal IPJ "Interphalangeal joints" are commonly affected (affects both right and left hands and so on..).**
- **Joints: warm, swollen & painful.**
- **Stiffness when inactive and in the morning (one of the major diagnostic clinical signs for RA) → the stiffness improves with movement.**
- **Waxing and waning chronic (patient's status shifts back and forth** يعني أيام تعبانين وأيام أحسن**).**
- **Ulnar deviation.**
- **Trx: Steroids, MTX(Methotrexate), Anti-TNF.**





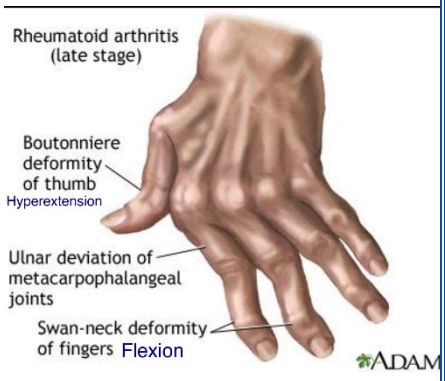




Fig. 21.39 Rheumatoid arthritis of the hand. Characteristic features include diffuse osteopenia, marked loss of the joint spaces of the carpal, metacarpal, phalangeal, and interphalangeal joints, periarticular bony erosions, and ulnar drift of the fingers.

# JUVENILE IDIOPATHIC ARTHRITIS (JIA):

- Side note: the disease was called Juvenile Rheumatoid Arthritis.
- Chronic, autoimmune, synovial-targeted, proliferative disease (same as RA with minor differences).
- **Heterogeneous group; arthritis of unknown cause; <16 years for at least 6 weeks (JIA is excluded from DDX (differential diagnosis) in older patients).**
- **Pathogenesis is similar to adult RA (autoimmune, autoantibodies).**
- **Prognosis variable** (mostly good)**; only 10% will have serious functional disability.**

| **In contrast to adults RA; JIA is characterized by** *(the major differences)***:** |
|---|
| **Oligoarthritis is more common (involving 1-3 joints).** |
| **Systemic disease is more common;** makes the disease harder to diagnose the patient presents with heart failure, renal failure,… |
| **Large joints are affected more than small joints (elbow, knee).** |
| **Rheumatoid nodules and Rheum Factor are usually absent.** |
| **Anti-Nuclear Antibody (ANA) seropositivity is common.** |

- Side note: ANA is a simple initial screening test for autoimmune diseases.
- Adults→ RF // Children→ ANA.
- Those autoimmune diseases produce an inflammatory reaction, so the treatment includes anti-inflammatory drugs.

# SERONEGATIVE ARTHROPATHIES

- Seronegative: RF negative.
- The main target of the disease is ligaments (ligamentitis).

| **HETEROGENOUS GROUP** WITH UNKNOWN ETIOLOGY **THAT SHARE THE FOLLOWING FEATURES:** |
|---|
| **Absence of rheumatoid factor** |
| **Ligaments pathology rather than synovium** |
| **Sacroiliac joints mainly (sacroiliitis)** |
| **Association with HLA-B27 (human leukocyte antigen)** |
| **Bony ankylosis (fusion)** |

- **Autoimmune T cell response to unidentified antigen (possibly infectious agent) that cross react with self-musculoskeletal antigens.**
- HLA-B27 + sacroiliac joint pain+ RF negative→ seronegative.
- **Ankylosing spondylitis: most common prototype.**
- **Destructive arthritis and bony damage and ankylosis of sacroiliac joint, main joint involved.**
- **90% HLA-B27.**
- **Anti-IL17 has shown some efficacy as treatment (targeted therapy).**

Sacroiliac joint test (Faber's test) elaboration: https://www.youtube.com/watch?v=zEFw64YxXYk

# SERONEGATIVE SPONDYLOARTHROPATHIES:

- **Ankylosing Spondylitis:**

  **Adolescent boys, HLA B27, axial joints (sacroiliac).**

- **Reiter Syndrome:**

  **Triad of arthritis, urethritis (males)/ cervicitis (females) and conjunctivitis,** usually induced by bacterial infections (mainly STD; sexually transmitted diseases) such as gonococcal infections.

  Good prognosis.

- **Enteropathic Arthritis:**

  **Secondary to bowel infection (salmonella, shigella).**

  **HLA B27 positive.**

- **Psoriatic Arthritis:**

  **5% of patients, starts in DIP (distal interphalangeal) joints, similar to RA (arthritis+ psoriasis).**

**Spondyloarthropathies: Subtype Classification**

| Ankylosing Spondylitis | Psoriatic Arthritis | Enteropathic (IBD-associated) | Reactive Arthritis | Undifferentiated SpA |
|---|---|---|---|---|
| Most common subtype along with uSpa<br>2.5:1 male:female<br>Gradual onset of IBP<br>Acute anterior uveitis most common extra-articular manifestation<br>Can lead to sacroiliac fusion and spinal syndesmophyte formation | Between 10% and 40% of patients with psoriasis develop PsA, depending on study population and psoriasis severity<br><br>Most phenotypically diverse SpA with 5 subtypes<br><br>Skin disease precedes joint disease in approximately 70% of cases | 5% to 29% of patients with IBD develop arthritis<br><br>Peripheral arthritis (not axial) can parallel bowel inflammation and can occur in up to 20% of patients<br><br>Spondylitis occurs in 3% to 6% | Typical acute asymmetric oligoarticular (<4 joints) arthritis 1-3 months after gastrointestinal and genitourinary infection<br>Characteristic triad of urethritis, conjunctivitis, and arthritis seen in < 35% of patients<br>Keratoderma blennorrhagica and circinate balanitis | Most common subtype along with AS<br><br>Typically used to describe patients not fulfilling criteria of any one SpA but presenting with IBP and other extra-articular SpA manifestations<br><br>Up to 50% of uSpA will develop into AS |

*uSpA = undifferentiated SpA; IBP = inflammatory back pain; PsA = psoriatic arthritis; IBD = inflammatory bowel disease; AS = ankylosing spondylitis*

# SUPPURATIVE ARTHRITIS:

- Side note: pyogenic osteomyelitis may cause suppurative arthritis and vice versa.
- **Bacterial infection.**
- **Hematogenous spread.**
- **< 2 years: *H. influenza;* older children & adults *S. aureus;* gonococcus young adults.**
- **Sickle cell disease: salmonella** (common in sickle cell patients but still not the most common).

- **Clinically: sudden acute pain, swollen and warm inflamed joints, mainly knee with systemic manifestation (fever, leukocytosis, elevated ESR (erythrocyte sedimentation rate, non-specific).**
- **Dx & Rx: aspiration of joint; antibiotics (empiric therapy).**

# LYME ARTHRITIS

- Common in Northeastern America.
- Caused by infection with the spirochete *Borrelia burgdorferi*.
- Transmitted by deer ticks.
- Responses to *Borrelia* may initiate late, autoimmune, arthritis.
- Note the phases of the disease ↓

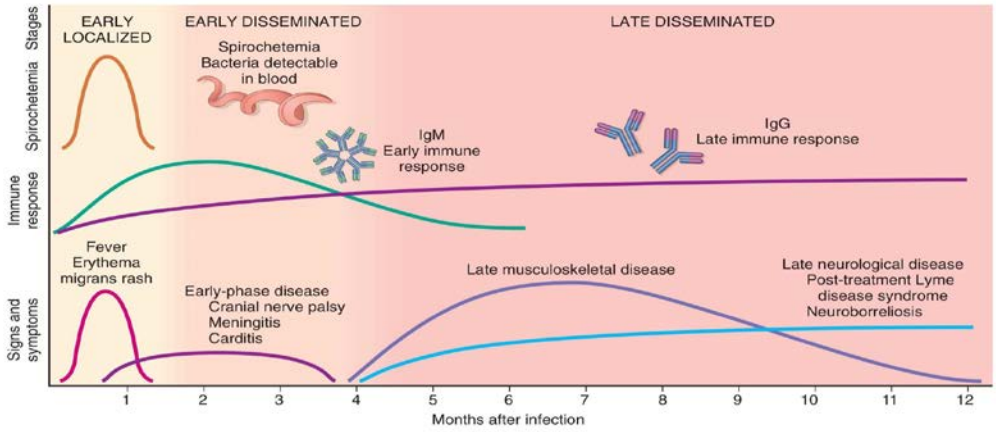



Fig. 21.40 Lyme disease progresses through three clinically recognizable phases: early localized, early disseminated, and late persistent. Although initial manifestations result directly from spirochete infection, later signs and symptoms are likely immune-mediated. *(Figure modified from Dr. Charles Chiu, University of California San Francisco, San Francisco, California. Used with permission.)*

# CRYSTAL-INDUCED ARTHRITIS:

- **Crystals deposited in joints causing severe inflammatory disease with acute, subacute and chronic attacks.**
- **Crystals triggers inflammatory reaction that destroys cartilage.**
- **Endogenous crystals:**
  - **Monosodium urate, MSU (GOUT).**
  - **Calcium pyrophosphate dehydrogenase, CPPD (PSEUDOGOUT).**

*Best wishes <3*

# V1