Bones and joints pathology

Joints diseases

Plan

- **Arthritis**

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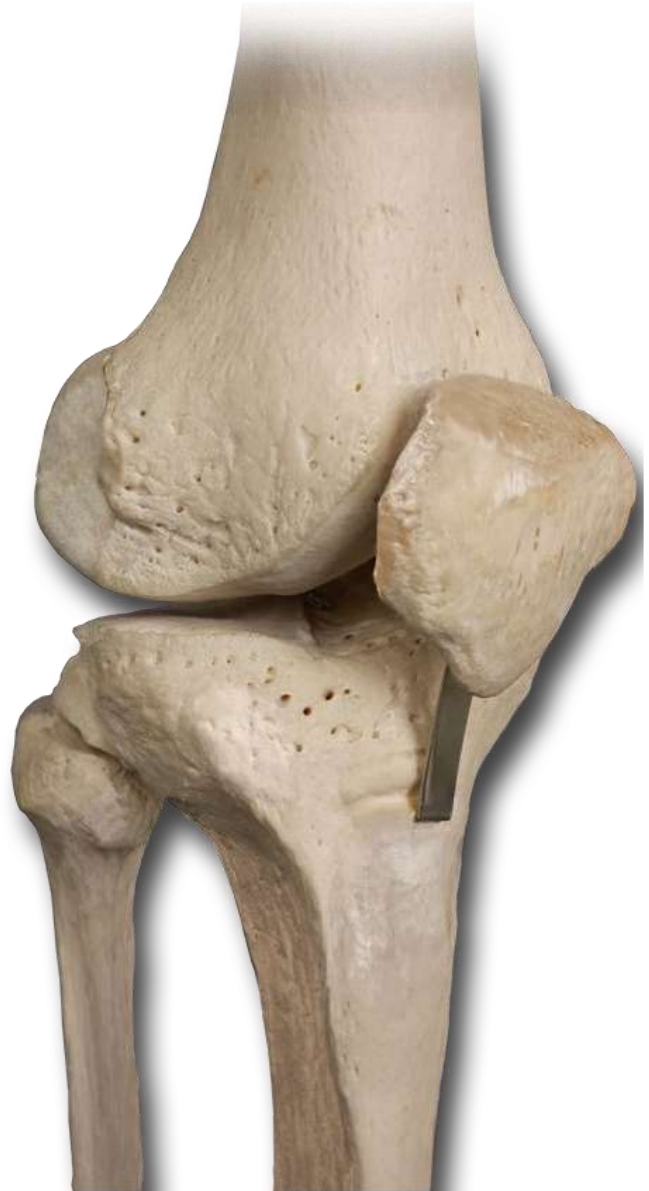

OSTEOARTHRITIS

- Also called degenerative joint disease is **the most common** type of joint disease and is one of the 10 most disabling conditions.
- It is characterized by the **progressive erosion of articular cartilage**.
- appears insidiously
- an **aging phenomenon** (idiopathic or primary osteoarthritis)
- usually **oligoarticular** (affects few joints) but may be generalized
- may appear in younger individuals with **predisposing condition** (injuries and congenital developmental deformity) or **underlying systemic disease** - diabetes, hemochromatosis, or marked obesity (secondary osteoarthritis)

Pathogenesis

- **multifactorial** disease that has **genetic and environmental** components
- The major environmental factors are **aging and biomechanical stress**, which is influenced by obesity, muscle strength, and joint stability, structure, and alignment.

Chondrocytes are at the center of the process, which can be divided into several phases:

- (1) **chondrocyte injury**;
- (2) **early OA**, in which chondrocytes proliferate and secrete active substances, which remodel the cartilaginous matrix and initiate secondary inflammatory changes;
- (3) **late OA**, in which repetitive injury and chronic inflammation lead to chondrocyte drop out, marked loss of cartilage, and extensive subchondral bone changes

Morphology

- In the early stages of osteoarthritis the chondrocytes proliferate, forming **clusters**.
- Grossly we see **granular soft articular surface**. The **dislodged pieces** of cartilage and subchondral bone tumble into the joint, forming loose bodies (**joint mice**).
- The exposed subchondral bone plate becomes the new articular surface, and friction with the opposing degenerated articular surface smooths and burnishes the exposed bone, giving it the appearance of **polished ivory** (**bone eburnation**).
- There is sclerosis of the underlying cancellous bone. Small fractures through the articulating bone are common.
- The loculated fluid collection increases in size, forming **fibrous-walled cysts**. Mushroom-shaped osteophytes (bony outgrowths) develop at the margins of the articular surface and are capped by fibrocartilage and hyaline cartilage that gradually ossify.

Clinical Course

- **Asymptomatic until 50 yo**.
- Characteristic symptoms are deep, achy pain that worsens **with use**, **morning stiffness**, **crepitus**, and **limitation of range of movement**.
- Cervical and lumbar **nerve root compression** and radicular pain, muscle spasms, muscle atrophy, and **neurologic deficits**.
- The joints commonly involved include the hips, knees, lower lumbar and cervical vertebrae, proximal and distal interphalangeal joints of the fingers (**Bouchard nodes and Heberden nodes**), first carpometacarpal joints, and first tarsometatarsal joints of the feet .
- There are still **no prevention** of primary osteoarthritis, and there are **no effective methods** of halting its progression.

RHEUMATOID ARTHRITIS

- is a chronic systemic inflammatory disorder that may affect **many tissues and organs**—skin, blood vessels, heart, lungs, and muscles—but principally attacks the joints, producing a **nonsuppurative proliferative inflammatory synovitis** that often progresses to destruction of the articular cartilage and ankylosis of the joints.

Morphology. Joints.

(1) infiltration of synovial stroma by **lymphoid aggregates**,

(2) increased vascularity with superficial **hemosiderin deposits**;

(3) aggregation of organizing fibrin and floating in the joint space as **rice bodies**;

(4) accumulation of **neutrophils** in the synovial fluid and along the surface of synovium;

(5) juxta-articular erosions, subchondral cysts, and osteoporosis;

(6) pannus formation.

The pannus is a mass of synovium and synovial stroma consisting of inflammatory cells, granulation tissue, and synovial fibroblasts, which grows over the articular cartilage and causes its erosion.

Morphology. Skin.

- Rheumatoid nodules are the **most common cutaneous lesion**.
- Arise in regions of the skin that are subjected to pressure, (forearm, elbows, occiput, and lumbosacral area).
- Rheumatoid nodules are firm, nontender, and round to oval, and in the skin arise in the subcutaneous tissue. Microscopically they have a **central zone of fibrinoid necrosis** surrounded by a prominent rim of epithelioid histiocytes and numerous lymphocytes and plasma cells

Morphology. Blood Vessels.

- Rheumatoid vasculitis is a **potentially catastrophic** complication of rheumatoid arthritis, particularly when it affects vital organs.
- The involvement of **medium- to small-size arteries**, the **kidneys** are **not involved**.
- Segments of small arteries such as vasa nervorum and digital arteries are obstructed by an **obliterating endarteritis** resulting in peripheral neuropathy, ulcers, and gangrene.
- **Leukocytoclastic venulitis** produces purpura, cutaneous ulcers, and nail bed infarction

Pathogenesis

- rheumatoid arthritis is triggered by exposure of a genetically susceptible host to an arthritogenic antigen
- breakdown of immunological self-tolerance and a chronic inflammatory reaction.
- the activation of CD4+ helper T cells, and the local release of inflammatory mediators and cytokines that ultimately destroys the joint.
- Specific HLA-DRB1 alleles have been shown to be associated with rheumatoid arthritis.
- **Environmental arthritogen**: Microbial agents (Epstein-Barr virus, retroviruses, parvoviruses, mycobacteria, Borrelia, Proteus mirabilis, etc) are implicated but **none has been proved to be significant**.
- **Autoimmunity**: About 80% of individuals with rheumatoid arthritis have autoantibodies to the Fc portion of autologous IgG (**rheumatoid factors**) among many other mediators and cytokines.
- From all of them only one has been firmly implicated in the pathogenesis of rheumatoid arthritis—**TNF**

Clinical Course

The clinical course of rheumatoid arthritis is extremely variable.

Can start slowly and insidiously.

Initially there is malaise, fatigue, and generalized musculoskeletal pain, and only after several weeks to months do the joints become involved.

The pattern of joint involvement varies, but it is generally symmetrical and the **small joints are affected before the larger ones**.

Symptoms usually develop in the hands (metacarpophalangeal and proximal interphalangeal joints) and feet, followed by the wrists, ankles, elbows, and knees.

The disease course may be slow or rapid, and fluctuates over the years, with the greatest damage occurring in the first 4 or 5 years

The radiographic hallmarks are joint effusions and juxtaarticular osteopenia with erosions and narrowing of the joint space with loss of articular cartilage.

Destruction of tendons, ligaments, and joint capsules produces characteristic deformities, including radial deviation of the wrist, ulnar deviation of the fingers, and flexion-hyperextension abnormalities of the fingers (**swan neck, boutonnière**).

The end result is deformed joints that have no stability and minimal or no range of motion.

Clinical Course

The diagnosis is based primarily on the clinical features and includes the presence of **four of the following criteria**:

(1) morning stiffness

(2) arthritis in three or more joint areas,

(3) arthritis of hand joints,

(4) symmetric arthritis,

(5) rheumatoid nodules,

(6) serum rheumatoid factor,

(7) typical radiographic changes.

The **treatment** of rheumatoid arthritis is aimed at **relieving the pain** and inflammation, and **slowing** or arresting the relentless joint destruction.

Therapies include corticosteroids, and synthetic and biologic disease-modifying drugs such as methotrexate and, most notably, antagonists of TNF.

JUVENILE IDIOPATHIC ARTHRITIS

- Encompasses all forms of arthritis that develop **before 16 years** of age and that persist for a **minimum of 6 weeks**
- The etiology of JIA is **unknown.**

- It is classified into seven discrete clinical subsets that may correspond to separate diseases and genetic backgrounds;
- (1) systemic arthritis,
- (2) oligoarthritis,
- (3) rheumatoid factor–positive polyarthritis,
- (4) rheumatoid factor–negative polyarthritis,
- (5) enthesitis (inflammation of a point of attachment of skeletal muscle to bone)-associated arthritis,
- (6) psoriatic arthritis,
- (7) undifferentiated arthritis

JUVENILE IDIOPATHIC ARTHRITIS

JIA **differs from rheumatoid arthritis** in adults in the following ways:

(1) oligoarthritis is more common,
(2) systemic disease is more frequent,
(3) large joints are affected more often than small joints,
(4) rheumatoid nodules and rheumatoid factor are usually absent,
(5) antinuclear antibody (ANA) seropositivity is common.

- As in rheumatoid arthritis, risk is associated with genetic susceptibility (with particular HLA alleles) and environmental factors.
- The inflammatory synovitis and morphologic changes are similar to those in rheumatoid arthritis.

SERONEGATIVE SPONDYLOARTHROPATHIES

- The seronegative spondyloarthropathies are a group of diseases that develop in genetically predisposed individuals and are initiated by ubiquitous environmental factors, especially infectious agents.
- The manifestations are **immune mediated**.
- Clinically, the diseases produce inflammatory peripheral or axial **oligoarthritis** and enthesopathies.
- The seronegative spondyloarthropathies include ankylosing spondylitis, reactive arthritis (Reiter syndrome and enteritis-associated arthritis), psoriatic arthritis, and arthritis associated with inflammatory bowel disease.
- All patients have **inflammation of synovial joints** and **extra-articular involvement** of the eyes, skin, and cardiovascular system.

Ankylosing Spondyloarthritis

- Also known as rheumatoid spondylitis and Marie-Strümpell disease,
- is a chronic synovitis that causes **destruction of articular cartilage** and resultant **bony ankylosis**, especially of the sacroiliac and apophyseal joints (between tuberosities and processes).
- Inflammation of tendinoligamentous, ossification, squaring and fusion of the vertebral bodies, bony outgrowths, which together result in **severe spinal immobility**.
- the **second and third** decades of life
- **men** are affected two to three times more frequently than women.
- low back pain, which frequently follows a **chronic progressive course**.
- Fracture of the spine, uveitis, aortitis, and amyloidosis are other recognized complications.
- 90% of affected individuals are **HLA-B27 positive**, but the other genes also contribute, like ARTS1, and IL23R.

Reiter Syndrome

- Reiter syndrome is a form of reactive arthritis and is defined by a **triad of arthritis, nongonococcal urethritis or cervicitis, and conjunctivitis**.
- 20s or 30s
- more than 80% cases are HLA-B27 positive.
- affects individuals infected with **HIV**, probably caused by an **autoimmune reaction** initiated by prior infection of the gastrointestinal tract (Shigella, Salmonella, Yersinia, Campylobacter) and the genitourinary system (Chlamydia).
- **Arthritic symptoms** usually develop within several weeks of the inciting bout of **urethritis or diarrhea**. Joint stiffness and low back pain are common early symptoms.
- The **ankles, knees, and feet** are affected most often, frequently in an **asymmetric** pattern. Synovitis of a digital tendon sheath produces the **sausage finger or toe**, and ossification of tendoligamentous insertion sites leads to calcaneal spurs and bony outgrowths.
- Extra-articular involvement manifests as inflammatory balanitis, conjunctivitis, cardiac conduction abnormalities, and aortic regurgitation.

Enteritis-Associated Arthritis

- Enteritis-associated arthritis is **caused by gastrointestinal infection** by Yersinia, Salmonella, Shigella, and Campylobacter, etc.
- The outer cell membranes of these organisms have lipopolysaccharides as a major component, and they stimulate a host of **immunological responses**.
- The arthritis appears abruptly and tends to involve the **knees and ankles** but sometimes also the wrists, fingers, and toes.
- It lasts for about **a year**

Psoriatic Arthritis

- is a chronic inflammatory arthropathy that affects **peripheral and axial joints** and entheses and is associated with psoriasis.
- Susceptibility to the disease is genetically determined and related to **HLA-B27 and HLA-Cw6 alleles**.
- Symptoms manifest between the ages of **30 and 50**.
- The **distal interphalangeal joints** of the hands and feet are first affected in an **asymmetric** distribution. The large joints may be involved as well.
- conjunctivitis and iritis.
- Psoriatic arthritis is usually **not as severe**, remissions are more frequent, and joint destruction is less frequent

INFECTIOUS ARTHRITIS

- Microorganisms of all types can seed joints during **hematogenous dissemination**.
- Articular structures can become infected by direct inoculation or from contiguous spread from a soft-tissue abscess or focus of osteomyelitis.
- Infectious arthritis is potentially serious, because it can cause **rapid destruction of the joint and produce permanent deformities**.

Bacterial Arthritis

- Almost always cause an acute suppurative arthritis.
- The bacteria usually seed the joint during an episode of bacteremia.
- The most common organisms are gonococcus, Staphylococcus, Streptococcus, Haemophilus infl uenzae, and gram-negative bacilli (E. coli, Salmonella, Pseudomonas, and others).
- **H. influenzae** arthritis predominates in **children under 2 years of age**, **S. aureus** is the main causative agent in **older children and adults**, and **gonococcus** is prevalent during **late adolescence and young adulthood**.
- These joint infections affect the sexes equally except for gonococcal arthritis, which is seen mainly in sexually active women.
- The classic presentation is the sudden development of an **acutely painful and swollen infected joint** that has a restricted range of motion. Systemic findings of fever, leukocytosis, and elevated sedimentation rate are common.
- In 90% of nongonococcal cases, the infection involves only a **single joint**, **usually the knee**, followed in frequency by the hip, shoulder, elbow, wrist, and sternoclavicular joints.

Tuberculous Arthritis

- is a chronic progressive **monoarticular disease** that occurs in all age groups.
- Onset is insidious and causes **gradual progressive pain**.
- Mycobacterial seeding of the joint induces the formation of **confluent granulomas with central caseous necrosis**.
- Chronic disease results in severe destruction with fibrous ankylosis and obliteration of the joint space.
- The **weight-bearing joints** are usually affected, especially the hips, knees, and ankles.

Lyme Arthritis

- By spirochete **Borrelia burgdorferi**, which is transmitted by the ticks of the Ixodes ricinus complex.
- The **initial infection of the skin** is followed within several days or weeks by dissemination of the organism to other sites, especially the joints.
- The arthritis is the dominant feature of late disease; it tends to be **remitting and migratory**, and primarily involves **large joints**, especially the knees, shoulders, elbows, and ankles.
- Infected synovium exhibits a **chronic papillary synovitis** with synoviocyte hyperplasia, fibrin deposition, mononuclear cell infiltrates, and onion-skin thickening of arterial walls.

Viral Arthritis

- Arthritis can occur in the setting of a variety of viral infections, including alphavirus, parvovirus B19, rubella, Epstein-Barr virus, and hepatitis B and C virus.
- The clinical manifestations of the arthritis are variable and range from **acute to subacute symptoms**.
- the viral infection generates an **autoimmune reaction**.

CRYSTAL-INDUCED ARTHRITIS

- Articular **crystal deposits** are associated with a variety of acute and chronic joint disorders.
- **Endogenous crystals** shown to be pathogenic include monosodium urate (**gout**), calcium pyrophosphate dihydrate, and basic calcium phosphate (hydroxyapatite).
- **Exogenous crystals**, such as corticosteroid ester crystals and talcum, and the biomaterials polyethylene and methyl methacrylate, may also induce joint disease.
- Endogenous and exogenous crystals produce disease by **triggering the cascade** that results in cytokine-mediated cartilage destruction.

Gout and Gouty Arthritis

- Human is the only mammal to spontaneously develop **hyperuricemia** and gout, as only humans **lack uricase**, the enzyme responsible for the degradation of uric acid in other mammals.
- Gout is marked by **transient attacks** of acute arthritis initiated by **crystallization of urates** within and about joints, leading eventually to **chronic gouty arthritis** and the appearance of **tophi**.
- Tophi represent large aggregates of urate crystals and the surrounding inflammatory reaction. Most, but not all, individuals with chronic gout also develop **urate nephropathy**.
- The various conditions producing hyperuricemia and gout are divided into **primary gout and secondary gout**.

Pathogenesis

- Uric acid is the **end product of purine metabolism**. Hyperuricemia develops from **overproduction of urate**. Decreased filtration and underexcretion of uric acid underlies most cases of primary gout.
- Two pathways are involved in purine synthesis: (1) **a de novo pathway** in which purines are synthesized from non-purine precursors and (2) **a salvage pathway** in which free purine bases derived from the breakdown of nucleic acids of endogenous or exogenous origin are recaptured (salvaged).
- Gout rarely appears before **20 to 30 years of hyperuricemia**. **Heavy alcohol** consumption, obesity, diet rich with meat and wine predisposes to attacks of gouty arthritis.
- Central to the pathogenesis of the arthritis is **precipitation of monosodium urate** (MSU) crystals into the joints. With prolonged hyperuricemia, crystals and microtophi of urates develop in the synovium and in the joint cartilage. Some unknown event, possibly trauma, causes the release of crystals into the synovial fluid.

Morphology

- The distinctive morphologic changes in gout are

- (1) acute arthritis,
- (2) chronic tophaceous arthritis,
- (3) tophi in various sites,
- (4) gouty nephropathy.

- The MSU **crystals** are arranged in small clusters in the synovium. They are long, slender, and **needle shaped**, and are negatively birefringent.
- Tophi are the pathognomonic hallmark of gout. They are formed by large aggregations of urate crystals surrounded by an intense inflammatory reaction.
- **Gouty nephropathy** is associated with the deposition of MSU crystals in the renal medullary interstitium, sometimes we observe production of uric acid renal stones.

Clinical Course

Gout is said to have four stages:

(1) asymptomatic hyperuricemia,

(2) acute gouty arthritis,

(3) intercritical gout,

(4) chronic tophaceous gout.

Progression leads to **severe crippling disease**.

gout does not materially shorten the life span, but it may **impair the quality of life**

Calcium Pyrophosphate Crystal Deposition Disease (Pseudo-Gout)

- also known as pseudo-gout and chondrocalcinosis, is one of the more common disorders associated with intra-articular crystal formation.
- It usually occurs in individuals **over 50 years of age** and becomes more common with increasing age. The sexes and races are equally affected.
- CPPD is divided into **sporadic (idiopathic), hereditary, and secondary types**.
- In the **hereditary variant** the crystals develop relatively early in life and are associated with severe osteoarthritis.
- The **secondary form** is associated with various disorders, including previous joint damage, hyperparathyroidism, hemochromatosis, hypomagnesemia, hypothyroidism, ochronosis, and diabetes.
- *The basis for crystal formation is not known*.

Calcium Pyrophosphate Crystal Deposition Disease (Pseudo-Gout). Morphology.

- The **crystals first develop in the articular matrix**, menisci, and intervertebral discs, and as the deposits enlarge they may rupture and seed the joint.
- The crystals form **chalky white friable deposits**, which are seen histologically as oval blue-purple aggregates.
- The joint involvement may last from several days to weeks and may be **monoarticular or polyarticular**; the knees, followed by the wrists, elbows, shoulders, and ankles, are most commonly affected.
- Approximately 50% of patients experience **significant joint damage**.
- Therapy is **supportive**.

Tumors and Tumor-Like Lesions

- **Reactive tumor-like lesions**, such as ganglions, synovial cysts, and osteochondral loose bodies, commonly involve joints and tendon sheaths.
- usually **result from trauma** or degenerative processes.
- **Primary neoplasms are unusual** and tend to recapitulate the cells and tissue types native to joints and related structures.
- **Benign tumors are much more frequent** than their malignant counterparts.

GANGLION AND SYNOVIAL CYST

- A ganglion is a small (1–1.5 cm) cyst that is almost always **located near a joint capsule or tendon sheath**.
- A common location is around the joints of the **wrist**, where it appears as a firm, fluctuant, pea-sized translucent nodule.
- the cyst wall **lacks a true cell lining**. The lesion may be multilocular and enlarges through coalescence of adjacent areas of myxoid change.
- Herniation of synovium through a joint capsule or massive enlargement of a bursa may produce a synovial cyst.
- A well-recognized example is the synovial cyst that forms in the popliteal space in the setting of rheumatoid arthritis (**Baker cyst**).

TENOSYNOVIAL GIANT-CELL TUMOR (LOCALIZED AND DIFFUSE)

- Tenosynovial giant-cell tumor is the term for several closely related benign neoplasms that develop in the synovial lining of joints, tendon sheaths, and bursae. They harbor a consistent chromosomal translocation, t(1;2)(p13;q37).
- Variants of tenosynovial giant-cell tumor include the **diffuse type,** and the **localized type**.
- Whereas the diffuse form tends to involve one or more joints, the localized kind usually occurs as a discrete nodule attached to a tendon sheath, commonly of the hand.
- Both variants usually are diagnosed in the **20s to 40s** and affect the sexes equally.

TENOSYNOVIAL GIANT-CELL TUMOR (LOCALIZED AND DIFFUSE). Morphology.

- Grossly, tumors are **red-brown** to mottled **orange-yellow**.
- In **diffuse tumors** the normally smooth joint synovium is converted into a tangled mat by red-brown folds, **finger-like projections, and nodules**. In contrast, **localized tumors** are **well circumscribed** and resemble a small walnut.
- Patients complain of pain, locking, and recurrent swelling. Tumor progression limits the range of movement of the joint. Aggressive tumors erode into adjacent bones and soft tissues. In contrast, the localized variant manifests as a solitary, slow-growing, painless mass that frequently involves the tendon sheaths;
- it is the **most common mesenchymal** neoplasm of the hand.
- **Surgery** is the recommended treatment.