MUSCULOSKELETAL PATHOLOGY-6 JOINT DISEASES

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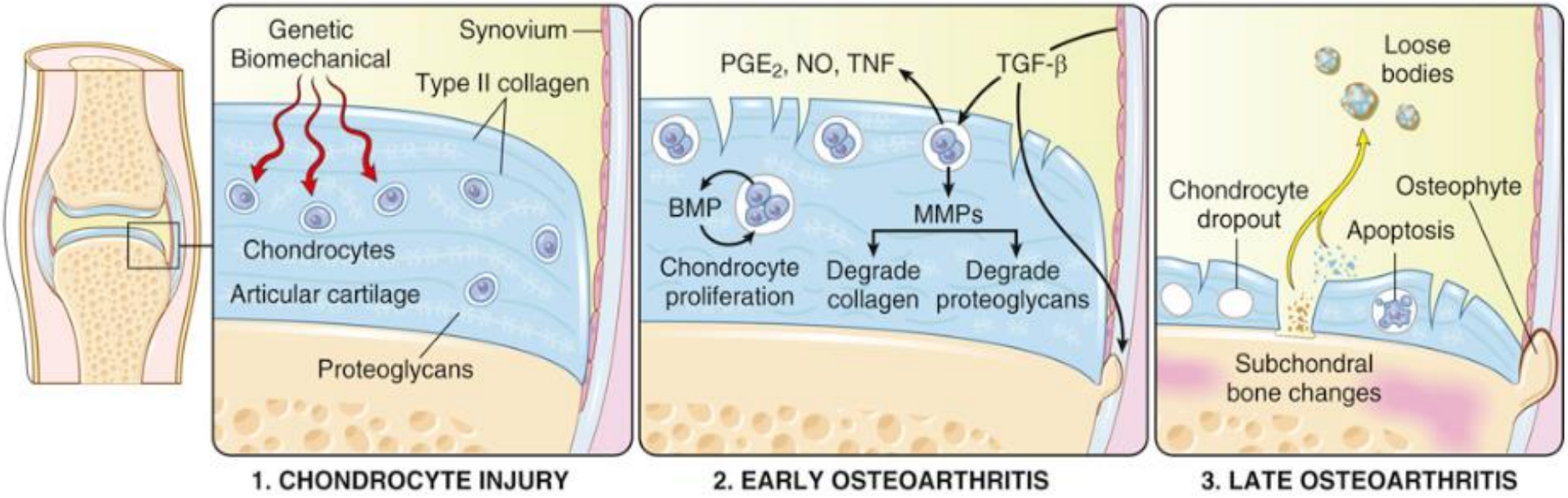
OSTEOARTHRITIS

- The most common joint disorder
- Important cause of physical disability in individuals over the age of 65
- Degenerative joint disease, results from cartilage degeneration
- Inflammation can be present as a minor and secondary process
- Primary OA (95%): most common, insidious onset, no initiating factor, oligoarticular, old age
- Secondary OA (5%): of cases, young age, history of trauma, DM, hemochromatosis, marked obesity, subchondral osteonecrosis, one or many joints
- Gender has some influence; knees and hands are more commonly affected in women, whereas hips are more commonly affected in men

PATHOGENESIS

* Mechanical stresses and aging causes damage to chondrocytes

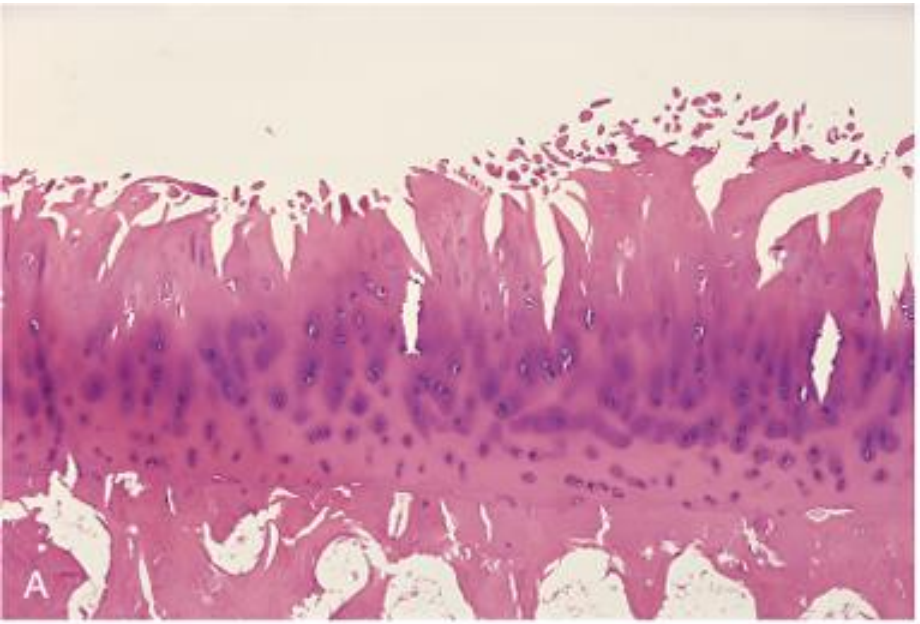
- Polymorphism in genes encoding components of the matrix and signaling molecules (repair)
- After injury, chondrocytes proliferate and secrete metalloproteinases, that degrade collagen-II (normally appears as horizontal lines in cartilage)
- Cartilage becomes more watery, the concentration of proteoglycans decreases
- Superficial cartilage becomes soft, shows clefts and cracks
- Cytokines, secreted from chondrocytes, synovial cells and macrophages (TGF-β), nitric oxide (NO), IL-1, IL6, prostaglandins induce production of metalloproteinases and further damage cartilage
- TGF-β & bone morphogenic proteins induce bone growth and formation of osteophytes (bone spurs)

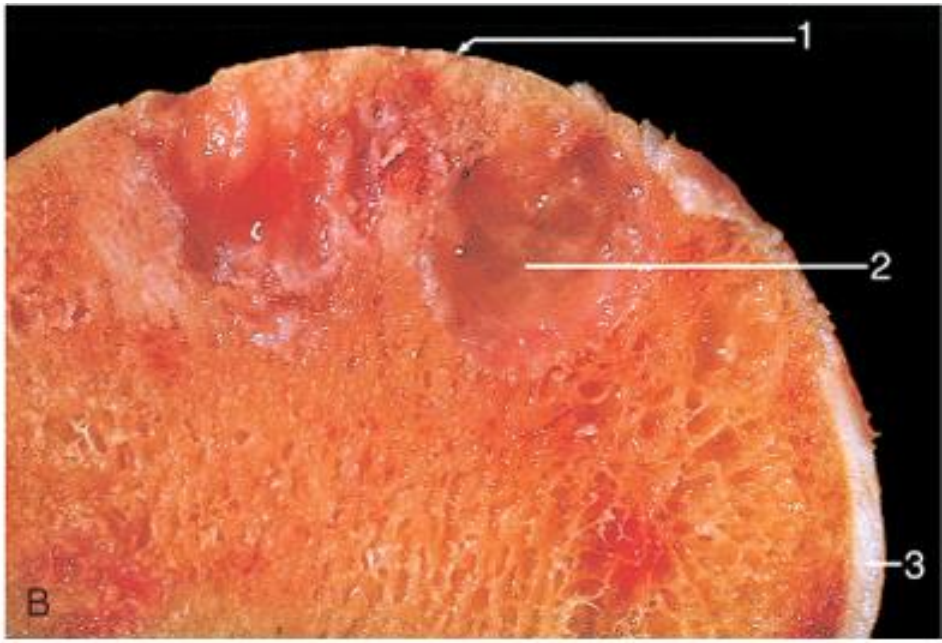


- Schematic view of osteoarthritis (OA). OA is thought to be initiated by chondrocyte injury (1) in a genetically predisposed patient leading to changes in the extracellular matrix. (2) Although chondrocytes may proliferate and attempt to repair damaged matrix, continued degradation exceeds repair in early OA. (3) Late OA is evidenced by loss of both matrix and chondrocytes with subchondral bone damage. BMP, Bone morphogenetic protein; MMPs, matrix metalloproteinases; NO, nitric oxide; PGE2, prostaglandin E2; TGF-β, transforming growth factor β; TNF, tumor necrosis factor.

MORPHOLOGY

- Advanced stage: full thickness cracking of the matrix occur as the
- Detached fragments of cartilage move freely in joint space (joint mice)
- Loss of chondrocytes
- Subchondral bone becomes exposed, friction between bones change their appearance as polished ivory (bone eburnation)
- Small fractures develop in exposed bones, allowing synovial fluid to accumulate in gaps and form a fibrous cyst in subchondral bone
- Mushroom-shaped **osteophytes** (bony outgrowths) develop at the margins of the articular surface





- Osteoarthritis. (A) Histologic demonstration of the characteristic fibrillation of the articular cartilage. (B) Eburnated articular surface exposing subchondral bone (1), subchondral cyst (2), and residual articular cartilage (3).

CLINICAL FEATURES

- Insidious onset
- Patients, in their 50s and 60s
- Characteristic symptoms include deep, aching pain exacerbated by use, morning stiffness, crepitus, and limited range of movement
- Vertebral involvement: osteophytes cause nerve impingement and neuropathy
- *Heberden nodes* in the fingers, representing prominent osteophytes at the distal interphalangeal joints, are characteristic in women.

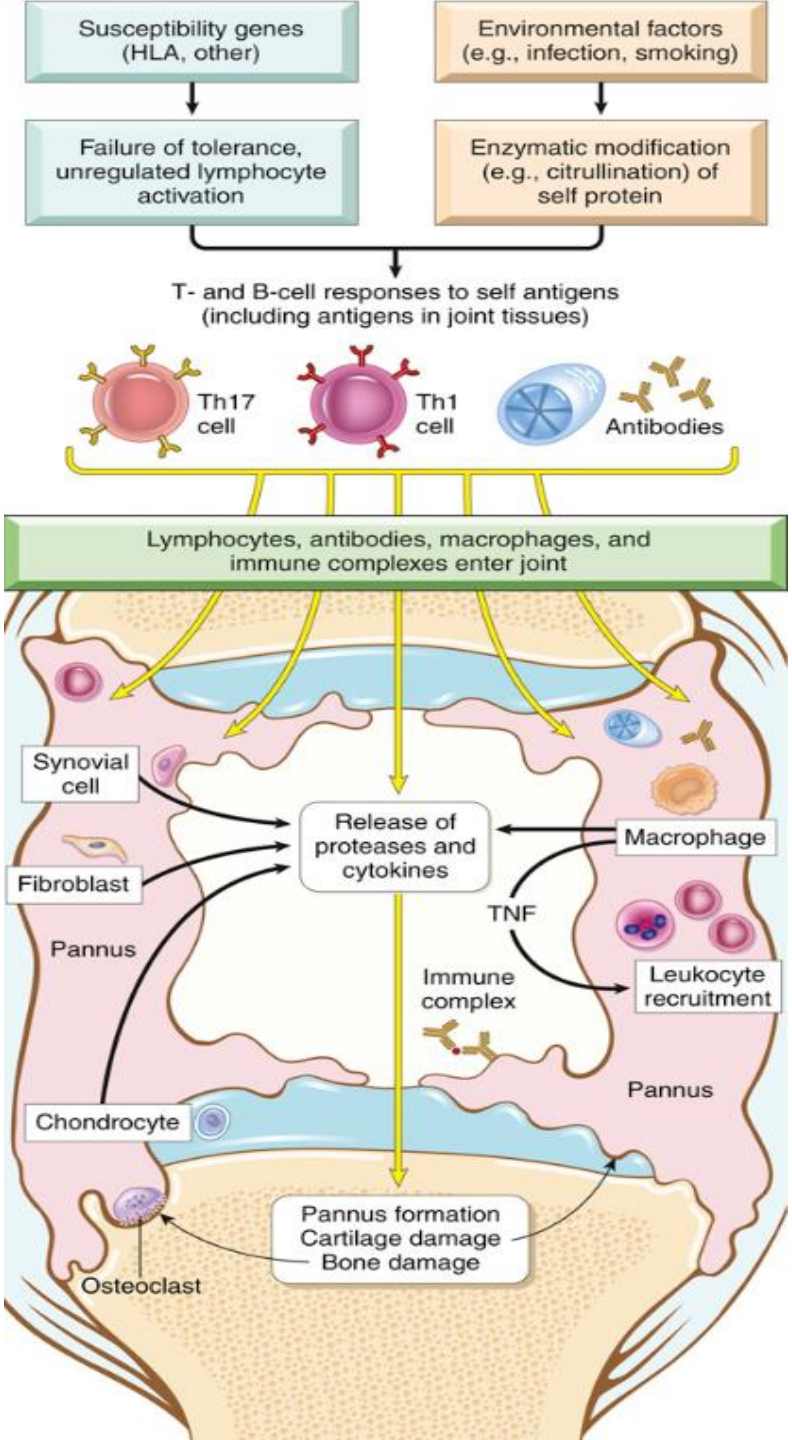
- With time, significant joint deformity can occur, but unlike rheumatoid arthritis, fusion does not take place.

RHEUMATOID ARTHRITIS

- Chronic autoimmune (non-suppurative) arthritis
- Severe inflammation, leading to joint destruction and joint fusion (ankylosis)
- Symmetric arthritis, affecting mainly small joints
- Extraarticular inflammation may affect skin, lung, blood vessels, heart
- More common in women, peaks in 30-50 years
- Insidious onset
- Joint pain and stiffness is more prominent in the morning or following inactivity

PATHOGENESIS

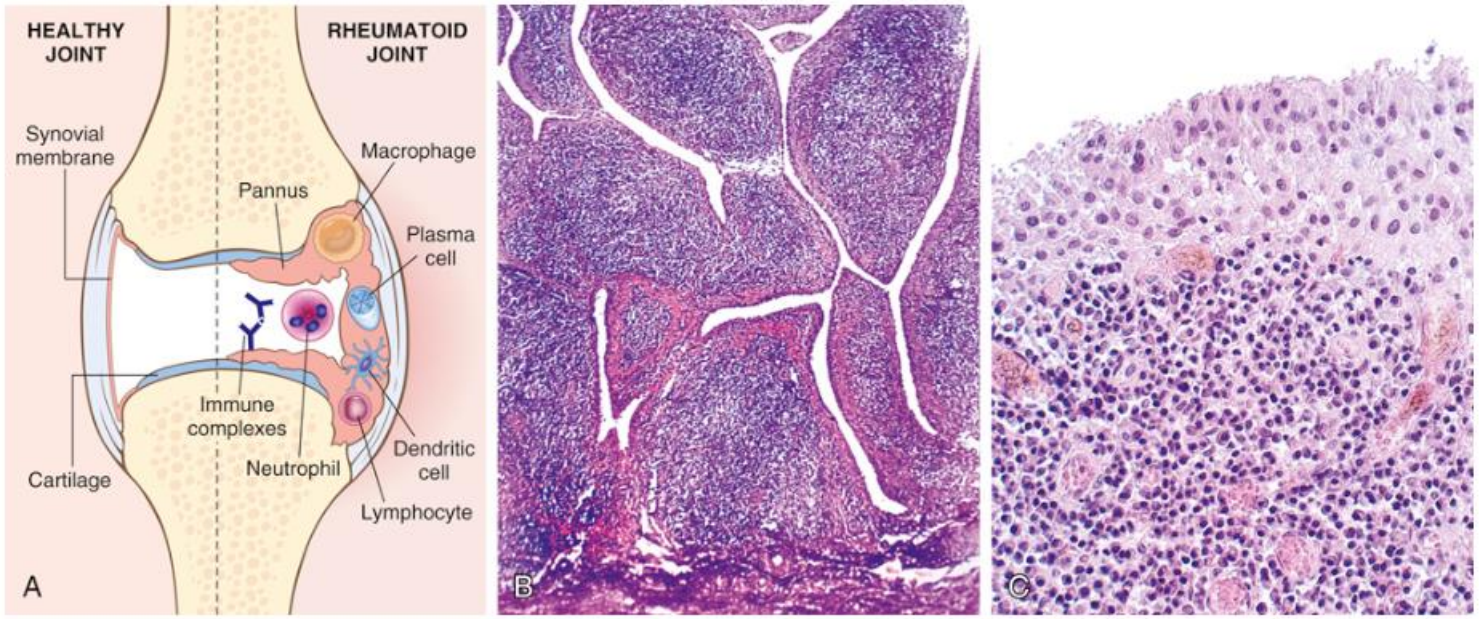
- CD4+ T-cells become autoreactive against joint antigens
- Secreted TNF, IL-1, IL-6 from macrophages lead to secretion of proteases that destroy cartilage
- IL-17 recruits neutrophils and monocytes
- RANKL is expressed on activated T-cells, stimulating osteoclasts which lead to bone resorption
- Activated B-lymphocytes and plasma cells secrete:
- 1) anti-citrullinated peptide antibody (ACPA): which targets fibrinogen, collagen-II, vinculin & α-enolase, present in 70% of patients
- 2) Rheumatoid factor: IgM or IgA autoantibodies that target Fc fragment of normal serum IgG, present in 80% of patients
- Genetic susceptibility: more common in people with HLA-DR4
- Environmental factors: smoking & local infection promote citrullination of proteins, triggering immune response



- Major processes involved in the pathogenesis of rheumatoid arthritis. HLA, Human leukocyte antigen; TNF, tumor necrosis factor

MORPHOLOGY

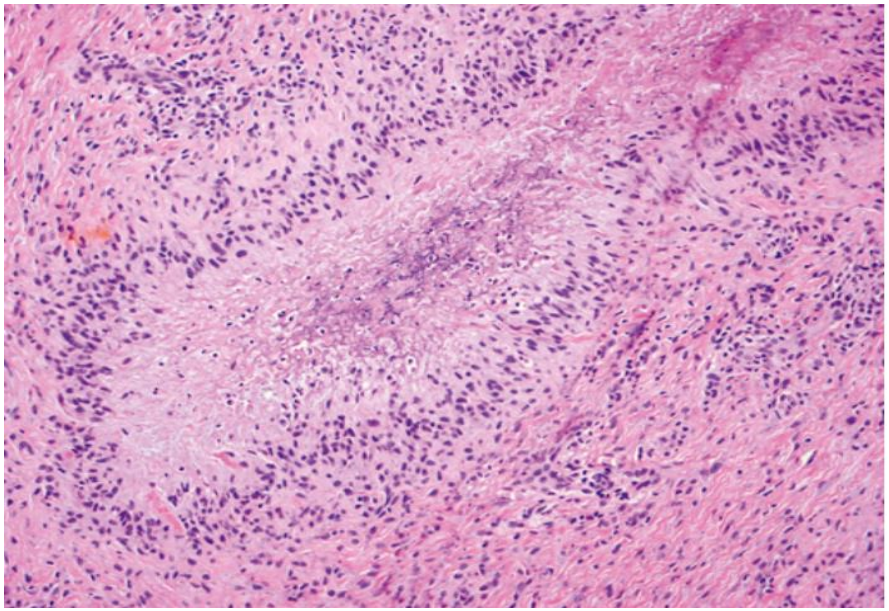
- Synovium is markedly thickened (pannus), secondary to synovial cell hyperplasia, inflammatory cells infiltration, fibroblast proliferation
- Granulation tissue: Neutrophils, new blood vessel formation (angiogenesis), fibrin
- Cartilage damage
- Prominent osteoclasts in bone trabeculae, subchondral cyst
- With time, pannus fills the joint space, make a bridge between bones, then ossifies, causing ankylosis

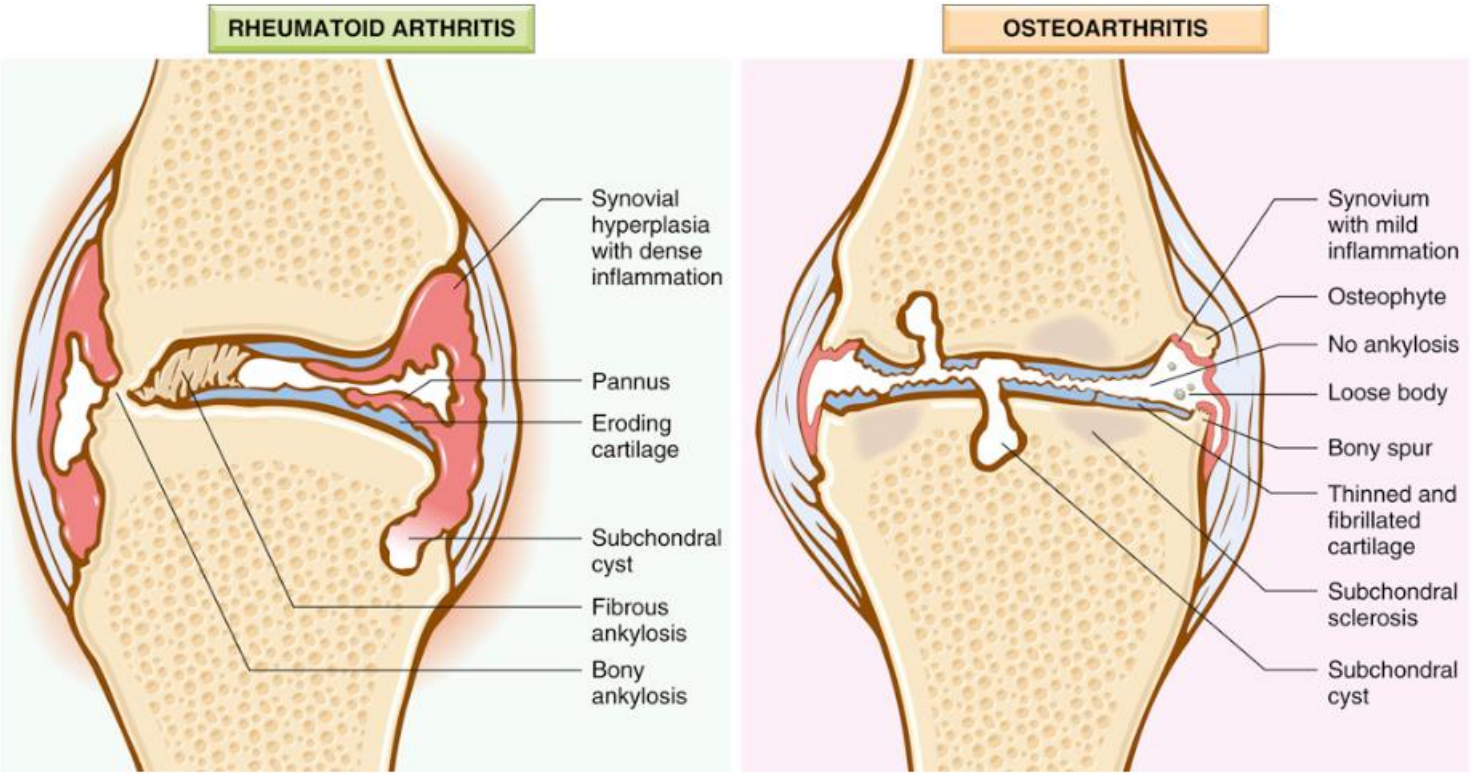


- Rheumatoid arthritis. (A) Schematic view of the joint lesion. (B) Low magnification shows marked synovial hypertrophy with formation of villi and a dense lymphocytic infiltrate. (C) At higher magnification, numerous plasma cells are seen beneath the hyperplastic synovium

RHEUMATOID NODULE

- A subcutaneous firm mass appears in forearm, occiput, lower back or lung
- Microscopically shows central necrosis rimmed by palisaded histiocytes





- Comparison of the morphologic features of rheumatoid arthritis and osteoarthritis.

Comparative Features of Osteoarthritis and Rheumatoid Arthritis

	Osteoarthritis	Rheumatoid Arthritis
Primary pathogenic abnormality	Mechanical injury to articular cartilage	Autoimmunity
Role of inflammation	May be secondary; inflammatory mediators exacerbate cartilage damage	Primary: cartilage destruction is caused by T cells and antibodies reactive with joint antigens
Joints involved	Primarily weight bearing (knees, hips)	Often begins with small joints of fingers; progression leads to involvement of multiple joints
Pathology	Cartilage degeneration and fragmentation, bone spurs, subchondral cysts; minimal inflammation	Inflammatory pannus invading and destroying cartilage; severe chronic inflammation; joint fusion (ankylosis)
Serum antibodies	None	Various, including ACPA, rheumatoid factor
Involvement of other organs	No	Yes (lungs, heart, other organs)

SUPPURATIVE ARTHRITIS

- Bacterial infection of joints
- Usually hematogenous route, but can be by direct implantation (trauma, drug abuse) or extension from adjacent infection (osteomyelitis)
- Staph aureus is the most common bacteria in children and adults
- Group B-strep and Neisseria gonorrhea in neonates
- Pseudomonas and Gram-negative in immune suppression or drug abuse
- Complement factors deficiency: gonoccoal polyarthritis

CLINICAL FEATURES

- Rapid onset of joint pain, warmth, swelling, limited motion, leukocytosis and fever.
- Most cases involve a single joint
- Joint fluid aspiration shows purulent fluid

LYME ARTHRITIS

- Caused by Borrelia burgdorferi, transmitted by Ixodes deer ticks
- Common in USA
- Initial infection of skin, called erythema migrans (early localized stage), then skin, cranial nerves, heart and meninges (early disseminated stage), then chronic arthritis and visceral infection (late disseminated stage).
- 60-80% of untreated patients develop arthritis, which drops to less than 10% if treated early
- Arthritis is most common in knee joints, migratory, lasts weeks to months
- Histology: Thick synovium (synovial hyperplasia, chronic inflammation, fibrin deposition) + thick-wall arteries (onion-skin), may resemble rheumatoid arthritis

CRYSTAL-INDUCED ARTHRITIS

- Endogenous: monosodium urate (gout) or calcium pyrophosphate dehydrate (pseudogout)
- Exogenous: joint prosthesis
- All crystals induce inflammation and destroy joint cartilage

GOUT

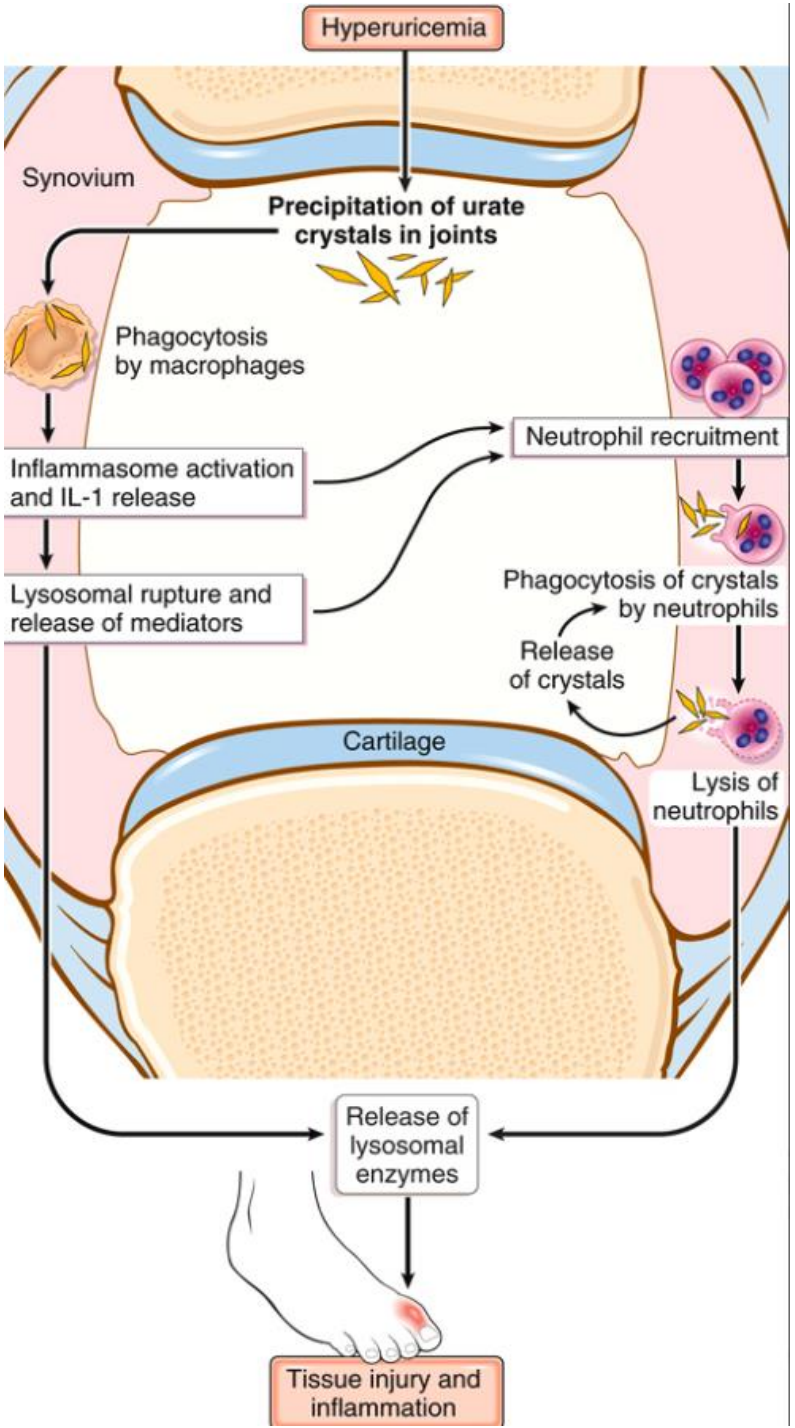
- Transient attacks of severe acute arthritis, induced by monosodium urate crystals deposition in and around joints
- Patients have hyperuricemia secondary to overproduction (enzymatic deficiency) or reduced excretion (more common, unknown pathway) or both
- 90% of cases are primary
- 10% of cases are secondary to renal failure, chemotherapy causing tumor lysis syndrome
- Only 10% of patients with hyperuricemia develops gout, usually after a long time (20-30 years)
- Old age, genetic predisposition, alcohol consumption, obesity, thiazide are risk factors

PATHOGENESIS

- Macrophages in synovium phagocytose urate crystals, causing activation of cytosolic inflammasome, which activates caspase-1, which leads to production of IL-1, which stimulates neutrophilic infiltration in the joint.
- Neutrophils release cytokines, free radicals, proteases, causing tissue damage
- Ingested crystals may damage phagosomes leading to leakage of lysosomal enzymes, causing further damage
- The disease shows acute onset, which subsides spontaneously within days or weeks, but recur later on
- Repeated attacks result in formation of tophi (large aggregates of crystals and inflammatory cells) in joint and adjacent soft tissue

PATHOGENESIS

- Urate crystals are phagocytosed by macrophages and stimulate the production of various inflammatory mediators that elicit the inflammation characteristic of gout. Note that IL-1, one of the major proinflammatory cytokines, in turn stimulates the production of chemokines and other cytokines from a variety of tissue cells

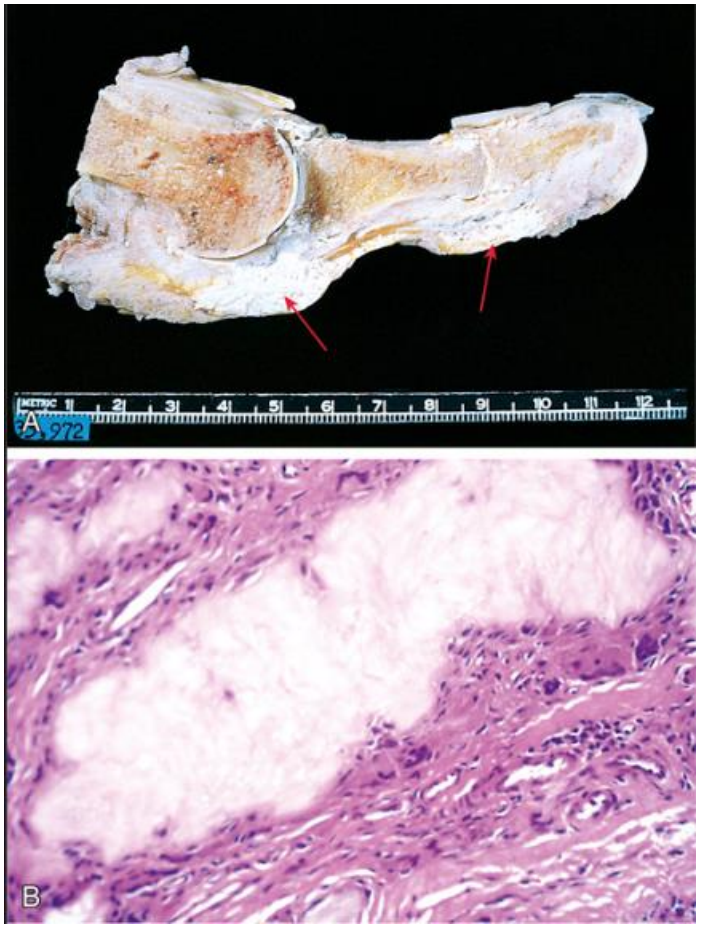


MORPHOLOGY

- Acute gout arthritis: intense inflammation (neutrophils) in synovium and synovial fluid
- Urate crystals appear in the cytoplasm of neutrophils
- They look long, needle shaped, negatively birefringent in polarized microscope

MORPHOLOGY

- Chronic tophaceous arthritis:
- Chalky deposits in synovium, causes pannus and cartilage damage
- out. (A) Amputated great toe with a tophi (arrows) involving the joint and soft tissues. (B) Gouty tophus—an aggregate of dissolved urate crystals is surrounded by reactive fibroblasts, mononuclear inflammatory cells, and giant cells



CLINICAL FEATURES

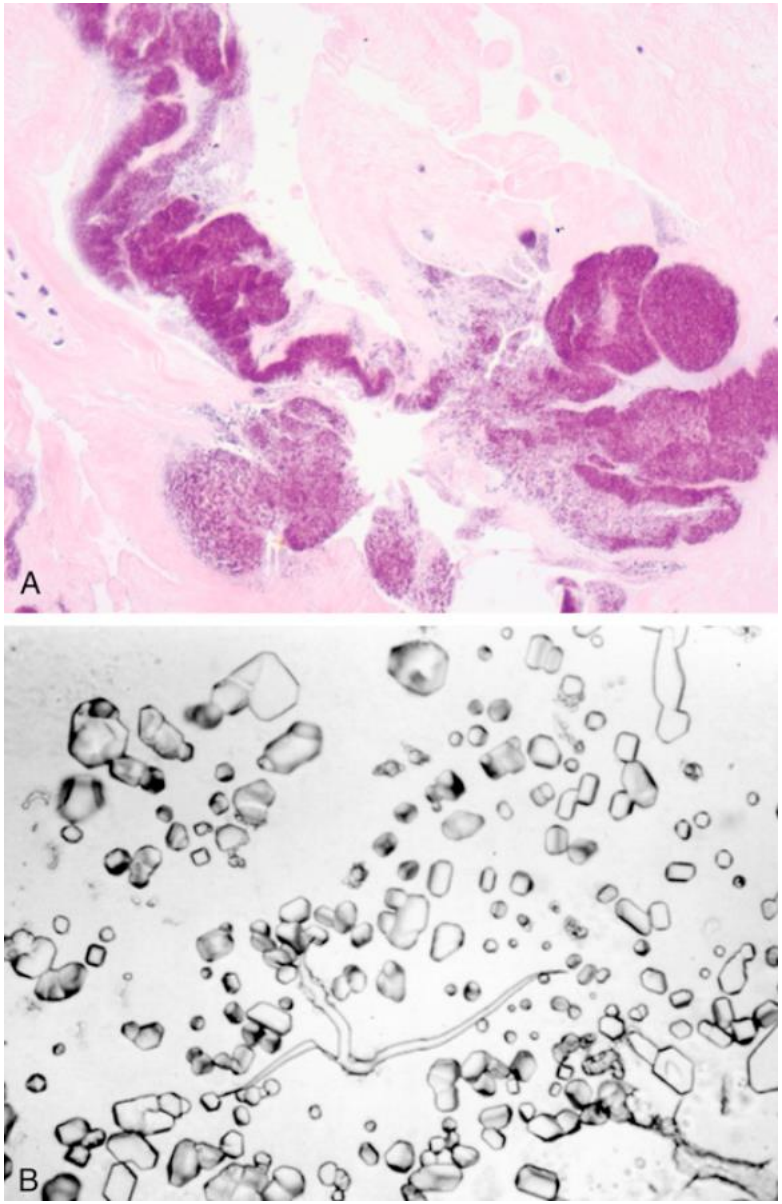
- Asymptomatic hyperuricemia begins around puberty in men and after menopause in women
- Acute arthritis: sharp onset and symptoms, 50% affect big toe, usually monoarticular, resolves spontaneously
- Repeated attacks become more progressive, polyarticular
- Chronic tophaceous gout: loss of join space

PSEUDOGOUT

- Calcium pyrophosphate crystals
- Most patients are older than 50 years
- Sporadic or hereditary (autosomal dominant), mutation in pyrophosphate transport channel
- Crystal formation occurs in joint cartilage, when they enlarge, they rupture and seed the joint
- Crystals appear oval or rhomboid, blue or purple in color in hematoxylin and eosin stain, appear positive birefringent in polarized microscope
- Inflammation is minimal, compared to gout

MORPHOLOGY

- Pseudogout. (A) Deposits are present in cartilage and consist of amorphous basophilic material. (B) Smear preparation of calcium pyrophosphate crystals



CLINICAL FEATURES

- Knee joint is the most common site
- Variable presentation, may be acute, subacute or chronic
- Can be monoarticular or polyarticular
- Significant joint destruction in 50% of cases