Non-Neoplastic Bone & Joint Lesions

Osteomyelitis/Infection

Infection is usually caused by **bacteria** (usually *Staphlococus*)
Can be difficult to diagnose and treat, requiring long periods of IV antibiotics and possible debridement.
"Primary" from hematogenous spread (often in kids in metaphysis of long bones or adults in spine).
"Secondary" from a contiguous infection of the adjacent soft tissue or wound direct inoculation (trauma or ulceration).
Risk factors: Diabetes, IV drug use, peripheral vascular disease, hardware/prosthetic body parts.
Classic other bacteria: *Pseudomonas* in IV drug users. *Salmonella* in Sickle Cell patients.

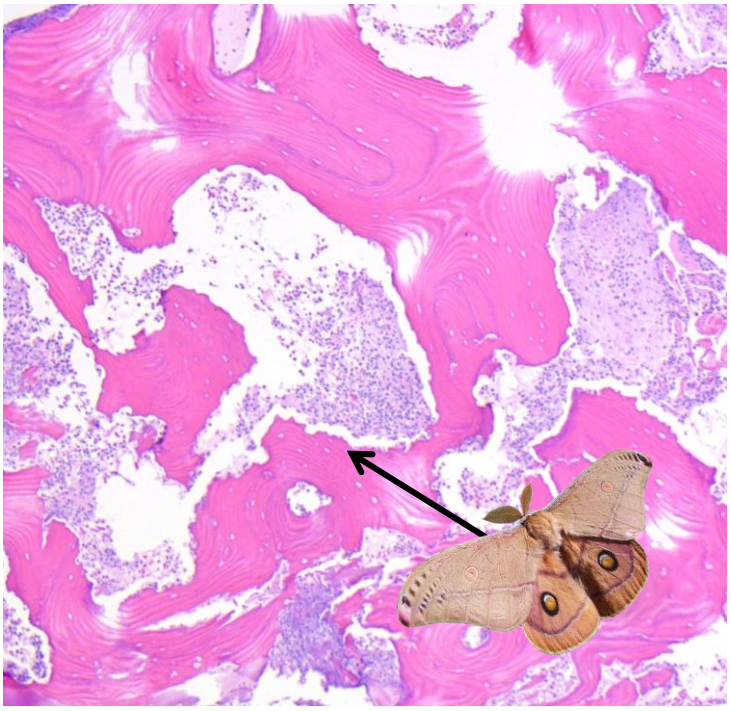
Definitive diagnosis hinges on **positive microbial studies**, either blood or bone culture, and **histological changes** in bone biopsy.

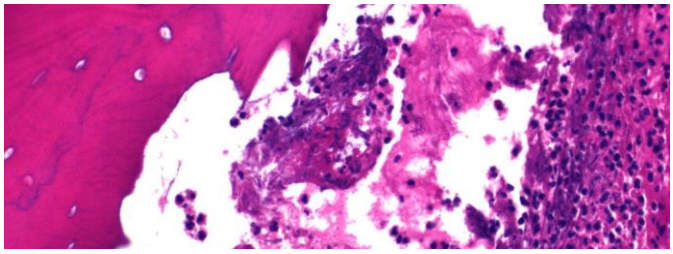
Acute Osteomyelitis

aka Suppurative or Pyogenic osteomyelitis

Histologic requirements:
1) Acute inflammation,
2) Bone destruction and/or damage/remodeling,
3) appropriate clinical context (not usually an incidental finding!).

Necrotic bone with empty osteocyte lacunae.
May see brisk osteoclast activity.
Bone often appears "moth eaten" (**irregular** erosions) with lots of "rat bites."



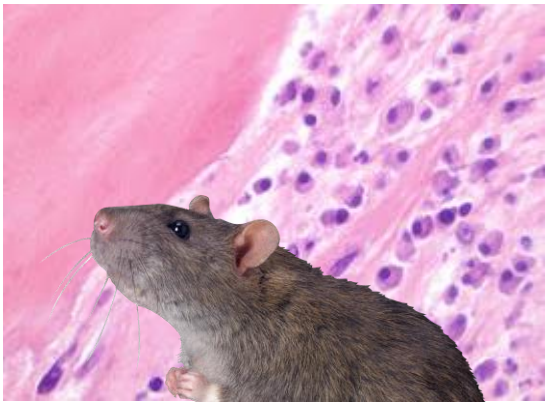


Chronic Osteomyelitis

Chronic **Inflammation** with **Bone Destruction**
Marrow replaced by fibrosis with plasma cells and lymphocytes
Often bone remodeling with osteoclasts and osteoblasts
- Plasma cells are polytypic (mixture of kappa and lambda)!
- Similar irregular rat/moth-eaten appearance
- Often granulation tissue

Necrotizing granulomas→ consider Tuberculosis ("Pott's disease" in spine),

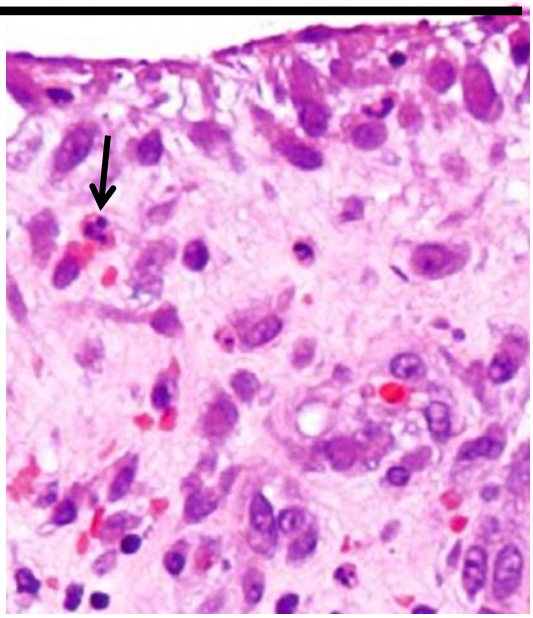
Can have sinus tract to surface line by squamous epithelium→ can turn into squamous cell carcinoma.



Septic Arthritis

Neutrophilic inflammation of synovium with accumulation of pus in joint space.
Often clinical/lab Dx.
Caused by bacteria, often *Staph* (esp. *S. epidermidis* with prosthetic joints).
Leads to rapid cartilage destruction→ acute medical emergency that needs rapid treatment.

Periprosthetic Joint Infection (PJI)



Can cause prosthetic loosening, requiring revision arthroplasty.
If there is concern for infection, will often send joint capsule for frozen section neutrophil count.

Frozen section cutoff often: **>5 neutrophils/single HPF in 5 separate HPFs in extravascular soft tissue, excluding surface fibrin and bone marrow**.

Be SURE it is PMN—lymphocytes can be twisty and mimic PMNs. *I like to see the characteristic pink cytoplasm and only call it if I'd be willing to take a picture to show y'all.*

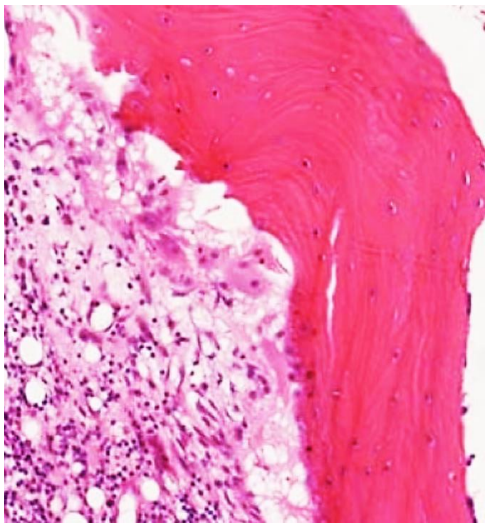
Treatment = prosthesis removal and subsequent reimplantation after eradiation (which is very inconvenient, hence wanting to be sure with your diagnosis!)

Notably, "Positive Histology" is only a *minor* criteria for periprosthetic joint infection! This should also be evaluated for clinically based on physical exam, culture, ESR, CRP, and synovial fluid studies.

The absence of PMNs does not exclude a PJI, and the presence of neutrophils does not confirm it (PMNs can also be seen with fracture, arthritis, etc…)

Full Definition of PJI with *clinical* scoring rubric here: PMID: 29551303

Chronic Recurrent Multifocal Osteomyelitis (CRMO)



Autoinflammatory disorder (*NOT* infectious)
Most common in kids and adolescents
Often present with bone pain and fatigue

Multiple sites of apparent **osteomyelitis**, but with **negative cultures** and no response to antibiotics
→ *Diagnosis of exclusion*: must rule out bacterial infection
→ Often do biopsy to get cultures and rule out tumor

Histologically, resembles infectious causes of osteomyelitis with neutrophils early on and chronic inflammation and fibrosis late (distinguish from infection by culture and/or PCR)

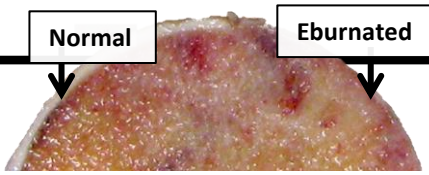
Can be associated with inflammation elsewhere (e.g., skin)

Treat symptomatically with NSAIDs

Degenerative/Reparative Changes

Degenerative Joint Disease

aka "DJD" or Osteoarthritis ("OA")

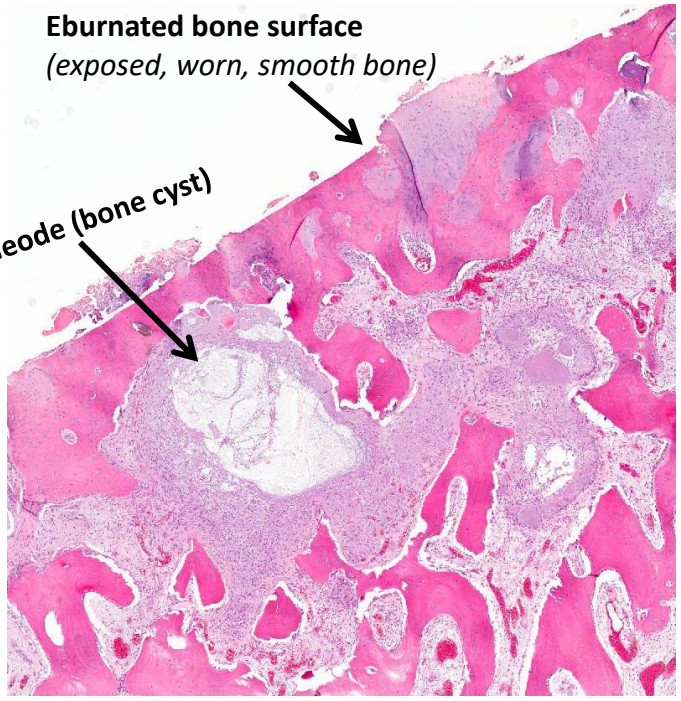


<u>Loss of joint cartilage</u> → secondary subchondral **bone sclerosis**, periarticular bone cysts (Geodes), **osteophyte formation**, and synoviocyte hypertrophy/hyperplasia.
Usually, *<u>Non-inflammatory</u>*, but can see some bone inflammation.
Adjacent synovium may show papillary hyperplasia and mild chronic inflammation

Most cases are primary, likely related to **"wear and tear"** (aging and overuse), but can be secondary to **trauma**, metabolic diseases (e.g., gout), avascular bone necrosis, and altered loading/anatomy.

Most common joints: Knee, Hip, hands

If treated surgically→ joint arthroplasty
Most common reason for arthroplasty



Fracture Callus

Reparative changes seen at **<u>a site of prior bone fracture</u>**

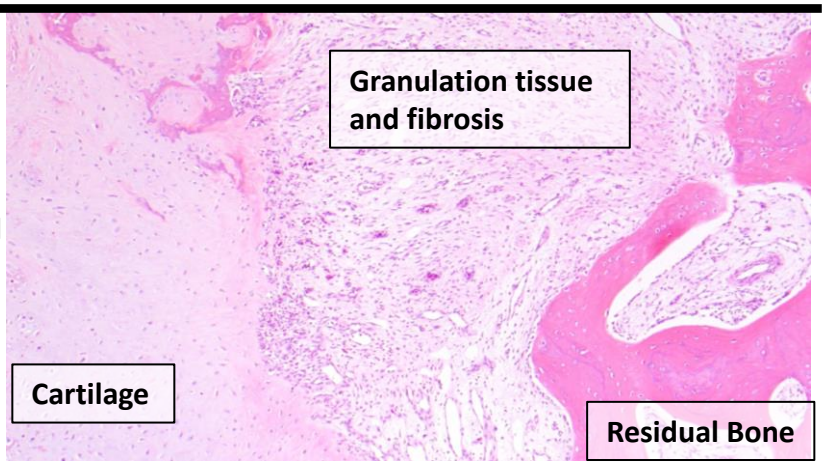
Immediately after fracture: hemorrhage, inflammation, necrosis→ gradually replaced by organizing granulation tissue and loose fibrovascular tissue → gradual growth of cartilage and woven bone

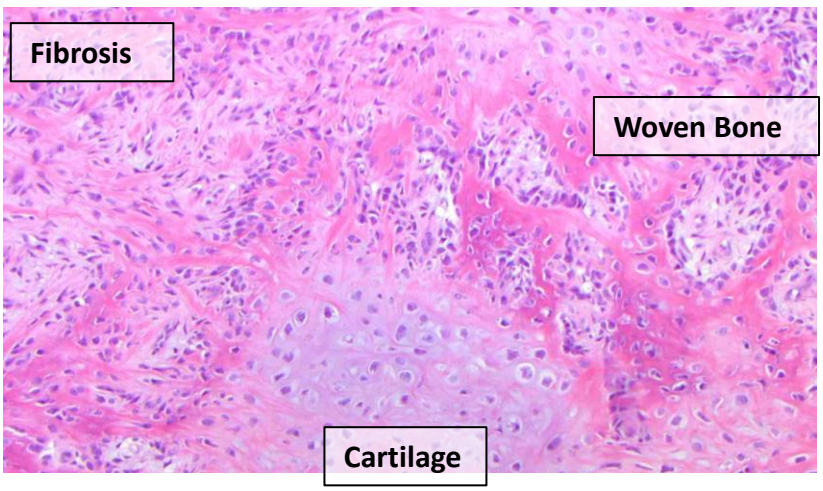
Mature callus shows:
1) Woven bone,
2) Fibrosis, and
3) Cartilage with endochondral ossification

Prominent osteoblastic rimming and bone remodeling

<u>Fracture can be seen on imaging</u> and <u>should have a history of trauma.</u>

Should *<u>NOT</u>* see: atypical mitoses, significant cytologic pleomorphism





Avascular Necrosis

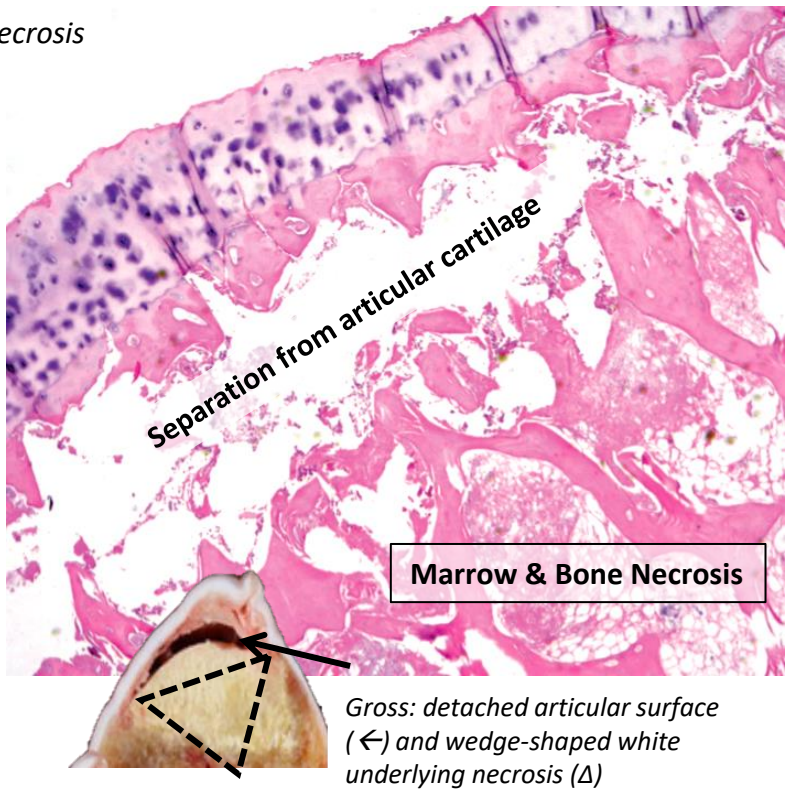
aka Aseptic Necrosis

Subchondral osteonecrosis in the *absence* of dislocation/fracture and infection.

Geographic area of subchondral bone and marrow necrosis with partially separated articular cartilage surface ("crescent sign"). Delaminated cartilage remains viable (it gets nutrients from synovial fluid).
Necrosis is most obvious in the marrow, as the bone trabeculae may still have scattered osteocytes remaining within lacunae

Can occur in any bone, most common in hip.
Risk factors: Trauma, Steroids, Alcohol, Chemotherapy, Collagen vascular disease, Pregnancy, etc… → somehow compromises blood flow→ necrosis

→ Leads to DJD/OA→ requires joint replacement



Gross: detached articular surface (←) and wedge-shaped white underlying necrosis (Δ)

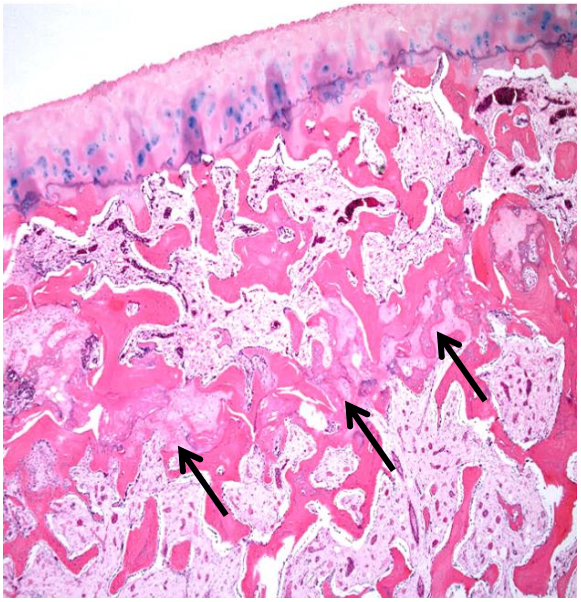
Subchondral Insufficiency Fracture

Microfractures due to deficient elastic resistance underneath articular cartilage

Histologic findings:
1) Superficial articular cartilage fracture
2) Focal '**microscopic' necrosis**, limited to the area of **fracture** and superficial subchondral bone, ± repair and fracture callus

Classically, **older women** (but anyone)
Risk factors: Kidney disease, SLE
Present with **acute pain after minor injury**

In contrast to AVN, this is microscopic and has a fracture.

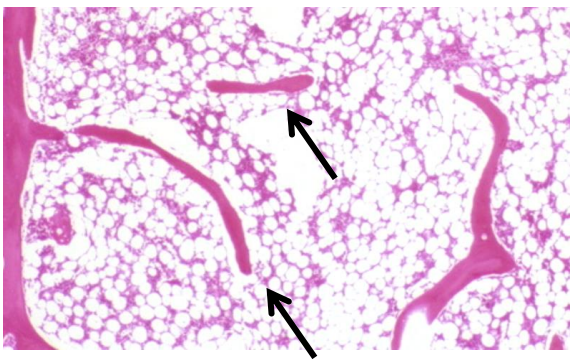


Osteoporosis

Decrease in mass of mineralized bone→ increased risk of fracture.

Frequent in postmenopausal women (due to estrogen loss) and with general aging. Can also be secondary to a variety of conditions (e.g., hyperparathyroidism, malnutrition) and medications (esp. Steroids).

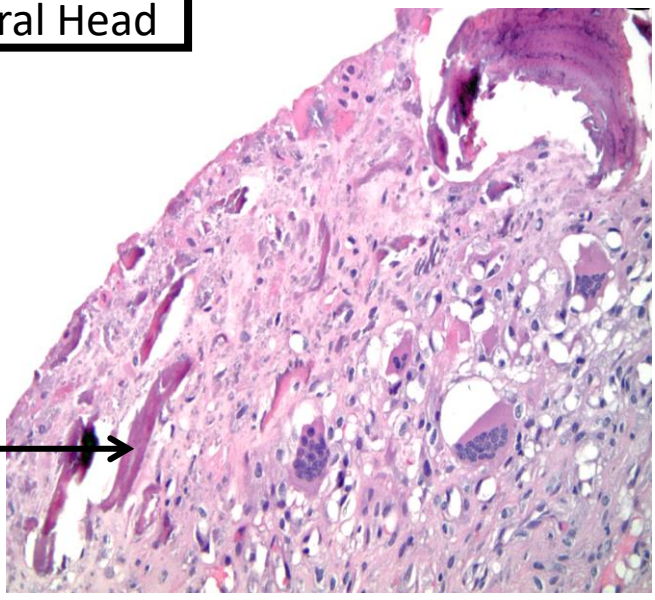
Micro: T**hin trabeculae** disconnected from each other, Increase in osteoclastic activity



Destructive Arthropathy of the Femoral Head

Rapidly progressive destruction.
Occurs over weeks to months.
Usually old women.
Culminates in femoral head collapse.
Articular surface is often completely lost with subchondral bone destruction/collapse.

Histology: Non-geographic osteonecrosis, fractures and callus/remodeling.
Necrotic bone detritus within the synovium and bone with granulomatous inflammation.

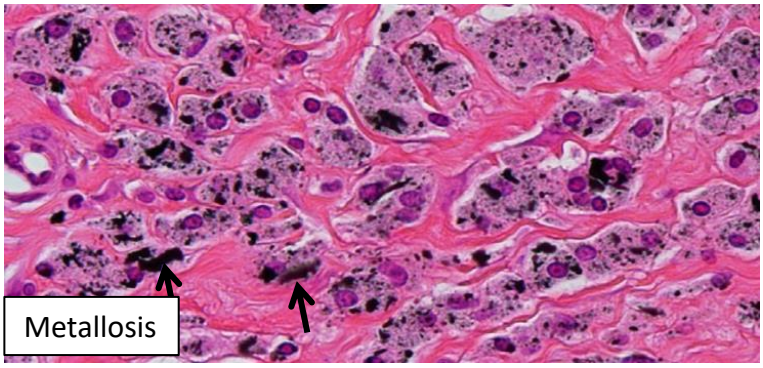


Aseptic Joint Loosening

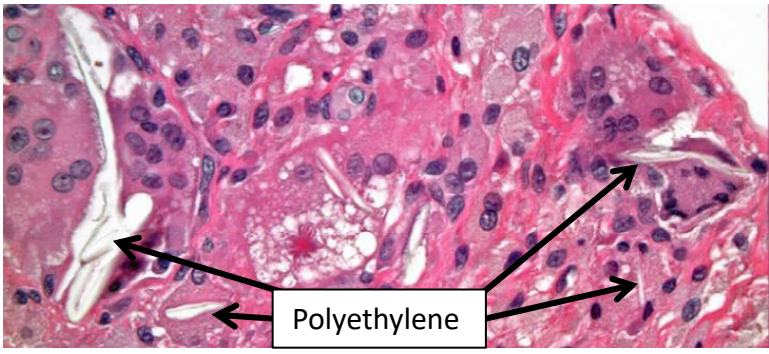
Foreign material wear particles (fragments of prosthetics that have broken off: metal, polyethylene glycol, cement, ceramic, etc..) are **ingested by macrophages**→ causes inflammation around joint → Osteolysis → Joint loosening

Abundant foamy histiocytes, Foreign body giant cells, and inorganic particles.
May see chronic inflammation, but no PMNs.

Wear particles from metal articular surfaces are small and appear black. Accumulate in macrophages and fibrous tissue→ "**Metallosis**"



Polyethylene debris looks like thread-like particles in histiocytes (very strongly birefringent)

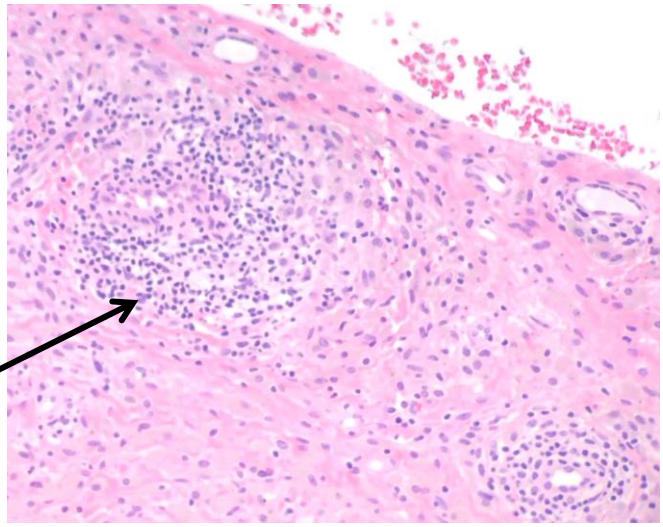


Metal can even make its way to regional lymph nodes!

Aseptic Lymphocytic Vasculitis-associated Lesion (AVAL)

Seen with metal-on-metal hip replacements.
Possibly a reaction to metal ions.
Despite name, no true vasculitis.

Classic finding: **Prominent lymphoid aggregates**, often near venules, sometimes with plasma cells.

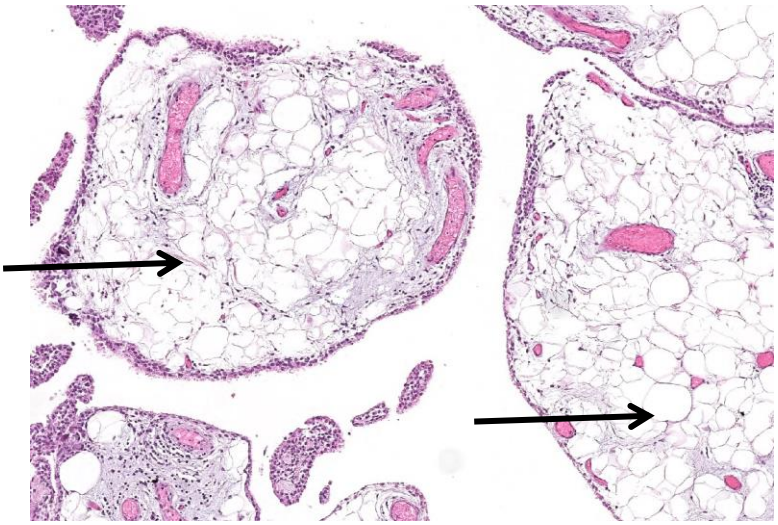


Can form large pseudotumors.
Also see: sheets of macrophages, necrosis and intracytoplasmic metal particles.

Lipoma Arborescens

aka synovial lipomatosis

Diffuse accumulation of mature fat within the synovium of a joint
→ Adipocytes present just below synovium (in contrast to normal tissue where they are separated by other fibrous tissues)



Reactive lesion associated with **trauma** or low-grade inflammation→ scattered inflammatory cells are often present.

Most common in **knee**.

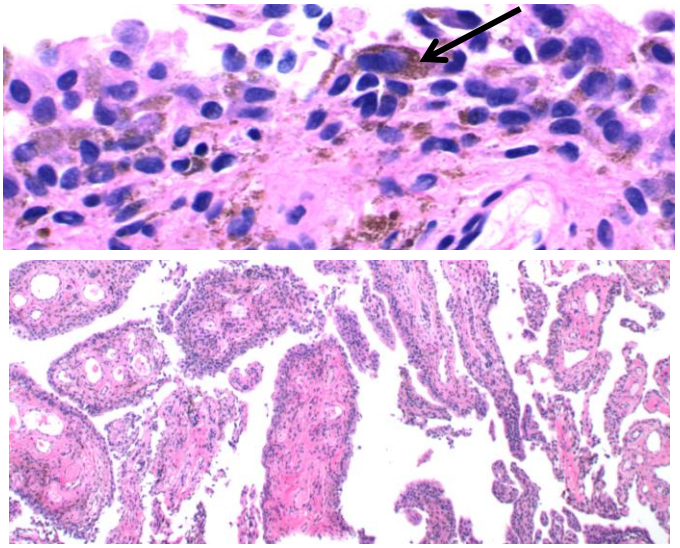
Hemosiderotic synovitis

Iron pigment deposition in synovium/histiocytes.

Can be have associated villous synovial hyperplasia and/or inflammation.

Frequent causes: Trauma ± Coagulopathies (classically hemophilia), prior surgery

DDX: Tenosynovial giant cell tumor (aka pigmented villonodular synovitis, PVNS)→ has monomorphic mononuclear cells and giant cells and expansile/tumefactive growth and nodule formation.



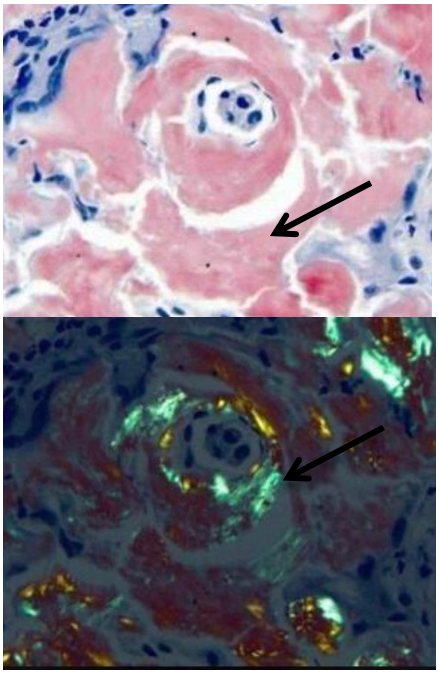
Amyloidosis

Deposits of abnormally folded protein (rich in β sheets) in vessels and tissues.
Various subtypes (see Vascular notes)

Soft tissue deposition → ***bilateral* carpal tunnel syndrome**.
Carpal tunnel involvement precedes cardiac involvement by ~5-10 yrs.

Congo red staining of carpal tunnel tenosynovium can be a useful for screening for early and reversible cardiac amyloidosis

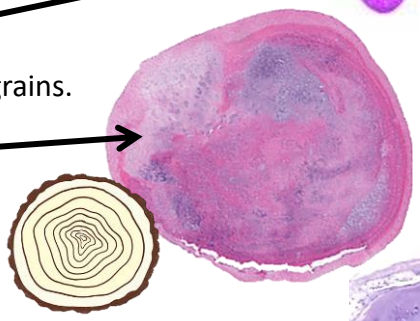
Extracellular eosinophilic amorphous material (H&E) Congo Red Stain
→ "Apple green" birefringence
Trichrome → greyish (vs Fibrosis→ bright blue)
→ reflex to mass spectrometry subtyping if positive.



Loose Bodies

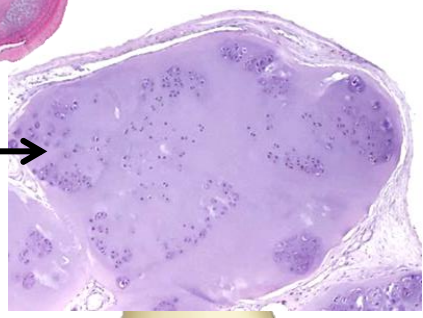
Loose fragments of tissue found floating free within the joint space
Can result from trauma, DJD, or neoplasm.
Most common in knee→ cause locking and pain

Fibrinous Loose bodies ("Rice Bodies")
Consist of laminated fibrin. Grossly resemble rice grains.

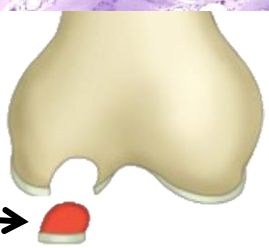


Osteocartilaginous (osteoarticular)Loose bodies
Detached fragments of articular cartilage ± bone.
Result from severe DJD or trauma. Often solitary.
Concentric ring architecture.

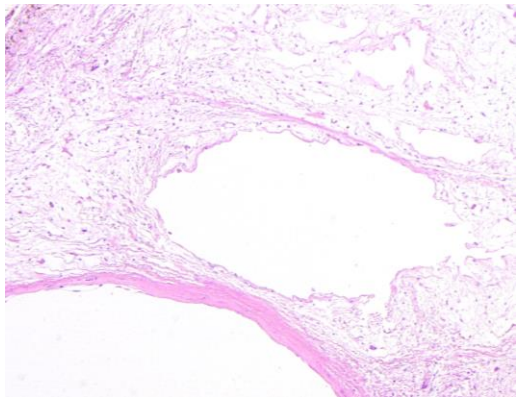
Synovial Chondromatosis
Locally aggressive (benign) *neoplasm*.
Multiple, uniform, cellular, hyaline cartilage nodules within synovium or loose in joint space. Chondrocytes cluster together in groups, with some cytologic atypia. Frequent FN1::ACVR2A fusions.



Osteochondritis dissecans
Classically children and teens, particularly active males.
Fragmentation and detachment of small focus of subchondral bone.
Usually knee→ crater shaped defect
Articular cartilage ± attached necrotic bone.



Ganglion Cyst



Cysts composed of fibrous tissue without a lining.
Contain **myxoid/mucous material**.
Seems to arise from joint capsule. Can be unilocular or multilocular.
Most often on **wrists** and hand/feet. Most common in young adults.

Can surgically excise if bothersome.
Historically, could strike and rupture with a large heavy book (e.g., a Bible)→ "*Bible bump*"

A word on Decalcification: *("Decal")*

Prior to decalcification, tissue should be properly fixed in formalin.
In order to be thinly sectioned, most bone specimens must go through decalcification.
Several methods, each with pro's and con's.

Acid decalcification
Pro: Fast. Con: Can alter chemical structure of tissue. This can alter immunogenicity and destroy DNA. Also, it can cause artifacts that mimic osteonecrosis.
So, if you're using acid, always consider decal-associated artifact if things aren't what you expect!

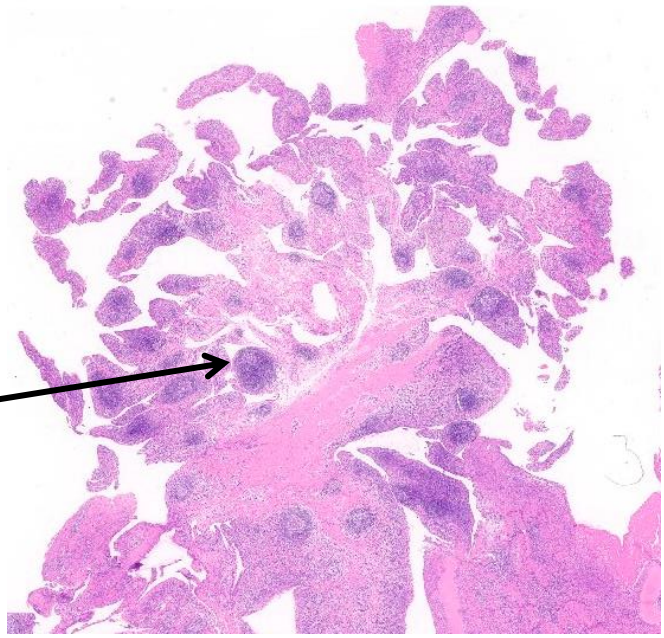
Ion Exchange (e.g., EDTA)
Pro: Gentle (fewer artifacts and molecular alterations). Con: Slow

Autoimmune Diseases

Rheumatoid arthritis and Seronegative spondyloarthropathies can show similar histologic changes, and are distinguished from one another *clinically*.

Rheumatoid Arthritis

Most common primary inflammatory arthropathy.
Chronic, idiopathic erosive symmetric polyarthropathy.
Impacts all joints, but worst impacted are small joints of hands (MCP & PIP), feet, and C-spine.
Many extra-articular manifestations (e.g., Lung disease)
Serology: Positive Rheumatoid Factor (RF)
Clinical diagnostic criteria: PMID: 20872595

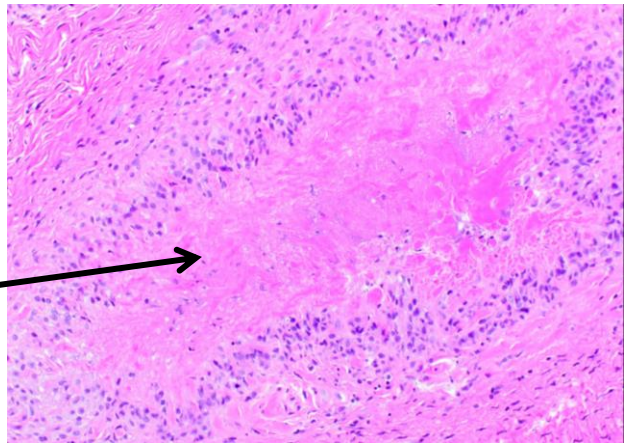


Chronic Synovitis:

Expands synovium with **chronic inflammation** (lymphocytes and plasma cells), often with lymphoid aggregates.
Often reactive/**hyperplastic synovium** with **surface fibrin/fibrinoid necrosis** and granulation tissue.
May erode nearby bone.
Sometimes occasional neutrophils.

Pannus

Synovium that erodes cartilage and other joint structures→ characteristic marginal erosions of bone on X-ray.



Rheumatoid nodule:

Necrotizing granulomas with central necrobiosis

DDX for nodule: Granuloma annulare, infection, and epithelioid sarcoma (CK+, INI1 loss)

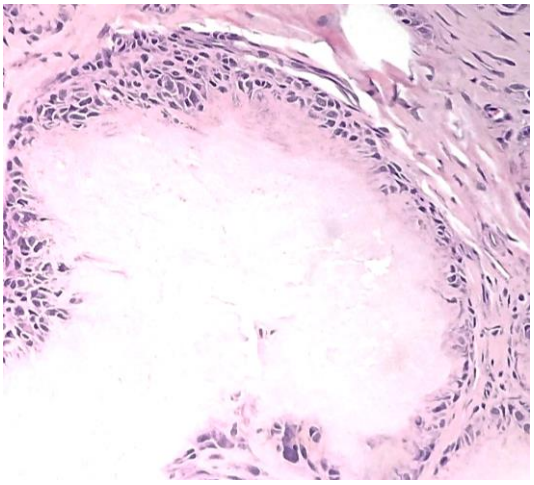
Be careful diagnosing a RA nodule in someone without a history of RA and consider getting a "screening" CK to exclude epithelioid sarcoma.

Crystalline Diseases

Modified from a presentation by Scott Kilpatrick, Cleveland Clinic, USCAP 2021

	Gout	Pseudogout	Tumoral calcinosis
Age	30-50 yrs (middle age)	>50 yrs (older)	10-40yrs (young)
Site	1st MTP	Knee	Shoulder, Hips
Crystal Shape	Needle	Rhomboid	Irregular gritty plates
Type	Uric acid	Calcium pyrophosphate	Calcium hydroxyapatite
Polarizable	+	+	-
Seen on H&E	-	+	+
Inflammatory reaction	+	-	+

Gout



Uric acid metabolic disorder: hyperuricemia→ deposit monosodium urate crystals in joint fluid and tissues.

Can be due to excess purine production (e.g., inborn error of metabolism), excess cell turnover (e.g., tumor lysis), excess ingestion (meat), or under excretion (kidney failure)

Classically middle-aged males
Most common joint: **1st MTP** (big toe), but can get anywhere
Often get recurring attacks of painful arthritis → eventually chronic gout.

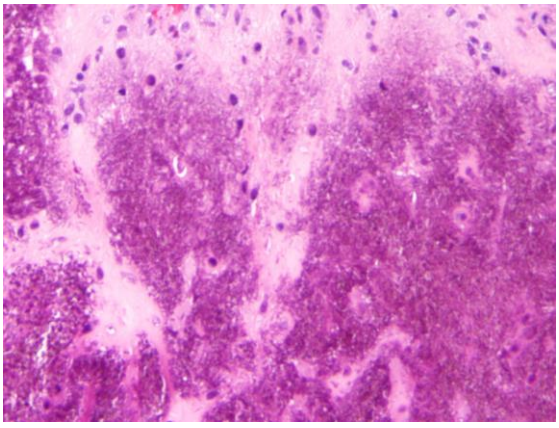
Uric acid dissolves in water during staining process (so often not seen well on H&E slides), but can be seen on fresh touch preps or unstained slides→ "**needle-shaped**" yellow, negatively birefringent crystals (yellow when the long axis of crystals is parallel to the axis of compensator and blue when the axis of the crystals are perpendicular).

Pro tip: To see the urate crystals, you can do a touch prep of the chalky tophi and polarize the unstained slide under the microscope.

On H&E: See **fluffy, feathery pink deposits** with associated **granulomatous inflammation and giant cells**. Varying associated inflammation. Soft tissue deposits = "**Tophi**"

Usually diagnosed through synovial fluid aspirations showing monosodium urate crystals. Joint fluid often neutrophil-rich.

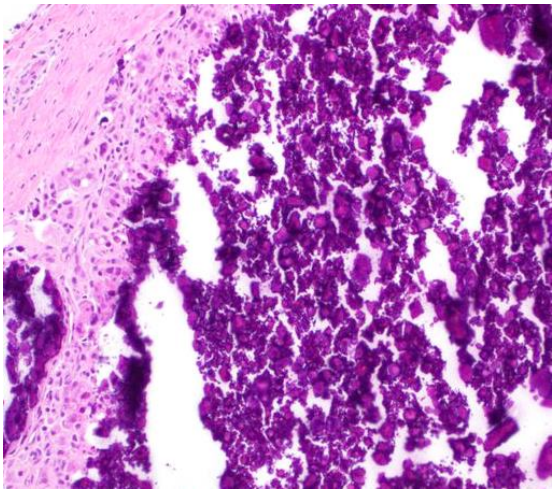
Pseudogout



Calcium Pyrophosphate Dihydrate (CPPD) deposits in cartilage and joint soft tissue.
Often *incidental* finding in arthroplasty soft tissue.
Often **associated with degenerative joint disease**.

On H&E: Well-demarcated **basophilic material** with virtually *no* inflammatory response. Aggregates within articular cartilage, synovial fronds and/or menisci.
Crystals are preserved with processing and appear **rhomboidal** purple and weakly positively birefringent.

Tumoral Calcinosis



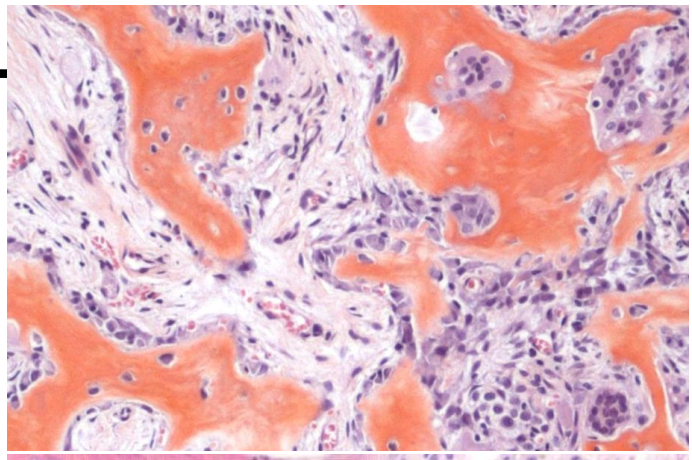
Calcium hydroxyapatite deposits
Common locations: shoulder, sites of pressure
Can be localized in relation to local **trauma** ("*dystrophic*") due to a widespread **systemic disorder** ("*metastatic*," e.g., renal failure and/or hyperphosphatemia)

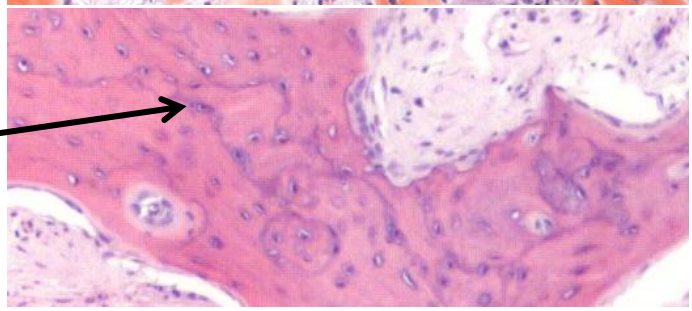
Lobules of apatite-type calcifications surrounded by chronic inflammation with a prominent foreign body giant cell reaction

In the skin and subcutaneous tissue→ Calcinosis cutis
Commonly seen in scrotum→ "Scrotal Calcinosis"

Metabolic/Endocrine/Idiopathic

Paget Disease





Localized disorder of bone remodeling characterized by focal areas of increased turnover **with excess bone synthesis and resorption.**
Often localized to a single bone in elderly men.
Early → more resorptive; Late → more synthesis.

Unusually **large osteoclasts** with increased nuclei and prominent nucleoli.
Prominent osteoblastic rimming.
Paratrabecular marrow fibrosis.
Unusually thick and thin bone trabeculae

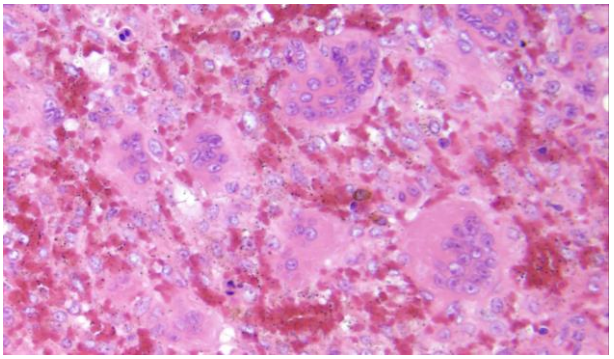
Numerous irregular reversal cement lines and bone scalloping. Mosaic pattern.

Etiology poorly understood

Increased risk of osteosarcoma

Pop Quiz: *What other disease(s) have the name "Paget"?!*
Intraepidermal spread of carcinoma in the breast and anogenital region: 1) Paget disease of the nipple, 2) Extramammary Paget disease. Also, melanocytes can have "pagetoid" spread. (And, some other diseases/phenomena not so relevant to pathology ;-)

Brown Tumor of Hyperparathyroidism

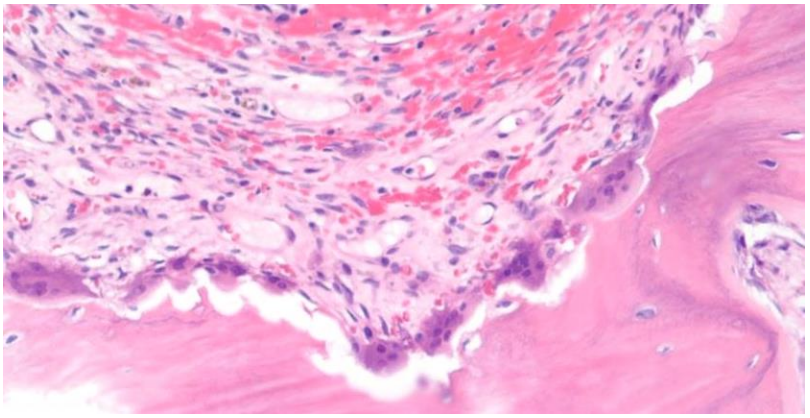


Forms a **mass** lesion.
Most common in **Mandible** and **Maxilla**.

Hyperparathyroidism (often due to adenoma) → stimulates a proliferation of **osteoclasts** with fibrous tissue and hemorrhage (resembles many other giant cell-rich lesions, like reparative granuloma), so knowing PTH is key.
Treat with parathyroidectomy.

Also can see generalized bone changes with cortical bone loss → *osteitis fibrosa cystica*

Renal Osteodystrophy



Seen in setting of **chronic renal failure.**
Increased osteoclast activity→ osteoporosis

With renal failure→ hyperphosphatemia → secondary hyperparathyroidism → increased osteoclast activity

Also, Vit D deficiency → Hypocalcemia