

Biology of Joint

Types of Joints

Synarthrodial: immobile

suture lines

Amphiarthrodial: modestly mobile

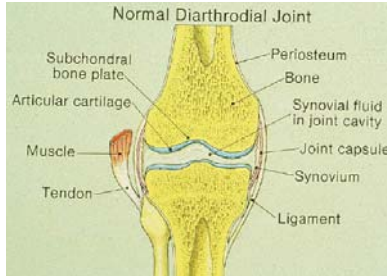
fibrocartilagenous joints

symphysis pubis, SI, IV disk

Diarthrodial: freely mobile

synovial lined

knees, hips, shoulders



Joint capsule

merges with tendon/ligament externally and with synovial cells internally

composed of Type I collagen

muscles & tendons are primary shock absorbers

Synovium

Functions

allows movement between solid structures

provides nutrients to chondrocytes

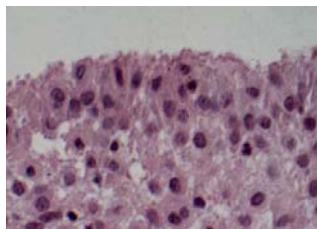
controls synovial fluid volume & composition

Histology

Intimal layer (1-3 cells thick)

Type A cells (minority): Macrophages

Type B cuboidal cells (most): Fibroblasts, synthesize extracellular matrix, secrete fluid into joint space



Other cells: Dendritic cells, Mast cells lack basement membrane

Subintima

superficial vascular plexus: fenestrated capillaries

nerve fibers ending within intima

lymphatics

more fibroblasts and macrophages

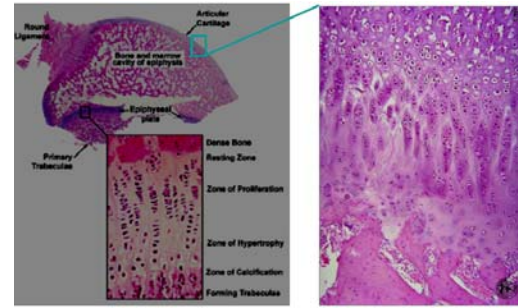
Synovial fluid

2-3 cc viscous fluid

contains hyaluronan: high MW polysaccharide, maintains film to lubricate cartilage

Normal < 200 WBC/cc, transparent, serum glucose

Articular cartilage



Function

low friction surface covering weight bearing portion of diarthrodial joints; absorbs shock

Molecular Structure

Type II collagen → tensile strength

interlocking proteoglycan, aggrecan provide compressive stiffness

hydrophilic GAG binds water → when compressed, extrudes water

once compression released, proteoglycan re-absorbs water and small solutes by osmosis

Histology

Avascular: nourished by diffusion of nutrients from synovial fluid

hypocellular: chondrocytes contribute only 1-2% of cartilage volume

4 regions of cartilage (Zones I-IV)

Subchondral bone

trabecular bone underneath cartilage

absorbs stress transmitted from thin articular cartilage

Inflammatory Mediators

Neutrophils

Migrates through blood vessels

(neutrophil integrin binds to endothelial ICAM-1 and VCAM-1)

Activated by bacterial peptides, C5a, leukotriene B4, IL8

Phagocytosis of opsonized food

Releases proteolytic enzymes

Produces free radicals

Macrophages

Migrates similar to PMN's

attracted by collagen, fibronectin, TGF-β

Phagocytosis of opsonized food

releases numerous cytokines: IL1, 4, 6, 8, 10, 12

Produces arachidonic acid-derived mediators

Platelets

attracted by PAF and collagen

release of granular contents → aggregation & clotting

releases other products that activate PMN's, induce SM proliferation, angiogenesis

Mast Cells & Eosinophils

Normal Skeleton & Congenital Abnormalities

Structure of Bone

Inorganic (65%)

Minerals: calcium hydroxyapatite, Na, Mg

Organic (35%)

Proteins

Type I collagen

backbone of matrix: 90% of organic component (about 30% of bone total)

produced in osteoblasts, assembled outside cell

forms foundation (osteoid), which then mineralizes to give bone strength

Adhesion proteins

osteopontin, fibronectin, thrombospondin

Ca-binding proteins

osteonectin, sialoprotein

Mineralization proteins

osteocalcin: unique to bone, can be used to measure osteoblastic activity

Cytokines

PG's, IL1, IL6

Growth factors

BMP = Bone Morphogenic Protein

FGF = Fibroblast Growth Factor

IGF, PDGF, TGF- β

Cells

Osteoprogenitor cells

pluripotent mesenchymal stem cells

can differentiate into osteoblasts

CBFA1 (Core Binding Factor A1) expression \rightarrow differentiation

Osteoblasts

Have receptors for PTH, Vit D, Estrogen, and growth factors

\downarrow CBFA1 \rightarrow nonfunctional osteoblasts, failed mineralization

CBFA1 knockout mice: normal skeleton pattern, but composed entirely of cartilage

Osteocytes

mature osteoblasts that live in lacunae

canaliculi: intercellular communications

detect mechanical forces \rightarrow \uparrow cAMP \rightarrow structural changes

Osteoclasts

multinucleated cells resorb bone

live in Howship's lacunae

ruffled border \uparrow surface area for bone resorption

tight seal between membrane and underlying bone contains lysosomal enzymes and HCl

Modeling and remodeling

Basic functional unit:

Opposites attract: Osteoblast + Osteoclast, forever in love and holding hands in the sunset

Regulation:

OsteoBLAST is the boss

RANKL (Receptor Activator of NF κ B Ligand)

Osteoblast surface protein that binds to osteoclast RANK receptor

Kind of like sex.

\rightarrow stimulates osteoclast differentiation (they make "children")

\rightarrow activates mature osteoclasts

PTH, D3, some malignancies, and IL-11

\rightarrow \uparrow RANKL

Cytokines feedback to stimulate osteoblasts

Osteoprotegerin: \downarrow resorption by binding RANKL and doing nothing.

Kind of like a condom

M-CSF \rightarrow \uparrow o-clasts

Normal Skeleton & Congenital Abnormalities

Bone growth and development

Regulated by *HOX* genes

Long bones: enchondral ossification

cartilage directly formed from mesenchyme
central cartilage resorbed by osteoclasts →
blood vessels and osteoblastic progenitor cells
grow in empty space

primary ossification center

periosteum makes osteoblasts → cortical
bone

secondary ossification center

gradual replacement of cartilage at
epiphyses → growth plate formed

Flat bones: intramembranous ossification

cellular fibrous tissue formed from
mesenchyme

progenitor cells → o-blasts → bone

Appositional growth

new bone can only be formed on surface of pre-
existing bone

only o-blasts involved (no o-clasts)

Types of bone

Osteoid: unmineralized bone matrix

Woven: random Type 1 collagen weave

rapidly deposited

normal in fetus, but always abnormal in adult
fracture, osteomyelitis, bone-forming tumor

Lamellar: orderly layers of bone matrix (cement
lines)

stronger than woven bone but more slowly
deposited

mature bone

cortical & cancellous bone

four types

cortical bone: circumferential, concentric, interstitial
medullary cavity: trabecular

Congenital anomalies

Malformations: dysregulation of HOX genes

supernumerary ribs/digits

syndactyly = fused bones

craniorachischisis: abnormal closure of skull &
vertebral column

Dwarfism

▶ Achondroplasia

Defect in cell signaling (*FGR3*) →
disorganized chondrocytes in growth plate
AD inheritance (but most often, spontaneous
mutations)

normal trunk, short limbs, normal lifespan

▶ Thanatophoric dwarf

Different *FGR3* mutation → dwarfism &
small thoracic cavity

early death (respiratory collapse)

Osteogenesis imperfecta

many genetic defects, all Type 1 collagen
deficiency

Type I: mild, AD, blue sclera

Type II: most severe (death), AR, blue sclera

Type III: moderate (fractures), AR, blue sclera

Type IV: moderate (fractures), AD, normal sclera

Defects in collagen metabolism

Defects in types 2, 10, 11 → fragile cartilage,
fractures, severe osteoarthritis

Mucopolysaccharidoses

defective degradation of cartilage

Osteopetrosis (marble bone disease)

Pathogenesis:

O-clasts can't produce carbonic anhydrase II
→ no HCl production → no bone or cartilage
resorption → no endochondral ossification

→ excess of bone deposition on pre-existing
bone

Features:

mishapen, brittle bones

no medullary canal

Clinically:

cranial nerve palsies (narrowed foramina)

↓ marrow production (anemia, neutropenia)

fractures

Treatment:

BM transplant (o-clasts come from bone
marrow stem cells)

Metabolic Bone Disease

Osteoporosis

What is it?

↑ porosity of skeleton (↓ bone mass)

Etiology

primary

postmenopausal

estrogen ↓ osteoporosis-related fractures (blah blah blah)

senile

osteoblasts from old fogies have ↓ synthetic activity

proteins embedded in matrix not as active as the young 'uns

secondary

endocrine

↑ PTH, hypothyroid, DM, addison's, pituitary tumors

neoplasia

carcinomatosis, multiple myeloma, paraneoplastic disease

GI

malabsorption\malnutrition, ↓ vitamin D or C, hepatic insufficiency

drugs

corticosteroids, chemotherapy, EtOH

immobilization

idiopathic

Pathogenesis

Peak bone mass achieved in young adulthood
inherited vitamin D receptor allele (accounts for 75% of peak bone mass)

physical activity (weight bearing exercise most important)

nutrition important (calcium during "formative years")

Regulatory factors:

PTH: defend serum calcium

Calcitonin: directly oppose PTH. ↓ bone resorption

Vitamin D

Ineffective remodeling sequence

during each clast/blast cycle, small defect leading to age-related bone loss (0.7%/year)

men and women afflicted equally, but whites more so than blacks

Clinical

vertebral body collapse due to microfractures
→ short old lady, lordosis

fractures of long bones

immobilized grandma has ↑ risk of PE, pneumonia

Evaluation

Fracture risk doubles for every SD decrease in bone mineral density

X-Ray

Not sensitive enough, must lose 30% of bone mineral density before osteopenia is detected

DEXA (Dual X-Ray absorptiometry)

measures bone density at different sites
high precision, low radiation, good correlation with fracture risk

Ultrasound: still experimental

Biochemical markers

can assess women with high turnover states
useful for monitoring effects of therapy and compliance

N-telopeptide (NTX) urine test most useful

Management

weight bearing exercise

supplemental calcium, Vitamin D

Antiresorptive agens (Estrogen, Calcitonin, Bisphosphonates)

Can also use recombinant PTH

Vitamin D Deficiency/Dysfunction

abnormal mineralization of osteoid

In kids: RICKETS → weak, misshapen long bones in growing skeleton

In grownups: OSTEOMALACIA
→ ↓ mineralization of mature skeleton

numerous etiologies

↓ synthesis (arabs wearing black cloth or northern europeans living without sunlight)

↓ intake or ↓ absorption (CF, malabsorption)
derangement in metabolism (liver, kidney disease)

abormal receptor

↓ phosphate

pathology: undermineralized matrix

overgrowth of epiphyseal cartilage

persistent masses of hyaline cartilage

deposition of osteoid matrix on inadequately minearlized cartilage

ingrowth of BV and fibrous tissue into sites of microfracture

skeletal deformities

rachitic rosary: enlarged costochondral cartilage of ribs

frontal bossing (↑ osteoid)

lumbar lordosis and bowed legs (weak weight-bearing bones)

Metabolic Bone Disease

Vitamin C Deficiency (Scurvy)

fragile capillaries and venules

subperiosteal hemorrhages

defective osteoid synthesis

microfractures → bony deformities

Hyperparathyroidism

Etiology

Primary: most common cause of hypercalcemia in general population

Secondary: hyperplasia due to ↓ Ca²⁺

Pathogenesis:

↑ PTH → stimulation of o-blasts to activate o-clasts (RANKL binding)

↑ osteoclasts → massive bony resorption affects all bones but digits more than others

Radiographic findings

pathognomonic: subperiosteal resorption of phalanx and distal tuft resorption

chondrocalcinosis

Osteitis fibrosa cystica: cystic lesion with hemorrhage usually involving the jaw

What is affected

cortical bone > cancellous bone

subperiosteal resorption of phalanges & teeth

What's the etiology?

↑↑ osteoclasts (only mild ↑ in osteoblasts)

activated bone cells → ↑ cytokines

→ granulation tissue & neovascularization

microfractures + hemorrhage → ingrowth of fibrous tissue → brown tumor can become cystic

von Recklinghausen's disease of bone: generalized osteitis fibrosa cystica

multifocal severe disease with numerous cystic brown tumors

characteristic of severe hyperPTH

Renal Osteodystrophy

Pathogenesis

chronic renal failure causes ↑↑ PTH by two mechanisms:

1) secondary to hypocalcemia due to ↓ renal vit D activation

2) ↑ phosphorous directly ↑ PTH secretion

→ disease from excess calcium resorption (osteitis fibrosa cystica)

Fe and Al accumulate in bone (from dialysate) → prevents further bone deposition

β₂ microglobulin amyloid deposits in bone (does not dialyze and accumulates in serum)

↑ osteoclastic resorption (due to hyperPTH)

→ osteomalacia, osteosclerosis, osteoporosis

Osteonecrosis

What is it?

Death of bone → collapse of bony structure → joint pain & loss of function

Who gets it?

Most commonly age 30-60 males (except for those with SLE, who tend to be female)

What causes it?

Compromise of blood flow to bone

Most often, trauma leading to ischemia of bone drugs (corticosteroids)

↑ apoptosis of osteoblasts & osteoclasts

directly kill osteocytes

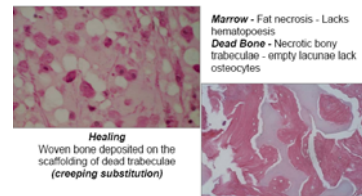
↑ adipocytes → ↓ femoral blood supply

↓ angiogenesis

diseases (sickle cell, SLE, gaucher's)

metabolic problems (alcoholism)

Pathology



medullary infarcts

bone marrow and cancellous bone only (cortex has collateral blood supply)

tend to be asymptomatic

subchondral infarcts → irregularity of articular surface → osteoarthritis

wedge-shaped chalky white discoloration

viable cartilage avulsed over time

(avascular, only gets nutrients from synovial fluid)

severe osteoarthritis, pain

rarely, sarcoma arises from necrotic bone

Where are common sites?

Femoral head → hip

medial femoral circumflex artery is main source of blood supply to head of femur → gives off lateral epiphyseal arteries

the lateral epiphyseal arteries do not have collaterals → occlusion → osteonecrosis

Femoral condyles → knee

Humeral head → shoulder

Talus → ankle

How do you treat it?

palliatively → analgesics

common sense: ↓ corticosteroid & EtOH use core decompression (early)

surgery: joint replacement/resurfacing

Metabolic Bone Disease

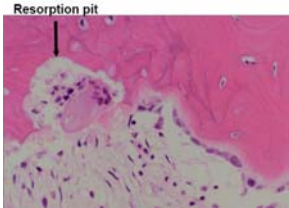
Paget's disease of bone

What is it?

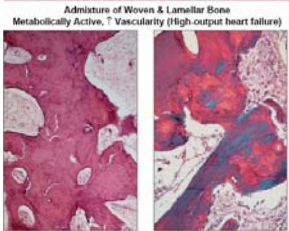
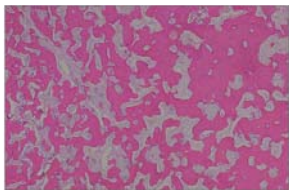
A focal disorder of bone remodeling that results in **weak, expanded, disorganized, vascular** bone

Begins with ↑↑ bone resorption, followed by ↑↑ bone formation

1) Osteolytic stage



2) Mixed lytic & blastic stage predominantly osteoblastic



3) Sclerotic stage (burn-out)

end-stage: ↑ bone mass

thickened lamellar bone, lacks stability

primary disturbance in ↑↑ osteoclast activity → initial bone loss

results in enlarged and deformed bones → abnormal mosaic pattern of lamellar bone with extensive vascularity & ↑ fibrosis in marrow → abnormally weak bones

What causes it?

Unknown, possibly viral etiology

Pathogenesis

virus stimulates IL-6 → with M-CSF, o-clasts activated

o-clasts hypersensitive to RANKL & vit D

Who gets it?

The elderly

some genetic basis (first degree relative with Paget's → 7x risk)

Mutations in SQSTM1 chromosome 5q35: encodes P62 (involved in RANKL signaling)

→ ↑ osteoclasts

What are the lab findings?

Serum markers of bone resorption (↑ osteoclastic activity)

Type I Collagen N or C Telopeptide, or Deoxypyridinoline cross-links

Serum markers of bone formation (↑ osteoblastic activity)

↑ serum alk-phos

Osteocalcin

Type I Collagen N-terminal propeptide

Urine markers of bone resorption

Most common: ↑ urinary hydroxyproline

pyridinium cross-linked peptide (relatively specific for bone collagen resorption)

Urine markers of bone formation

No urinary markers for new bone formation have been identified

↑ serum/urine uric acid

serum/urine Ca^{2+} typically normal unless the patient is immobilized

rapid uptake of radioactive isotopes by highly vascular lesion → easily visualized by bone scan

What are the clinical features?

Usually, Paget's disease is asymptomatic and diagnosed by accident

Can involve the skull

clue: hats don't fit anymore

leonin appearance

dilated superficial cranial vessels

deafness

compression of posterior fossa → ataxia or even cerebellar herniation

Can involve the spine → nerve compression but compression of cord is rare

Bone pain, skeletal deformities, pathologic fractures, nerve compression

osteosarcoma (rare) → would see big rise in alk-phos

Complications

▶ high output cardiac failure during osteoblastic phase

▶ deformities

▶ pain due to compressed nerves

▶ degenerative joint dz

▶ tumors (high grade sarcoma & others)

How is it treated?

Generally, should only treat if symptomatic (bone pain, bone abnormality causing neurological defect, high-output cardiac failure)

Can use NSAIDs to suppress pain/inflammation

Calcitonin/bisphosphonates (antiresorptive agents) may ↓ pain and ↑ function

Crystalline disease, infectious arthritis, bursitis, osteomyelitis

Gout

Excess levels of uric acid

↑ production (10%)

- ▶ enzymatic abnormalities
- ▶ ↑ cell turnover (hemolytic anemia)
- ▶ eating lots of purine-rich food (BUCKETS OF MEAT)
 - beer is rich in purines too

↓ excretion (90%)

Estrogen promotes renal excretion

low GFR

- CHF, renal disease
- volume contraction (due to diuretics or anything else)
- All diuretics ↑ uric acid by causing volume contraction

Males vs. Females

Males

- males reach the "adult" level of uric acid as a teenager
- it takes ≈ 20 yrs to develop gout
- so it's not unheard of for a male to develop gout in his 30's

Females

- only reach male level after menopause because estrogen promotes excretion in kidney
- so a young woman's "gout" is most likely due to an enzyme deficiency (or something else that's NOT gout!)

Pathogenesis

Crystal deposition are chemotactic for neutrophils, which release cytokines that bring macrophages to the scene to fuck shit up with all their explosive cytokines and poor temper

Gout tends to affect joints in the periphery, probably due to ↓ temperature

Pathology

- lots of neutrophils
- gout crystals are negatively birefringent: yellow under polarized light
- tophi: collections of urate acid crystals in joints or ears, but can occur anywhere
 - chronic reaction involving fibrosis and foreign body giant cells

Complications

- gouty nephropathy: 20% die of renal failure
- interstitial tophi
- ↑ renal stones
- polynephritis, obstruction
- fibrous/bony ankylosis
- inflammatory pannus grows over articular surface around tophi
- leads to cartilage/bone destruction

Treatment

acute attack

Colchicine! (inhibits microtubules so PMN's can't migrate to the crystals singing their siren song)

must take at the very very beginning of an attack

NSAIDS (any NSAIDS are effective)

chronically

goal: ↓ serum uric acid level → allopurinol

in general, asymptomatic ↑ uric acid level shouldn't be treated

indications for treatment:

Hx of kidney stones, repeated attacks, Tophi, gouty erosions in bone

Pseudogout

Excess calcium pyrophosphate dihydrate (CPPD) crystals

In joints (tendency towards axial skeleton)

cartilage deposition = chondrocalcinosis

Etiology

Hereditary

early onset, severe, chromosome 8

Secondary

- ▶ hyperPTH
- ▶ hypothyroid
- ▶ Wilson's
- ▶ hemochromatosis
- ▶ diabetes
- ▶ hypomagnesemia
- ▶ ochronosis

Idiopathic

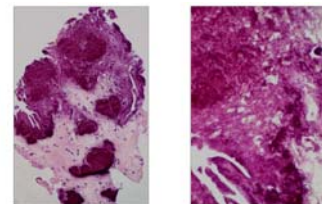
Pathogenesis

same as for gout: crystals are chemotactic for PMN's

Pathology

crystals are positively birefringent

purple rhomboid crystals



Deposits may enlarge → rupture and seed the joint → Acute Inflammation

Treatment

Colchicine & NSAIDs

Hydroxyapatite

What is it?

"tumoral calcinosis"

massive accumulations of hydroxyapatite crystals

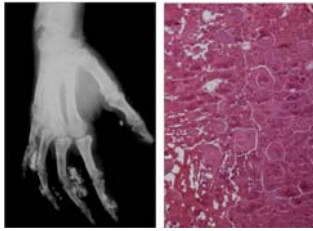
→ nodules in soft tissues near joints

Crystalline disease, infectious arthritis, bursitis, osteomyelitis

Pathogenesis

mechanism unknown, may even occur in children

Pathology



Septic bursitis

What is it?

Infection of the bursa

Bursa = closed, synovial lined sacs containing a little synovial fluid

Pathogenesis

abrasion, chronic friction, repeated minor trauma
→ skin pathogens enter

S. Aureus 80%

Hematogenous spread is RARE

Clinically

Most common sites:

elbow (olecranon bursa)

knee (prepatellar bursa)

Symptoms:

few days to week onset of pain/swelling

If the joint has normal, painless range of motion
→ suggests that joint is sterile

bursa and joint may communicate with penetrating trauma or severe inflammation
→ septic arthritis

Diagnosis

needle aspiration with gram stain & culture.

gold standard: culture

will typically have lower-than expected WBC count despite active infection

Treatment

daily drainage

penicillinase-resistant penicillin/cephalosporin

IV antibiotics usually required

Osteomyelitis

What is it?

Infection of bone (or bone marrow)

Species

S. aureus: 50% of bacterial cases

GNR in elderly

Salmonella in sickle cell

P. aeruginosa in IV drug abusers

Fungus in IC

M. TB in developing countries

Pathogenesis

Normal bone is highly resistant to infection

large inocula of bacteria, trauma, severely arthritic joint, or foreign body normally necessary for infection

new bone apposition from periosteal activation
→ bony bridging

Acute Osteomyelitis

pathology

acute inflammation → bone destruction & regeneration → bone necrosis → subperiosteal abscess

sequestrum: segmental bone necrosis due to progressive ischemia

involucrum: viable bone surrounding sequestrum

can extend into joint space

Chronic Osteomyelitis can result if not diagnosed or cured in time

pathology

chronic inflammation

resorption of dead bone

deposition of woven bone

brodie's abscess: intracortical abscess

sequelae

▶ recurrent acute exacerbations

▶ pathologic fracture

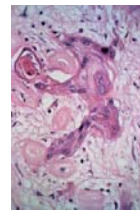
▶ amyloidosis

▶ endocarditis

▶ sepsis

▶ septic arthritis

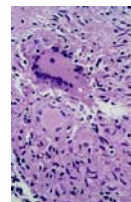
▶ squamous cell carcinoma of fistula tract



▶ sarcoma of infected bone

specific agents

skeletal TB



location: spine > knees > hips

very destructive, difficult to control

spreads through medullary cavity causing extensive necrosis

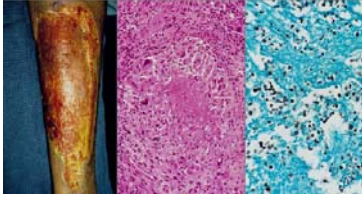
extends through IV discs → multiple bones involved

Crystalline disease, infectious arthritis, bursitis, osteomyelitis

actinomycosis

mandible, poor dentition

coccidioidomycosis or other fungal



granulomatous w/ extensive bone necrosis & destruction

syphilitic osteomyelitis

pathology

granulation tissue with plasma cells, ↑ bone necrosis

congenital syphilis

5th month of gestation

osteochondritis, periostitis

acquired syphilis

tertiary syphilis (2-5 yrs post primary)

nose, palate, skull, extremities

saber shin: periostitis in tibia

Biphasic age distribution:

growing children can get osteomyelitis in vascular metaphysis of long bones

fever, chills, bone pain, leukocytosis

bone metaphysis tender to palpation

often have + blood cultures

adults over 50

vertebral osteomyelitis: ill-defined neck/back pain days/weeks after fever

usually: hematogenous seeding of bone from GU or skin source

blood cultures positive only 50%

diagnosis: direct bone aspiration or bone biopsy

Diagnosis

Bone biopsy and culture

Radiographic changes

XR: gradual changes, absent in early stages

MRI can reveal osteomyelitis early

Treatment

IV antibiotics for 4-6 weeks

But children with hematogenous spread can be treated orally for some reason

surgery for removal of intramedullary or subperiosteal pus

decompression surgery may be necessary for vertebral osteomyelitis

infected joint prostheses: require 2-step surgical procedure:

1) prosthesis removed with debridement of bone & soft tissue

2) prosthesis reinstalled 4-6 weeks later

Septic arthritis

What is it?

infection in a joint

Pathogenesis

- ▶ extension from osteomyelitis
- ▶ soft tissue abscess
- ▶ hematogenous seeding

Pathology



Rapid destruction of articular cartilage
Joint space narrowing
Focal subchondral OM
Permanent disability

Clinically

non-gonococcal

infectious monoarthritis (just one joint infected): *S. aureus*

IC, elderly, or diabetic: GNR

IV drug users: weird joints (SI, sternoclavicular)

Non-IV drug users: common joints (knees, hips, shoulders)

gonococcal

sexually active, any age!

skin lesion

migratory or additive oligoarthralgias (a few joints affected)

hard to culture from blood → culture urethra, rectum, pharynx, skin lesions, synovial fluid

ALWAYS TREAT FOR CHLAMYDIA AND ALWAYS TREAT THE PARTNER, AMEN.

viral

B19

HBV: polyarthritis in the preicteric phase

HCV: arthritis & palpable purpura (Type III HSR)

lyme disease

initial stage: erythema migrans: bullseye rash

tertiary: arthritis!

If you see a rash + arthritis, then it's NOT lyme!

Tx: tetracyclines

Involved joints

non-IVDU: knee > hip > shoulder > elbow > wrist

IVDU: axial joints (sternoclavicular, disc, sacroiliac)

Treatment:

IV antibiotics, joint drainage, joint rest

What is Rheumatoid Arthritis?

Out of control synovial-lining cells

Synovial lining cells becomes activated by cytokines and invades cartilage, tendons, and bone

Synovial cell derived either from macrophage-like (Type A) or fibroblastic-like (Type B)

Activated synovial cells (pannocytes) cause tissue injury by release of proteinases and cytokines.

T cells probably initiate the whole process

What is this, psychology? Pts must have 4/7

* starred items must be present ≥ 6 weeks

Morning stiffness lasting more than 1 hr*

swelling in 3+ joints*

swelling in hand joints*

symmetric joint swelling*

erosions or decalcifications on hand XR

rheumatoid nodules

serum RF

Pathogenesis

Immunogenetics

70% of RA patients are HLA-DR4

DR- β chain contains a "susceptibility cassette"

Several bacterial proteins or EBV surface proteins have a similar sequence to this cassette

Therefore, cross-reactivity could activate T cells

RA pathogenesis is complex and polygenic, since different ethnic groups can get RA with different HLA types

T cells

RA antigen + HLA-DR4 \rightarrow presented to T cell

Perivascular Lymphocytes show up in synovial biopsies taken very early in the disease

The CD4 T cells in RA joints contain CD44, which is a ligand for hyaluronic acid which is a major component of synovial fluid

Co-stimulation is essential for clonal proliferation

B7 macrophages surround T cells in lymphoid aggregates

thrombospondin, a chemotactic agent, can provide a constimulation signal without the need for other cells to be involved

activated T cells stimulate:

macrophages to release cytokines

IL-1 β : activates lymphocytes & synovial cells

TNF- α : synergizes with IL-1 β

TGF β : reparative

B cells to produce RF \rightarrow immune complexes

B cells & rheumatoid factor

About 70% of RA patients have circulating RF

B cells make RF after stimulation by T cells

RF: IgM antibody against the Fc portion of IgG forms immune complexes (by itself or with normal IgG)

\rightarrow activation of complement cascade

RF found in up to 5% of normal people

RF can be associated with other diseases

Leukocyte translocation from blood to synovium

adhesion molecules upregulated

VLA-4 : VCAM-1

LFA-1 : ICAM-1

CD44 : hyaluronan

Synovial translocation into adjacent tissues

A new network of blood vessels must form in the inflamed tissue in order for the bad-actor synovium cells to invade.

Angiogenesis facilitated by endothelial cell growth factors

Cytokines

T cells control production of cytokines and joint tissue damaging enzymes

NF κ B responsible for gene activation of many cytokines

TNF α and IL-1 β are the most important mediators of joint inflammation and tissue injury

Current therapy: Ab against the soluble receptors for these molecules

Rheumatoid synovium

IL-1 β , TNF α , PDGF all stimulate synovial cell growth

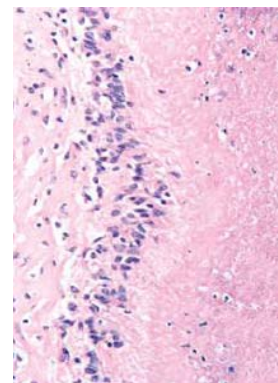
Activated synovium looks like a malignancy and even has upregulated oncoproteins.

Early aggressive therapy is needed

Pathology

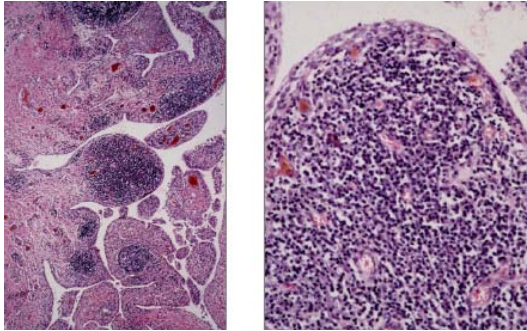
synovial hyperplasia \rightarrow chronic inflammation \rightarrow organizing fibrin \rightarrow overgrown of synovium (pannus) \rightarrow erosion of underlying cartilage \rightarrow narrowing of joint space

Rheumatoid nodule



necrosis with palisading macrophages and chronic inflammatory cells

Bulbous fronds

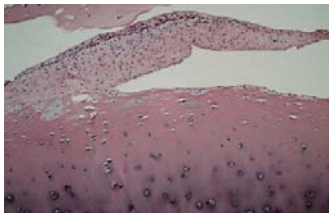


lymphocytes + plasma cell infiltrate

Rice bodies

organizing fibrin over synovium and in joint space

Pannus



synovial overgrown on articular surface

Erosion of cartilage with ingrowth of synovium

↑ o-crest activity (due to ↑ RANKL produced by activated T cells and synovial fibroblasts)
→ subchondral cysts and osteoporosis

Narrowing → fusing of joint space

narrowed with pannus (fibrosing ankylosis)
eventually ossifies (bony ankylosis)

Clinical Features of RA

Hallmark features

symmetric polyarthritis and joint stiffness after rest (“morning stiffness”)

Timeline of joint pain

joint disease normally begins insidiously over weeks to months, although it may occur acutely.
prolonged morning stiffness (one or more hours), fatigue and malaise, and gelling (stiffness after immobility) may be prominent symptoms

joint stiffness tends to improve with activity in the morning and early afternoon, only to be followed by later afternoon and early evening fever and pain

most often, progressive, sustained disease

Distribution of joint involvement

dominant side usually more severely affected

Physical deformities of the hands

synovitis of the hands → symmetric fusiform swelling, most prominently affecting the 2nd and 3rd MCP and PIP and wrist joints of dominant side



ulnar deviation: fingers deviate laterally with soft tissue injury @ MCP’s



swan-neck deformities: soft tissue injury to MCP and IP joints causes flexion contracture of MCP and DIP joints with hyperextension of PIP joint



boutonniere deformity: may also develop as a result of a flexion contracture of the PIP and hyperextension of the DIP joints

“bent down at the middle joint and back at the end joint”

www.e-hand.com/hw/hw004.htm



Other physical manifestations

Wrist involvement: swelling, can cause subluxation (dislocation), carpal tunnel

Elbow involvement

Cervical spine

Hip disease: in contrast to OA, pain may be significant even with non-weight bearing

Knee

Baker’s cyst: cystic swelling behind knee in popliteal space

can enlarge and rupture into calf causing “pseudothrombophlebitis” (mimics thrombophlebitis)

RA

Feet

“hammer toe” deformity: phalanges sublux superiorly

pressure ulcers may form

Systemic complaints

diffuse muscle aching

low grade fevers

malaise, weight loss

depression

Laboratory Features of RA

normochromic normocytic anemias

WBC counts usually normal unless pt has a different subset of RA:

Stills: systemic onset → leukocytosis

Felty's syndrome: leukopenia (granulocytopenia) and splenomegaly with RA

Treatment of RA

NSAIDs

hydroxychloroquine

biological agents

recombinant molecules designed to block the action of cytokines

corticosteroid injections

Juvenile RA

begins before age 16

Distinct from adult RA

systemic onset more common

large joints > small joints

NO rheumatoid nodules or RF

ANA+ common

OA

What is osteoarthritis?

slowly progressive degenerative dz characterized by loss of articular cartilage

repetitive mechanical injury is often initiating factor → begins with cartilage breakdown

most common form of arthritis

females: knees + hands

males: hips

OA pathogenesis

Primary pathogenesis

1) Cartilage breakdown

overuse/microtrauma/atrophy leads to degeneration of cartilage/menisci

→ ↑ joint and ligament stress

→ bony overgrowths

2) Catabolic cytokines

IL-1 and TNF- α cause chondrocytes to ↓ synthesis of collagen and proteoglycans

→ Disorganized collagen

→ ↓ proteoglycan and collagen synthesis

→ inflammatory cells

Risk factors

age is strongest of all risk factors

heredity

some OA can be inherited AD

most common inherited OA: primary generalized (Heberden's nodes)

secondary OA due to a variety of inherited conditions

congenital hip dislocation

hip dysplasias, Ehlers-Danlos

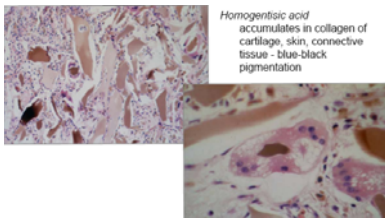
trauma

obesity

crystals

hemochromatosis

ochronosis (alkaptonuria)



↓ homogentisic oxidase

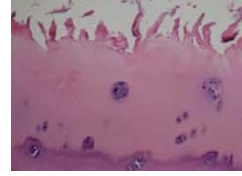
can't metabolize homogentisic acid in Phe-Tyr pathway

blue-black pigment accumulates in joints

early onset severe osteoarthritis

OA Pathology

Fibrillation

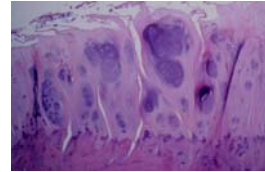


injury → chondrocyte proliferation

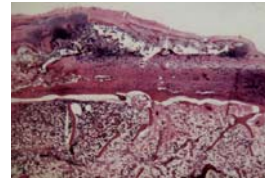
↑ water but ↓ proteoglycan

↓ Type II collagen synthesis and ↑ breakdown
eburnation = subchondral bone remodeling as a result of cartilage thinning

Vertical cracking



Osteophytes

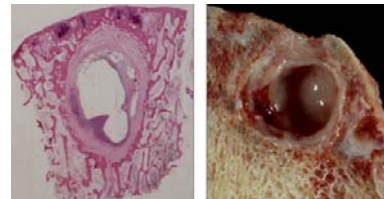


fibrocartilage flows over articular cartilage

Microfractures

leads to chunks of dislodged bone and cartilage
→ loose bodies

Subchondral cysts



synovial fluid forced into subchondral microfractures in a ball-valve manner
fluid collection walled off

OA

Clinical OA

signs

- bony enlargement
- ↓ ROM
- crepitus
- tenderness
- pain on motion
- joint effusion
- joint deformity

symptoms

- pain
 - cartilage has no innervation
 - pain from ischemia/impingement of structures, or release of fragments or crystals
 - osteophytes in spine can impinge on nerves
- morning stiffness
- gel phenomenon (hurts after inactive)

buzzwords

- heberden nodes: DIP joint
- bouchard nodes: PIP joint

joints

- knee
- hip

XRay findings

- osteophytes
- joint space narrowing

Treatment

- no way to stop progression of disease
- just treat the pain (NSAIDS, don't use narcotics)
- lose weight, don't run, common sense stuff here

Comparison of RA and OA

	RA	OA
AM Stiffness	> 1 hr	< 30 min
Worse in	AM	PM
Hand Joints	MCP, PIP	PIP, DIP, CMC (base of thumb)

Fractures

Fractures

Definitions

complete vs. incomplete

closed (simple): overlying tissue is intact

open (compound): fracture site communicates with skin surface

comminuted: when bone is splintered

displaced: when ends of bone at fracture site are not aligned

pathologic fracture: break in bone already altered by disease process

stress fracture: when bone is subject to new repetitive loads

Etiology

“healthy bone” can be damaged by trauma

repetitive trauma

broken leg type of trauma

“unhealthy bone” is more susceptible to damage

↑PTH

osteoporosis

tumors

Stages

1) Inflammatory



▶ immediately after fracture blood vessels rupture → hematoma

▶ hematoma provides fibrin framework for inflammatory cells, fibroblasts, and cytokines (FGF, PDGF, IL, TGF- β)

↑ osteoprogenitors in periosteum

↑ inflammatory cells

▶ soft tissue callus by the end of the first week provides some anchorage between ends of fractured bones but NO rigidity for weight bearing

▶ organizing fibrin

▶ granulation tissue

▶ inflammatory cells

2) Reparative



▶ newly activated osteoblasts/osteoprogenitor cells deposit woven bone in the subperiosteum

oriented perpendicular to cortical bone

▶ fracture (cartilage) callus: stabilizes site but still can't bear weight

▶ chondroblasts make fibrocartilage and hyaline cartilage

▶ bony callus results from endochondral ossification of cartilage in 2-3 weeks. Can bear some weight. Visible on X-Ray as ↑ diameter.

3) Remodeling



▶ callus remodeling results in complete resolution

▶ woven bone replaced by cancellous bone

▶ young healthy patients can have perfect reconstitution

Complications

pseudoarthrosis (false joint):

If the bone fragments don't line up properly, the callus undergoes cystic degeneration and the luminal surface becomes lined by synovial-like cells

→ must remove interposed soft tissue and stabilize fracture site to complete healing

infection

→ must be eradicated before bones can join

poor healing can be due to ↓ Ca²⁺ or phosphorous, diabetes, whatever

permanent deformity

Drug-induced Lupus

Let me guess:

it's like lupus, but caused by a drug....
should be called "drupus"

I guess we should memorize these

- ▶ hydralazine
- ▶ methyldopa
- ▶ procainamide
- ▶ isoniazid
- ▶ chlorpromazine

Clinical features

less severe than real SLE
fever, arthritis, serositis, pleuritis fairly common
rare CNS or renal involvement

Clue for boards

antihistone antibodies present
absence is more statistically significant,
since antihistone Ab's are present in 60% of
normal SLE

SLE

Who?

F>M 5:1
but in pre and post-menopausal, F>M 2:1
Blacks and Hispanics > Whites

What is it?

Immune complex disease!
Systemic, multiple organ system vasculitis &
tissue inflammation
CNS shows only little signs of inflammation

What is it caused by?

disordered regulation of all immunocytes
including T and B cells
lack of down regulation
hyperactive B cells
aberrant early signal transduction defects
augmented calcium responses
↑ antigen receptor-mediated
phosphorylation of tyrosine kinases
T cell role less clearly defined, but can involve
dysregulation due to intrinsic defects or
response to cytokines
diminished response to apoptotic signals
probably play a role
defect in Fas gene is associated with SLE
in a mouse model, restoring a working Fas
reduces the symptoms of "mouse-SLE"

What about those damn antibodies?

antinuclear antibodies (ANA) are found in
≈100% of SLE patients
antibodies directed against components of
cell nucleus
can bind DNA, RNA, or nuclear proteins
certain ANA's are specific enough to SLE to be
part of serologic criteria for diagnosis
anti-dsDNA
react to a conserved nucleic acid determinant
widely present in DNA
↑ titer more likely to have glomerulonephritis
anti-Smith (named after Ms. Smith)
Smith antigen is a U-rich RNA-protein complex
target specific RNA core proteins
other antibodies may be associated with
neuropsychiatric dz, vascular thrombosis,
recurrent fetal loss, thrombocytopenia, etc.

Autoantibodies themselves have not been
demonstrated to exert direct cytopathologic
effects

auto-Ab can be passively transferred to
other people with no adverse effect
IgG ANA which crosses the placenta does
NOT harm the fetus

What are the genetic correlates?

HLADR2-DR3
inherited complement deficiencies ↑ disease
susceptibility (C4a commonly)
theory: impaired neutralization and clearance of
foreign antigens → ↑ disease susceptibility since
the antigen persists long enough to allow
autoreactivity to emerge
Inheritance may create a *predisposition* to SLE,
but the environment plays a role as well
(infectious agents, stress, diet drugs, daylight)

SLE and pregnancy

fertility rates not altered, but ↓ chance of
carrying pregnancy to term due to ↑
spontaneous abortion, prematurity, and
intrauterine death
may be hard to differentiate lupus nephritis from
preeclampsia/eclampsia

SLE & Systemic Sclerosis Pathophysiology

Clinical features

Musculoskeletal

arthralgias, arthritis

- symmetrical involvement, similar to RA
- wrists, fingers, elbows, knees
- can cause reversible ulnar deviation of fingers and toes = "Jaccouds arthritis"

myalgias, inflammatory muscle disease (myositis)

- myalgias = full strength but achey
- myositis = reduced strength, ↑ CK

Osteonecrosis

- sudden onset of pain aggravated by weight bearing

Systemic:

Cutaneous

- the famous malar/butterfly rash
- and lots of other stuff

Cardiac

- pericarditis, myocarditis

Vascular

- vasculitis of any vessel size
- vasospasm, thrombosis

Pulmonary

- pleural effusion
- interstitial lung dz

GI

- oral mucosal ulcers
- esophageal motility disorders

Renal

- glomerulonephritis

CNS

- neuropsychiatric
- stroke, TIA, migraine, epilepsy

RES system

- h-s-megaly

Heme

- autoimmune hemolytic anemia, thrombocytopenia, leukopenia

Percentages of organ involvement

Joints: 90%

Skin

Rashes: 70%

Alopecia: 40

Discoid: 30%

Pleuropericardium: 60%

Kidney: 50%

Raynaud's: 20%

Mucous membrane: 15%

CNS (psychosis/convulsions): 15%

Systemic Sclerosis Overview

What

uncommon idiopathic disease of ↑ collagen

Who

F>M 3:1; 20-50

genetics & environment plays a role (vinyl chloride, rape seed oil, pentazocine, bleomycin)

Pathogenesis of Systemic Sclerosis

Easy version:

vascular injury → cytokines → fibrosis

Little more detailed (but still easy) version:

instigating event: vascular lesion

interstitial lymphocytic infiltrates but no direct immunofluorescence

later, arterial intimal proliferation of collagen
↑ vWF and VIII reflects endothelial cell injury

Immune cells come in and fuck shit up

When T cells see laminin they get all excited and start spewing out IL2 and all that crap

→ autoimmunity to type IV collagen & laminin

hyperactive T cells in dermis

↑ granzyme (type IV collagenase made by T cells)

TGF-β

major fibrogenic cytokine

stimulates autocrine release of PDGF

causes:

↑ mononuclear cell infiltrates

angiogenesis

→ FIBROSIS

autoAb's are present:

anti-DNA topoisomerase I (Scl-70) is the "big one"

ANA and anticentromere Ab also present

Changes in the ECM in SS

abnormal fibroblast proliferation

↑ fibroblast production of fibronectin & proteoglycan

fibronectin is scaffolding of scar tissue

↑ fibroblast secretion of collagen I, III, IV

disproportionately ↑ collagen IV, fibronectin & GAG

normal proportion of collagen I and III

normal collagen degradation

Seronegative Spondyloarthropathies

Overview of Seronegative Spondyloarthropathies

Group of arthropathies with:

- 1) No RF or rheumatoid nodules
No RF: that's why they're called "seronegative"
- 2) predilection for axial skeleton & SI joints
- 3) enthesopathy = inflammation at sites of attachment of tendons/ligament/tissue to bone
- 4) oligoarticular arthritis
- 5) extraarticular involvement frequently involving eyes, but can also involve skin, mucous membranes
- 6) commonly young males
- 7) HLA B27

Epidemiology:

disease frequency parallels B27 frequency, BUT most people with B27 don't have disease
concordance between monozygotic twins is only ≈75% → environment must play a role

Pathogenesis

Sing it loud and clear: **HLA B27**

Here's a CONCEPT: What type of MHC molecule does HLA B27 code for? MHC-I. What type of T cells bind to MHC-I? So therefore that's all you have to know – this disease involves some sort of hyperactivation of CD8+ cytotoxic T cells. Wow, that was easy!

Here's another CONCEPT: What type of MHC molecules does HLA DR2 or DR3 (Lupus) code for? MHC II. So there you go – lupus has to do with out of control CD4+ T cells. And what do CD4+ T cells do? They copulate with B cells and have them spew out ANTIBODIES.

What's the big deal about HLA B27? A bunch of cool theories...

theory 01) HLA B27 has special affinity for special "arthritogenic" peptides which it presents to CD8+ cells

theory 02) antigenic cross-reactivity between HLA B27 and bacterial antigens

theory 03) accumulation of B27 heavy chains in ER → NFκB activation somehow

theory 04) the evil monkey did it

Infection probably plays a role
role of GI system

theory: subtle GI inflammation may ↑ mucosal permeability, allowing antigens to enter systemic circulation

because other spondyloarthropathies pts often have asymptomatic GI inflammation

rats transfected with HLA B27 (& β₂ microglobulin) get spondyloarthropathy

but if they are raised in a sterile environment, then they don't

remember any other diseases like this? What about CD and UC? Abnormal response to normal pathogens.....

Ankylosing Spondylitis (AS)

What joins?

SI and axial spine

Pathology

inflammation in joints and enthesis
erosions, ligamentous calcifications, eventual ossification follow prolonged inflammation

Clinical

pts present with inflammatory back pain
insidious in onset
prolonged morning stiffness; > 1 hr
improves with activity
lasts for > 3 months
extra articular manifestations
inflammatory eye dz (anterior uveitis) in 25%
CV: aortic insufficiency, conduction defects in 10%

Labs/Radiography

Don't order HLA B27 to screen for AS since only 2% of the HLA B27 people get AS
Late changes: "bamboo spine" with formation of new bone bridging the vertebral bodies (syndesmophytes)
→ complete fusion of sacroiliac joints

Treatment

physical therapy
potent NSAIDS
Sulfasalazine helps morning stiffness and ↓ inflammation
Methotrexate
ineffective for axial symptoms
may provide more relief of peripheral joint disease
anti-TNF therapies very effective

Seronegative Spondyloarthropathies

Reactive Arthritis(ReA)/Reiters Syndrome (RS)

clinical triad

- ▶ arthritis
- ▶ conjunctivitis
- ▶ urethritis

post-infectious arthritis

The guilty bugs

Chlamydia trachomatis
Yersinia enterocolitica
Shigella flexneria
Salmonella typhimurium & enteritidis
Campylobacter jejuni and *fetus*

about 3% of pts with these infections will develop reactive arthritis

begins 2-6 weeks after infection

role of persistent bacteria?

joint fluid and synovial cultures are sterile
but bacterial antigens have been detected

PCR has shown chlamydia DNA and RNA within synovial cells

(but also found in normals too so big hoot)

long term antibiotics are NOT effective

what joints?

asymmetrical arthritis
lower extremities > upper
sausage digits or entheses
sacroiliitis only in 20%
progression to ankylosing spondylitis is < 3%

extraarticular manifestations

conjunctivitis 40%
uveitis 20%
skin lesions that can look like psoriasis

treatment

conservative: NSAIDS

Enteropathic Arthritis

what is it?

arthritis associate with UC and CD

how is it associated with IBD?

in UC, if diseased colon is removed, peripheral arthritis resolves

in CD, surgery may not affect arthritis

what joints?

knees and ankle
axial skeleton involvement with sacroiliitis or AS in 15% of pts wit IBD
HLA B27 only present in 50% of pts with axial dz

treatment

treat underlying bowel inflammation
anti-TNF α

Psoriatic Arthritis (PsA)

who gets it?

5-8% of pts with psoriasis will develop inflammatory arthritis

HLA B27 present in only 50%

no B27 association with normal psoriasis

what joints?

peripheral assymetrical oligoarticular arthritis
25% will have symmetrical polyarticular arthritis indistinguishable from RA

treatment

- 1) control skin disease
topical agents, phototherapy, methotrexate
- 2) limit articular inflammation
NSAIDS, physical therapy, steroid injections, methotrexate
sulfasalazine, gold, hydroxychloroquine
cyclosporin, anti-TNF therapy

HIV Disease Associations

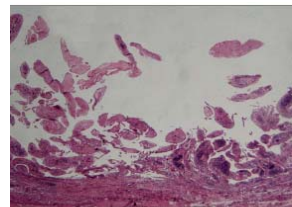
if immunosuppressive agents are necessary to control disease, MUST KNOW HIV STATUS!

Pathology of Seronegative spondyloarthropathies

Similar histology to RA, but milder disease

General characteristics

	Sex	Relapse	Extraskeletal Disease	HLA-B27
Ankylosing Spondylitis (begins in adolescence)	M>F	Yes	Uveitis, Aortitis	90%
Reiter's Syndrome (20-30 yrs)	M>F	Rarely	Conjunctivitis, Aortitis, Urethritis/Cervicitis	80%
Psoriatic Arthritis (30-50 yrs)	M>F	Yes	Uveitis, Conjunctivitis	Yes
Enteropathy Associated Arthritis	M>F	Rarely	Uveitis, IBD	Yes



Chronic synovitis
Papillary synovial hyperplasia
Pannus



chronic synovitis – joint swelling

destruction of articular cartilage

most common in ankylosing spondylitis:

fibrosing ankylosis = fibrosis and narrowing of joint space

bony ankylosis = ossification of fibrous tissue

→ joint immobility

Bone and Soft Tissue Tumors

Tumors of Fat

Liposarcoma (Malignant)	Malignant Diagnostic cell: lipoblast Well-differentiated Liposarcoma <ul style="list-style-type: none">▶ does NOT metastasize, but it can dedifferentiate into High Grade Myxoid Liposarcoma <ul style="list-style-type: none">▶ Intermediate grade Round Cell Liposarcoma, Pleomorphic Liposarcoma <ul style="list-style-type: none">▶ High grade▶ ↑ metastatic potential
-----------------------------------	--

Tumors of Fibrous Tissue

Nodular fasciitis	Reactive tumor-like proliferation	Often due to trauma
Myositis ossificans	Fibroblastic proliferation with metaplastic bone	Occurs in athletes / young adults
Fibromatoses	Inappropriate growth of fibroblasts Superficial <ul style="list-style-type: none">▶ Penile: Peyronie's disease▶ Palmar: Dupuytren's contracture Deep: Infiltrative but no metastasis <ul style="list-style-type: none">▶ Gardner's syndrome can have intra-abdominal fibromatoses▶ Can be pregnancy related in anterior abdominal wall	

Fibrohistiocytic Tumors

Malignant Fibrous Histiocytoma (Malignant)	Misnomer: has nothing to do with histiocytes Retroperitoneum
---	---

Tumors of Skeletal Muscle

Rhabdomyosarcoma (Malignant)	Embryonal <ul style="list-style-type: none">▶ most common▶ children < 10 years old▶ mucosa-lined hollow organs	Alveolar <ul style="list-style-type: none">▶ adolescents/adults▶ deep soft tissue Pleomorphic <ul style="list-style-type: none">▶ rare, adults
--	--	---

Vascular Tumors

Bacillary angiomatosis (Tumor-like lesion)	Infection with <i>Bartonella henselae</i> in immunosuppressed Silver stain to see bacteria
Hemangioma (Tumor-like lesion)	Juvenile hemangioma = "strawberry hemangioma" Cavernous Hemangioma Pyogenic Granuloma
Kaposi's Sarcoma (Intermediate malignant)	AIDS associated
Angiosarcoma (Intermediate malignant)	In liver, can be due to chemical exposure (arsenic, PVC, thorotrast) Prolonged lymphedema (breast cancer)

Bone and Soft Tissue Tumors

Bone Tumors

Osteoid Osteoma (Benign)	Young adults Nocturnal pain due to ↑ PGE ₂ alleviated by aspirin < 2 cm in diameter (by definition), sharp, round/oval lesion Resolves without treatment ~ 33 months
Osteoma (Benign)	Not clinically significant unless it causes obstruction/impingement Multiple seen in Gardner's Syndrome (with intra-abdominal desmoid tumors)
Osteosarcoma (Malignant)	Most common primary bone sarcoma Bimodal age distribution <ul style="list-style-type: none">▶ children/young adults<ul style="list-style-type: none">▶ Metaphysis of long bones▶ elderly, often arising secondarily from Paget's, radiation, or bone infarct<ul style="list-style-type: none">▶ flat and long bones equally involved Many variants Osteoid production by tumor cells necessary for diagnosis

Cartilage Tumors

Osteochondroma (Benign)	Cartilage tumor of metaphysis in young adults Mushroom shaped outgrowth from bone, grows diagonal to long axis of bone Only occurs in bones with enchondral ossification
Enchondroma (Benign)	May present with pathologic fracture May give rise to chondrosarcoma, but rare for solitary tumors to do this Peripheral enchondral ossification Multiple Enchondromatosis: 20% chance of progression to chondrosarcoma in both disorders <ul style="list-style-type: none">▶ Ollier's disease<ul style="list-style-type: none">▶ disfiguring▶ Maffucci's disease<ul style="list-style-type: none">▶ enchondromas & vascular tumors▶ all develop another extraskeletal malignancy
Chondrosarcoma (Malignant)	Cartilage producing malignant tumor older adults (40+), but clear cell variant in teens Gelatinous cut surface