11th Annual Canadian Association of Pathologists Residents Review Course: Orthopedic Pathology

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Disclosure Statement

I have received an honorarium from Astra Zeneca for participation on the national advisory committee for PD-L1 testing

I have received an honorarium from Roche for lecturing

I have received an honorarium from Novartis for participation in an advisory meeting for ROS-1 testing

Educational Objectives

1. Summarize the basis for classification soft tissue lesions.
2. List new entities in the 5th Edition WHO Classification of Bone and Soft Tissue Tumors 
3. List microscopic features that distinguish soft tissue lesions
4. List immunohistochemical tests that distinguish soft tissue lesions
5. Discuss FNCLCC grading and AJCC 8th edition staging for soft tissue lesions.
6. List gross and microscopic features of common non-neoplastic bone and joint conditions
7. List distinct clinical, radiographic, gross, and microscopic features that distinguish bone lesions
8. Discuss appropriate handling of bone specimens
9. Discuss grading and AJCC 8th edition staging of bone tumors

Entities Suitable for Practical Slide Exam

- osteoarthrosis
- gout
- pseudogout
- implant related materials
- osteoporosis
- paget disease
- hyperparathyroidism
- osteonecrosis
- osteomyelitis
- osteoma
- osteoid osteoma / osteoblastoma
- chondromyxoid fibroma
- chondroblastoma
- osteosarcoma
- fibrous dysplasia
- giant cell tumor of bone
- angiolipoma
- myxoid liposarcoma
- nodular fasciitis
- schwannoma
- fibromatosis
- alveolar soft part sarcoma

Entities Suitable for Practical Gross Exam

- intramuscular myxoma
- osteoarthrosis
- rheumatoid arthritis
  - rheumatoid nodule
  - rice bodies
- synovium
  - synovial chondromatosis
  - synovium with gout or pseudogout
  - synovium with implant related changes
  - synovium with iron related changes
  - reactive synovium
- articular cartilage with CPPD
- osteonecrosis
- osteoma
- osteoid osteoma
- aneurysmal bone cyst
- osteosarcoma
- osteochondroma
- enchondroma
- multiple enchondroma (Ollier’s disease)
- chondrosarcoma

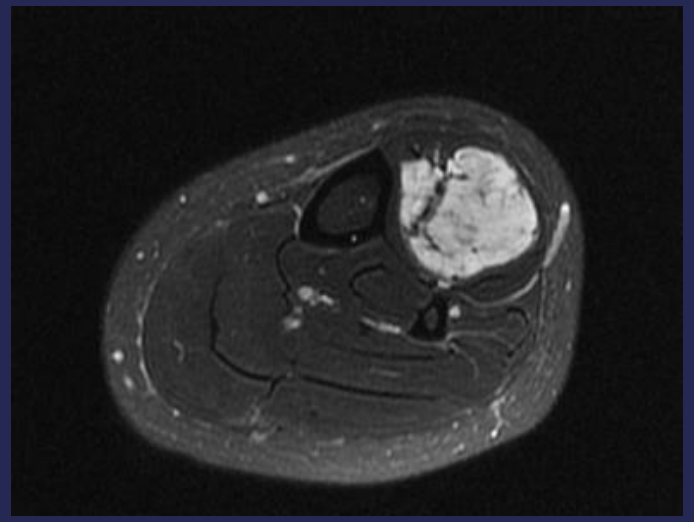
Topics Suitable for Written & Oral Exam

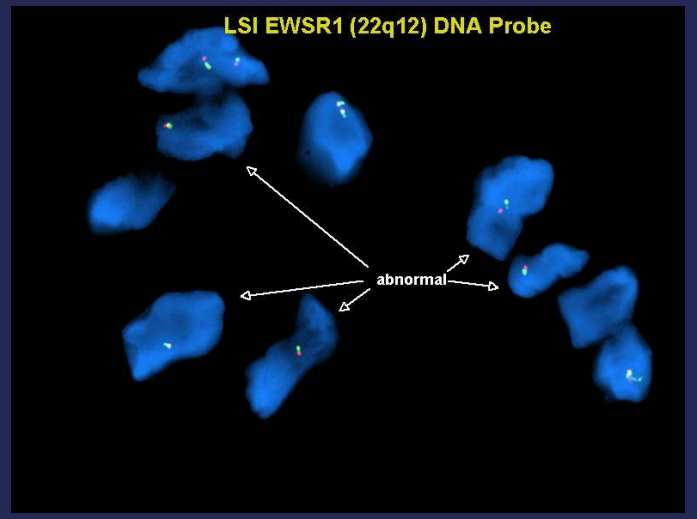
Written:

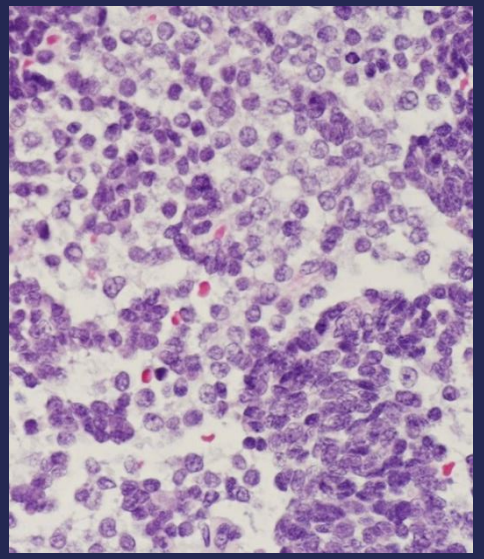
- Osteosarcoma versus fracture
- Chondrosarcoma versus enchondroma
- Ewing sarcoma
- Synovia sarcoma
- Grading and staging of soft tissue tumors
- Grading and staging of bone tumors
- Tumor syndromes
- Indications for molecular testing
- INI-1 deficient tumors
- Features used to distinguish soft tissue tumors

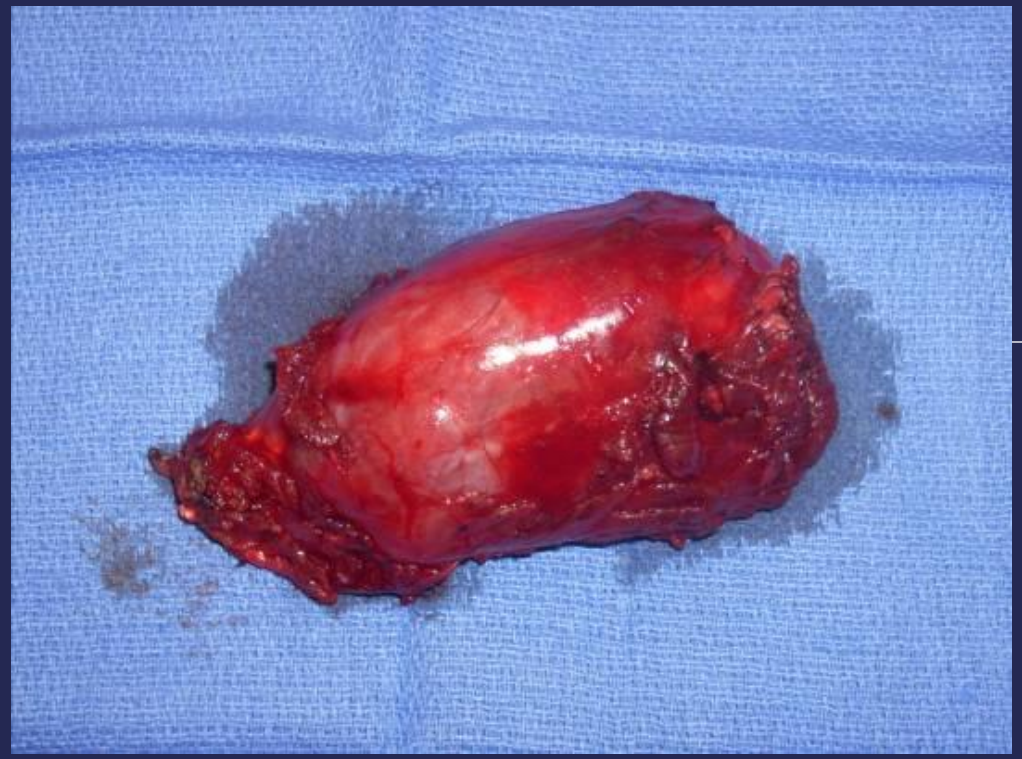
Oral Examination:

- Approach to poorly differentiated tumor
  - Spindle cell pattern
  - Epithelioid (polygonal) cell pattern
  - Pleomorphic pattern
  - Primitive (round) cell pattern
  - Biphasic or mixed patterns
  - Myxoid pattern
- Immunohistochemistry
- Molecular testing
- Joint revision surgery & frozen sections
- Specimen Handling
- AJCC 8th Edition Staging
- 5th Edition WHO Classification

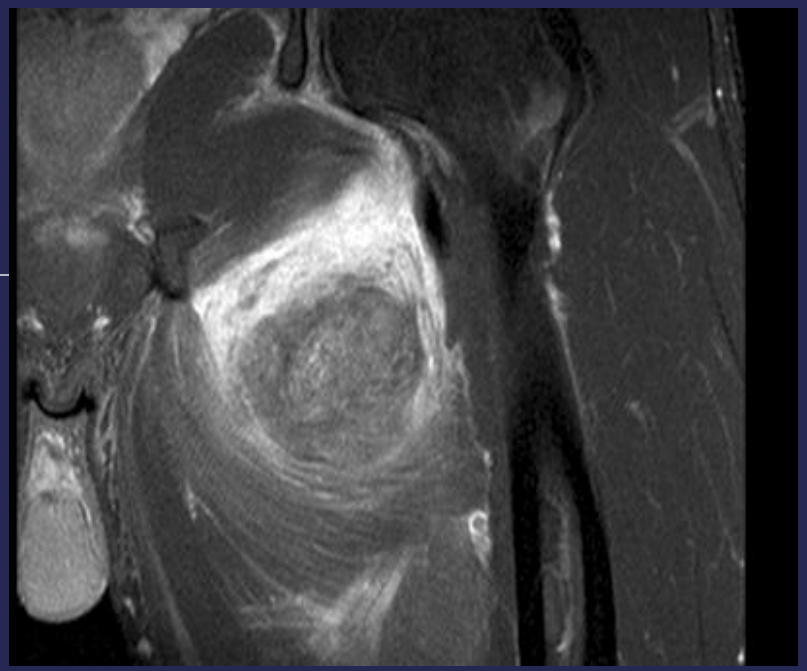








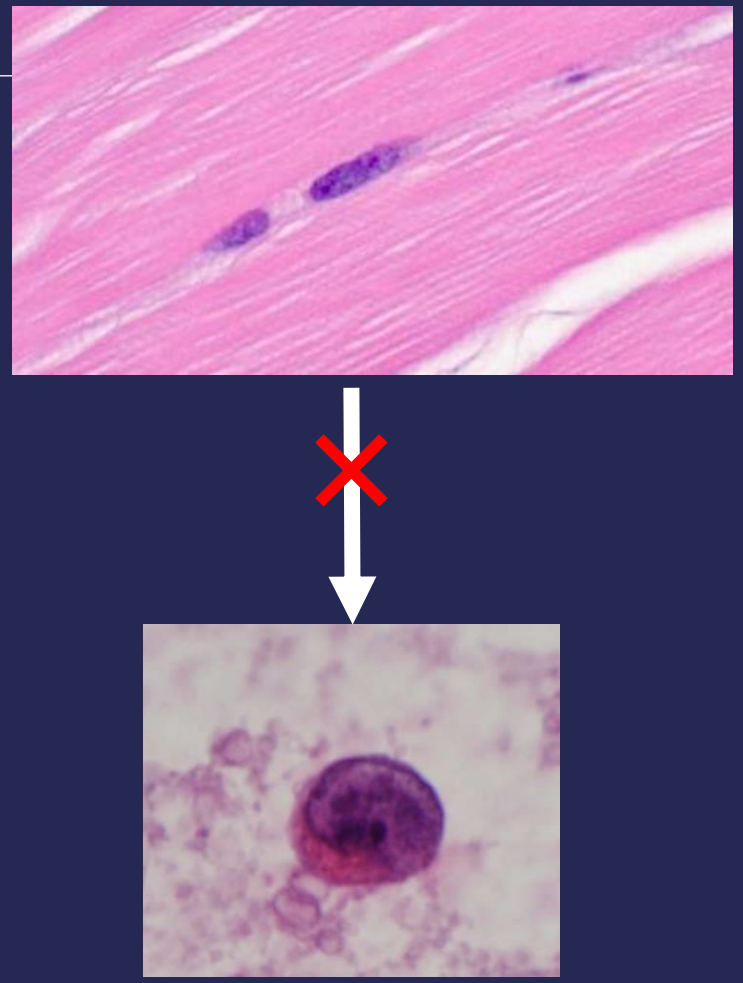
Soft Tissue Pathology



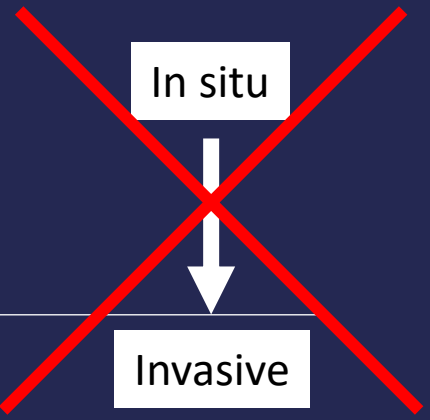
How Are Soft Tissue Lesions Classified?

Classification of soft tissue lesions is based on the “cell of origin” or “cell differentiation” that the lesion tries to recapitulate

- Adipocytic Tumours
- Fibroblastic / Myofibroblastic Tumours
- So-called Fibrohistiocytic Tumours
- Vascular Tumours
- Pericytic (perivascular) Tumours
- Smooth Muscle Tumours
- Skeletal Muscle Tumours
- Gastrointestinal stromal tumours
- Chondro-osseous tumours
- Peripheral nerve sheath tumours
- Tumours of Uncertain Differentiation
- Undifferentiated Small Round Cell Sarcomas of Bone and Soft tissue



Soft Tissue Treatment



Each group is sub-classified based on behavior which determines treatment

Benign
- Does not recur
- Does not metastasize

Treatment:
- Simple excision

Intermediate (locally aggressive)
- Locally aggressive
- No metastatic potential

Treatment:
- Complete excision with a cuff of normal tissue

Intermediate (rarely metastasizing)
- Locally aggressive
- Very low rate of metastasis

Malignant
- Locally aggressive
- Recurs locally
- Metastatic potential

Treatment:
- Wide local excision
- Radical resection
- Amputation

+/- chemotherapy
+/- radiation therapy

Circumscription
Infiltration
Mitotic activity
Cytological atypia

5th Edition WHO Bone and Soft Tissue

The 5th Edition WHO now adds molecularly defined entities

Atypical spindle cell / pleomorphic lipomatous tumor
Pleomorphic myxoid liposarcoma

Adipocytic Tumours

Fibroblastic / Myofibroblastic Tumours

EWSR1-SMAD3 positive fibroblastic tumour (emerging)
Superficial CD34 positive fibroblastic tumour

So-called Fibrohistiocytic Tumours

Vascular Tumours

EBV associated smooth muscle tumor
Inflammatory leiomyosarcoma

Pericytic (perivascular) Tumours

Smooth Muscle Tumours

Malignant melanotic nerve sheath tumour

Skeletal Muscle Tumours

NTRK-rearranged spindle cell neoplasm (emerging)

Gastrointestinal Stromal Tumour

Chondro-osseous Tumours

Ewing Sarcoma
Round cell sarcoma with EWSR1-non-ETS fusion
CIC-rearranged sarcoma
Sarcoma with BCOR genetic alterations

Peripheral Nerve Sheath Tumours

Tumours of Uncertain Differentiation

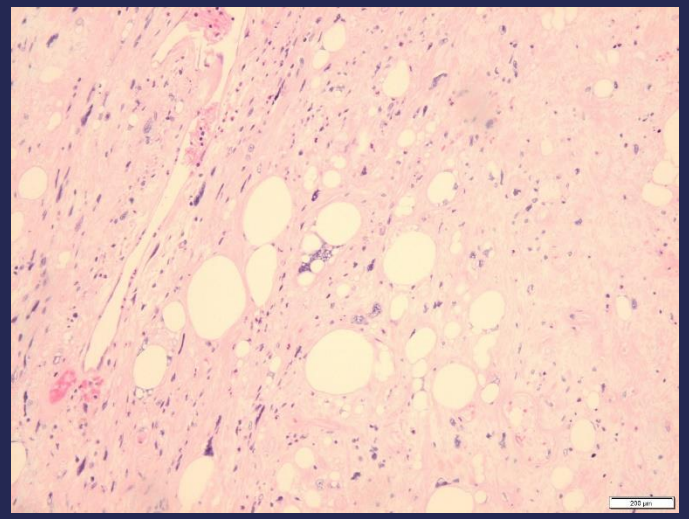
Undifferentiated small round cell sarcomas of bone and soft tissue

NEW ENTITIES (IN BRIEF)

Atypical spindle cell / pleomorphic lipomatous tumour

- ***Essential Criteria:*** variable proportions of atypical spindle cells, adipocytes, univacuolated or bivacuolated to multivacuolated lipoblasts, pleomorphic (multinucleated) cells, and a myxoid to collagenous extracellular matrix.

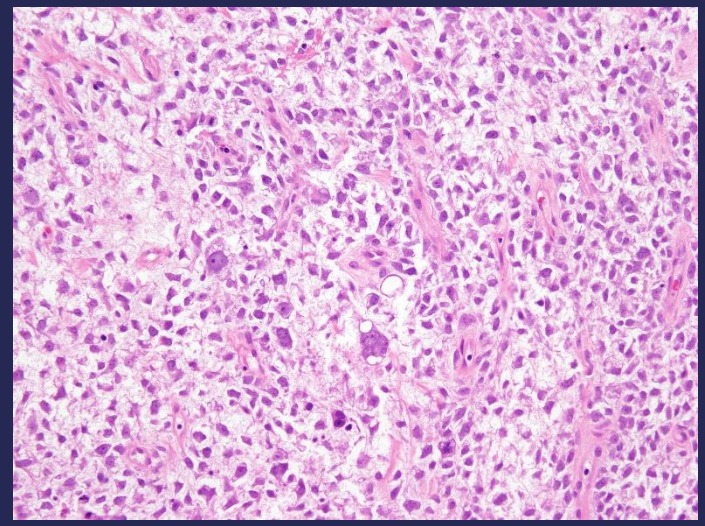
- ***Desirable Criteria (in selected cases):*** in a substantial subset of cases, RB1 expression is lost, correlating with *RB1* deletion; lack of *MDM2* or *CDK4* amplification.



Myxoid pleomorphic liposarcoma

- ***Essential Criteria:*** distinctive admixture of relatively bland zones resembling conventional myxoid liposarcoma and much more cellular and atypical areas, resembling pleomorphic liposarcoma.

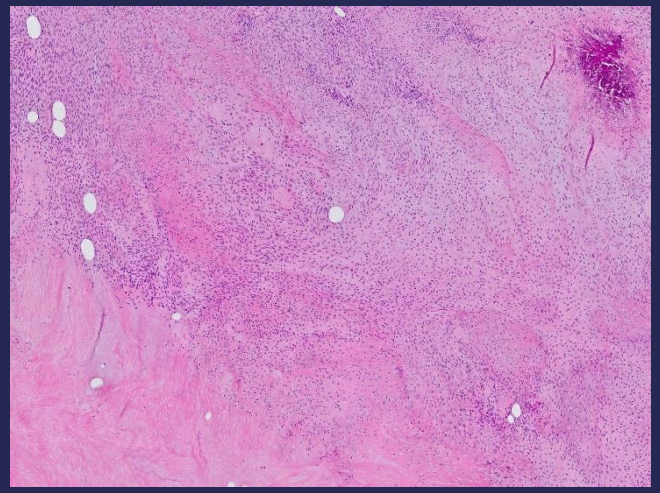
- ***Desirable Criteria (in selected cases):*** Absence of *FUS*/*EWSR1*-*DDIT3* gene fusions and *MDM2* amplifications.



EWSR1-SMAD3-positive fibroblastic tumour (emerging)

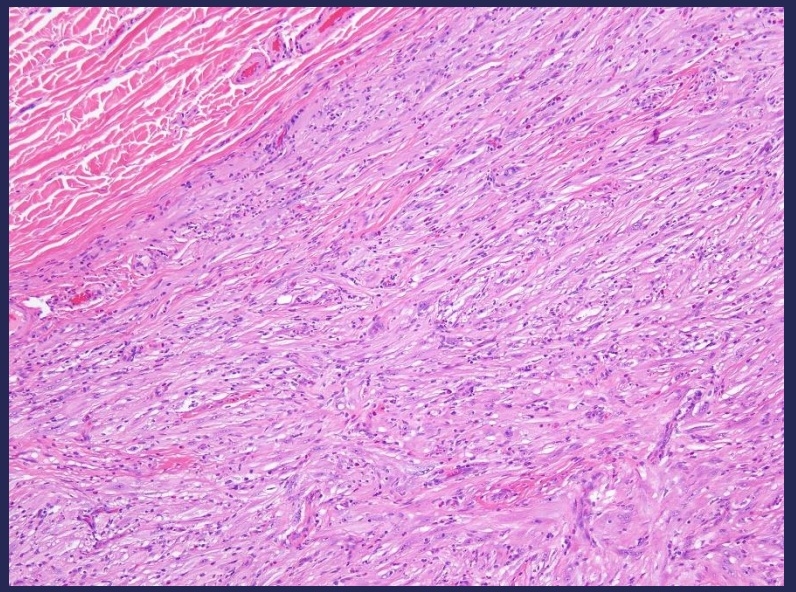
- ***Essential Criteria:*** small dermal and subcutaneous acral nodule; histological zonation with acellular hyalinized centre and peripheral fascicular spindle cell growth; immunoreactivity for ERG.

- ***Desirable Criteria (in selected cases)****: EWSR1-SMAD3* fusion (if available).



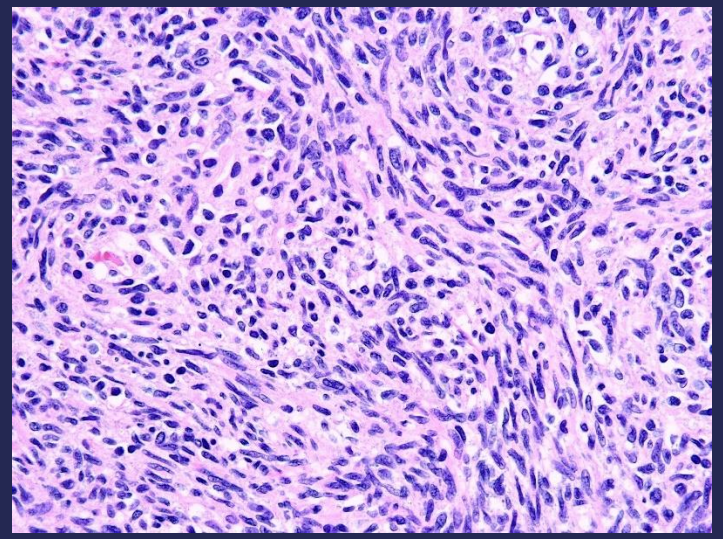
Superficial CD34-positive fibroblastic tumour

- ***Essential Criteria:*** superficial location; large eosinophilic cells with granular to glassy cytoplasm; marked nuclear pleomorphism but a **very low mitotic count**; diffuse **CD34** expression and frequent **keratin** immunoreactivity.



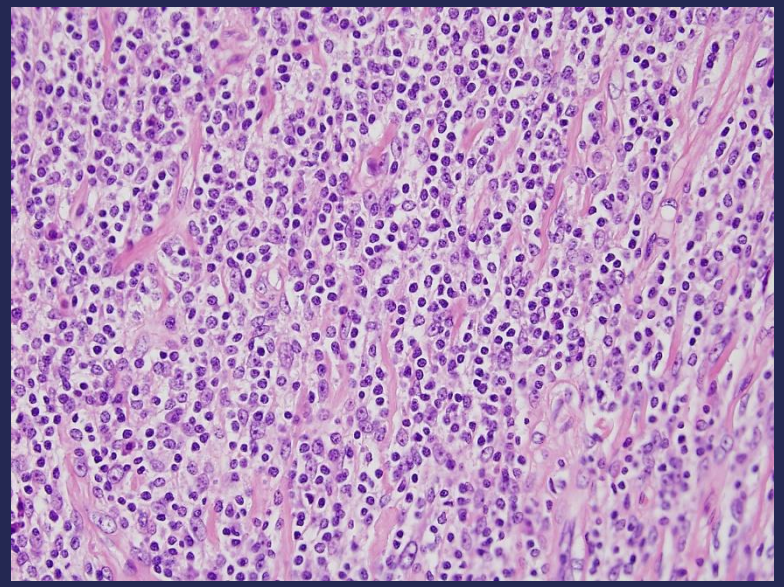
EBV-associated smooth muscle tumour

- ***Essential Criteria:*** clinical history of immunosuppression; neoplasm with smooth muscle differentiation; positivity for EBER transcripts by in situ hybridization.



Inflammatory leiomyosarcoma

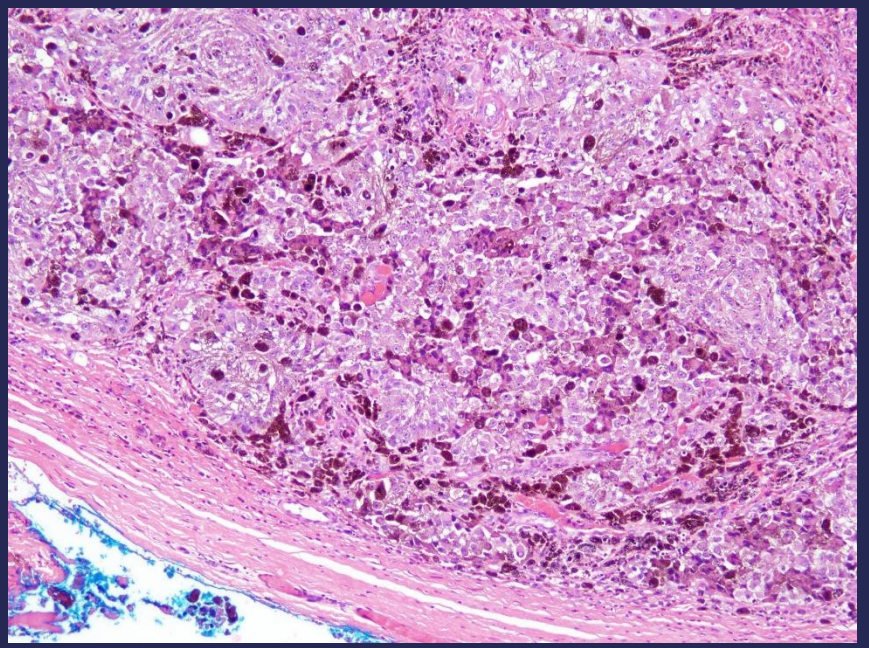
- ***Essential Criteria:*** fascicular proliferation of variably atypical eosinophilic spindle cells, which show mitotic activity; dense inflammatory infiltrate, most often lymphoid or histiocytic/xanthomatous, but the composition is variable; immunopositivity for smooth muscle antigens.



Malignant melanotic nerve sheath tumour

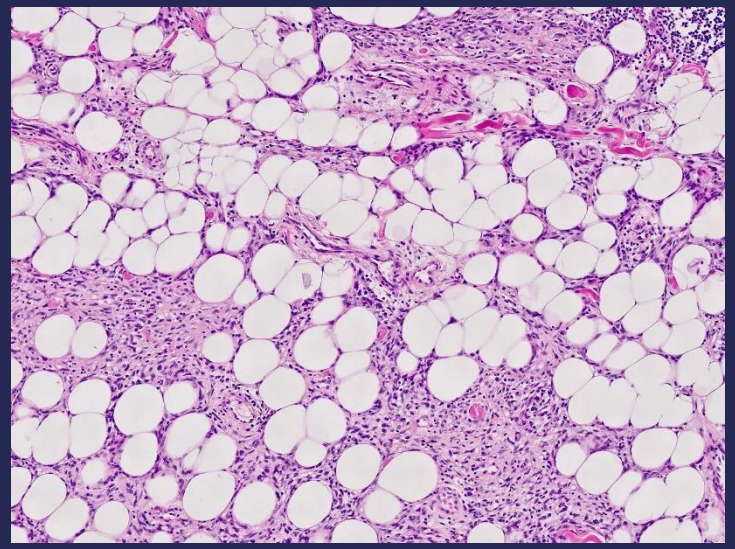
- ***Essential Criteria:*** frequent origin from paraspinal or visceral autonomic nerves; fascicular to sheet-like proliferation of heavily pigmented, relatively uniform plump spindled cells; coexpression of S100/SOX10 and melanocytic markers (e.g. HMB45, melan-A).

- ***Desirable Criteria:*** loss of PRKAR1A expression.



NTRK-rearranged spindle cell neoplasm (emerging)

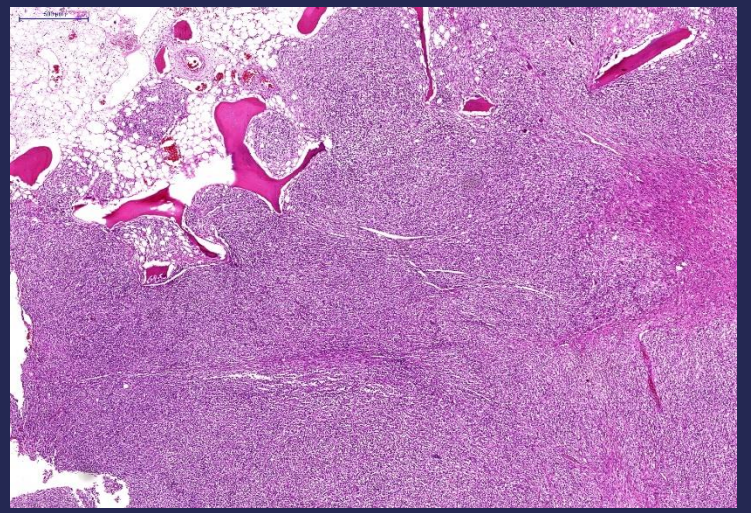
- ***Essential Criteria:*** tumours span a **wide spectrum of morphologies** and histological grades; characterized by haphazardly arranged monomorphic spindle cells; infiltrative growth within fat resembling lipofibromatosis; distinctive stromal and perivascular keloid collagen; immunohistochemically tumours are **positive for S100 and CD34** in many cases, whereas **SOX10 is negative**; tumours with *NTRK1* fusions will show **NTRK1 (and pan-TRK) immunoreactivity**.



- ***Desirable Criteria:*** detection of NTRK fusions is usually required for determination of therapy.

Round cell sarcoma with EWSR1-non-ETS fusions

- ***Essential Criteria:*** spindled to rounded cytomorphology; mostly low-grade features, but high-grade cases are reported; fibrohyaline stromal changes are common; *EWSR1* break-apart FISH shows amplification of the 5’ probe in *EWSR1-NFATC2*–rearranged sarcomas; identification of the fusion transcript remains the gold standard.

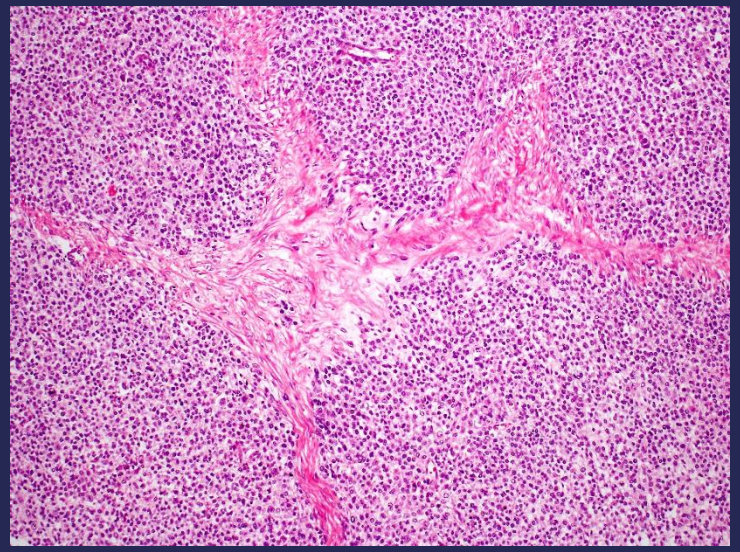


- ***Desirable Criteria:*** most *NFATC2*-rearranged tumours are located in long bone; *PATZ1*-rearranged sarcomas: round to spindled cells with divergent phenotype, both myogenic and neurogenic.

CIC-rearranged sarcoma

- ***Essential Criteria:*** predominant round cell phenotype; mild nuclear pleomorphism; epithelioid and/or spindle cell components; variably myxoid stroma; immunoprofile shows **variable CD99 staining, with frequent WT1 and ETV4 positivity.**

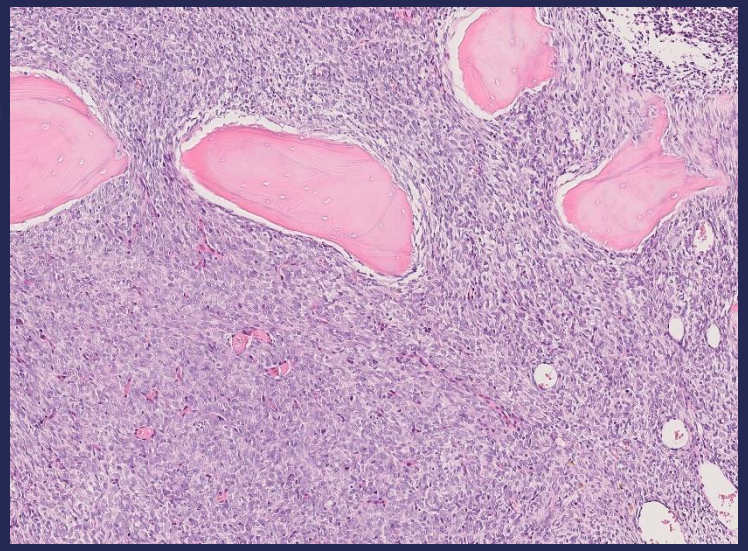
- ***Desirable Criteria:*** *CIC* gene rearrangement (in selected cases) – low sensitivity for detection.



Sarcoma with BCOR genetic alterations

- ***Essential Criteria:*** primitive round to spindle cells arranged in nests, sheets, or fascicular growth; variably myxoid stroma with delicate vasculature; immunohistochemical positivity for BCOR, SATB2, and cyclin D1.

- ***Desirable Criteria (in selected cases):*** molecular confirmation of *BCOR* genetic abnormality (*BCOR* fusion, *BCOR*-ITD).



How Are Soft Tissue Lesions Diagnosed?

IMAGING EVALUATION

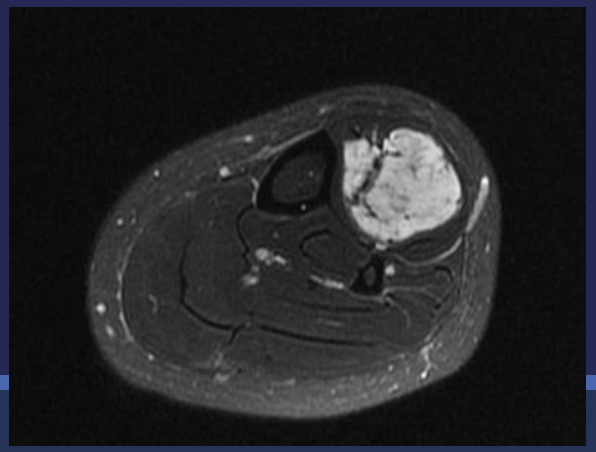
Radiograph

US

CT

MRI

PET



DIAGNOSTIC EVALUATION

Tissue sampling

Fine needle aspiration

Core biopsy

Open biopsy

Excisional biopsy

Classification of soft tissue lesions is very difficult and FNA is not usually helpful.

However, touch preparations on fresh biopsy and excision specimens can be very helpful in the triage of tissue.

Biopsy of Soft Tissue Tumor

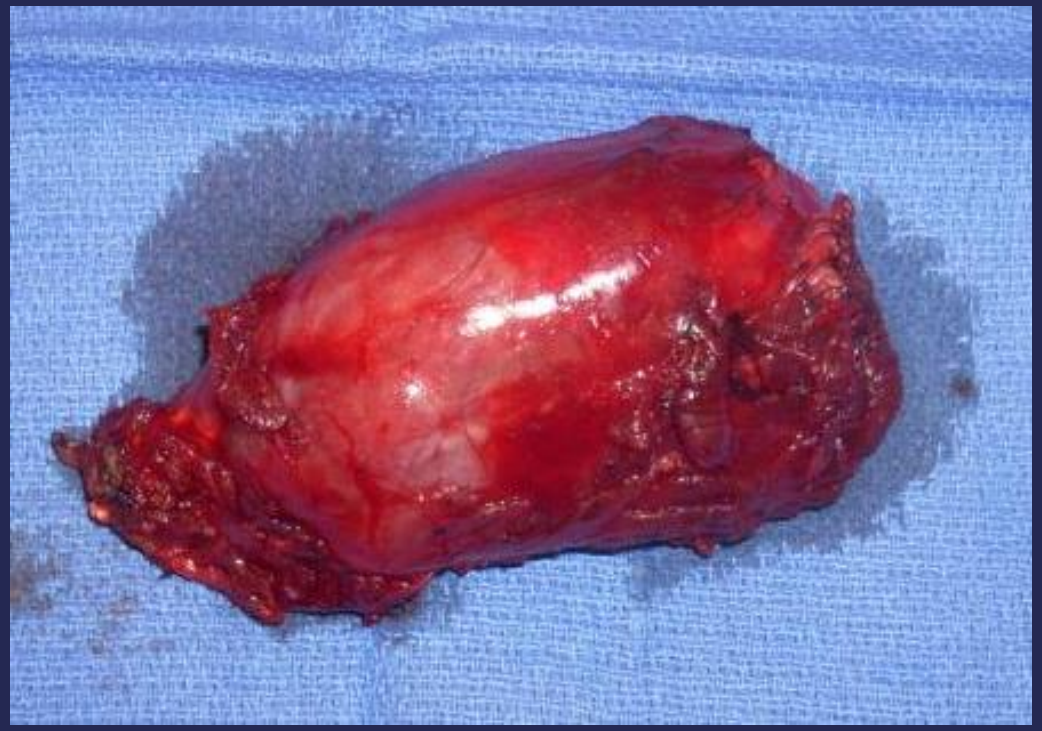
Describe the biopsy type (incisional biopsy or core biopsy), size (aggregate, largest fragment), color, consistency, recognizable components (fibrous tissue, fat, skeletal muscle)

A touch preparation can be used to triage material for special studies if there is sufficient material available

If there is limited material, then it is submitted entirely for formalin fixation and histological evaluation

Resection for Soft Tissue Tumor

- Describe the specimen components (skin, subcutis, skeletal muscle, nerve, bone, organs) and given the dimensions of each
- Describe the specimen orientation and ink appropriate margins to maintain orientation
- Serially section the specimen and describe the lesion
- Size
- Color and consistency
- Borders (circumscribed, infiltrative)
- Location (centered in and involved structures)
- Hemorrhage (%), necrosis (%), myxoid change (%), cystic alteration (%)
- Distance to margins (anterior, deep, proximal, distal, medial, lateral)
- Submit at least 1 section per cm of tumor including closest margins.



AJCC Cancer Staging Manual 8th Edition: Soft Tissue Sarcoma

AJCC Cancer Staging Manual 8th Edition recognizes shortcomings of prior editions in staging more than 50 distinct entities that can occur throughout the body using a single system

Biological behavior of soft tissue sarcoma is best determined by the histological diagnosis, but it is not feasible to have 50 different staging systems

Goal is for the AJCC staging to better predict the risk of recurrence and death

AJCC Cancer Staging Manual 8th Edition: Soft Tissue Sarcoma

Greater emphasis is placed on the anatomical primary site

New staging systems are introduced for soft tissue sarcomas of the

- Extremity and trunk
- Retroperitoneum
- Head and neck
- Abdominal and thoracic viscera

Primary tumor staging no longer distinguishes superficial and deep locations and rather puts emphasis on new size criteria

Soft Tissue Sarcoma of the Extremities and Trunk

T Category	T Criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor ≤ 5 cm
T2	Tumor > 5 cm and ≤ 10 cm
T3	Tumor > 10 cm and ≤ 15 cm
T4	Tumor > 15 cm

Soft Tissue Sarcoma of the Retroperitoneum

T Category	T Criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor ≤ 5 cm
T2	Tumor > 5 cm and ≤ 10 cm
T3	Tumor > 10 cm and ≤ 15 cm
T4	Tumor > 15 cm

Soft Tissue Sarcoma of the Head and Neck

T Category	T Criteria
TX	Primary tumor cannot be assessed
T1	Tumor ≤ 2 cm
T2	Tumor > 2 cm and ≤ 4 cm
T3	Tumor > 4 cm
T4	Tumor with invasion of adjoining structures
T4a	Tumor with orbital invasion, skull base / dural invasion, invasion of central compartment viscera, involvement of facial skeleton, or invasion of pterygoid muscles
T4b	Tumor with brain parenchymal invasion, carotid artery encasement, prevertebral muscle invasion, or central nervous system involvement via perineural spread

Soft Tissue Sarcoma of the Abdomen and Thoracic Viscera

T Category	T Criteria
TX	Primary tumor cannot be assessed
T1	Organ confined
T2	Tumor extension into tissue beyond organ
T2a	Invades serosa or visceral peritoneum
T2b	Extension beyond serosa (mesentery)
T3	Invades another organ
T4	Multifocal involvement
T4a	Multifocal (2 sites)
T4b	Multifocal (3 to 5 sites)
T4c	Multifocal (> 5 sites)

AJCC Cancer Staging Manual 8th Edition: Soft Tissue Sarcoma

Histologic three-grade system as determined by the French Federation of Cancer Centers Sarcoma Group (FNCLCC) system is recognized as the superior grading system and the AJCC four-grade system is abandoned

GRADE

Basically, if you can't find it in the table of differentiation scores, then you don't have to grade it with the FNCLCC system

FNCLCC (French) System

Tumor differentiation	Score 1 – resembles normal Score 2 – histological type certain Score 3 – primitive and undifferentiated
Mitotic count	Score 1 – 0 to 9 mitoses per 10 hpf Score 2 – 10 to 19 mitoses per 10 hpf Score 3 – >19 mitoses per 10 hpf
Tumor necrosis	Score 0 – no necrosis Score 1 - <50% tumor necrosis Score 2 - ≥50% tumor necrosis
Grade	Grade 1 – Score 2, 3 Grade 2 – Score 4, 5 Grade 3 – Score 6, 7, 8

TUMORS NOT GRADED UNDER FNCLCC SYSTEM

Gastrointestinal stromal tumor

Malignant peripheral nerve sheath tumor

Embryonal rhabdomyosarcoma

Alveolar rhabdomyosarcoma

Angiosarcoma

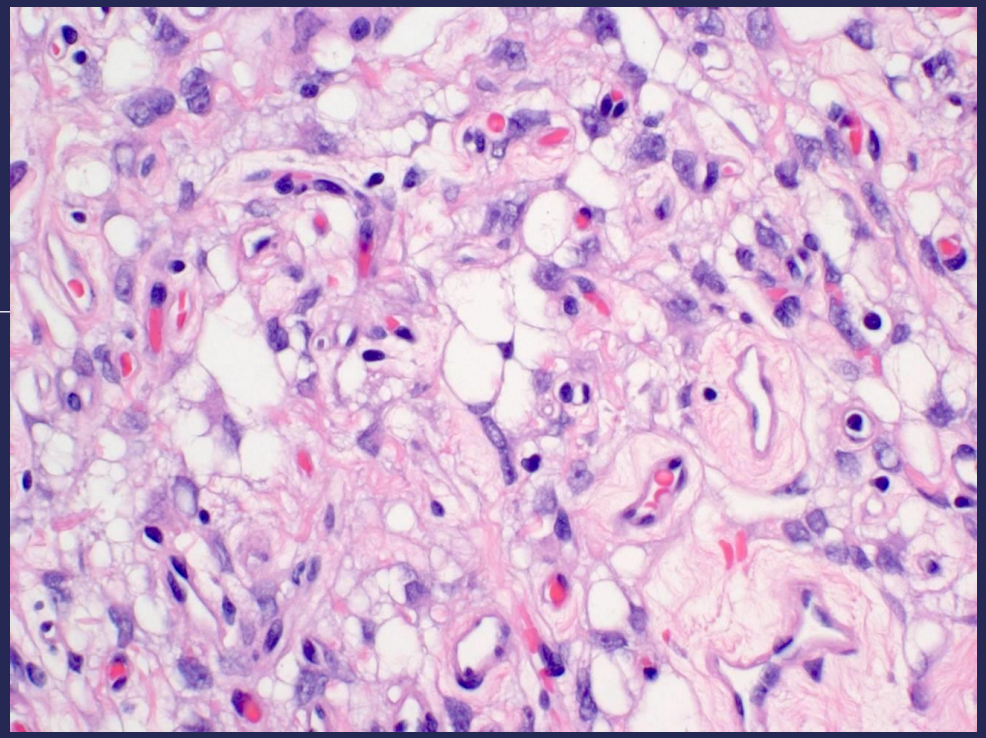
Extraskeletal myxoid chondrosarcoma

Alveolar soft part sarcoma

Clear cell sarcoma

Epithelioid sarcoma

How Are Soft Tissue Lesions Diagnosed?



Histological evidence of differentiation
- Pattern recognition
- Cellular features
- Architectural and growth patterns

Immunohistochemical evidence of differentiation
- Antibodies detect proteins expressed by the cells that are characteristic of specific tissue differentiation

Molecular
- Some tumors have recurrent genetic abnormalities that are characteristic of a specific tumor type

Histological Patterns

Spindle cell pattern

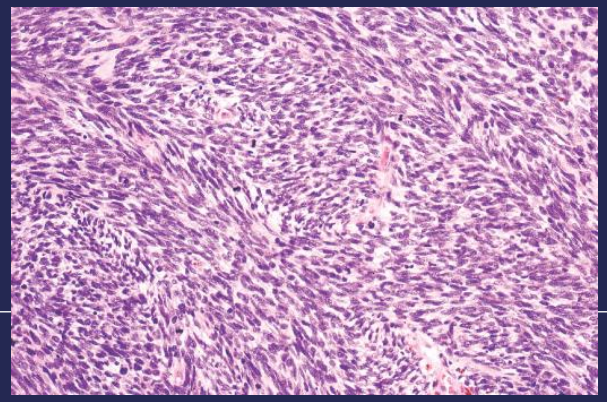
Epithelioid (polygonal) cell pattern

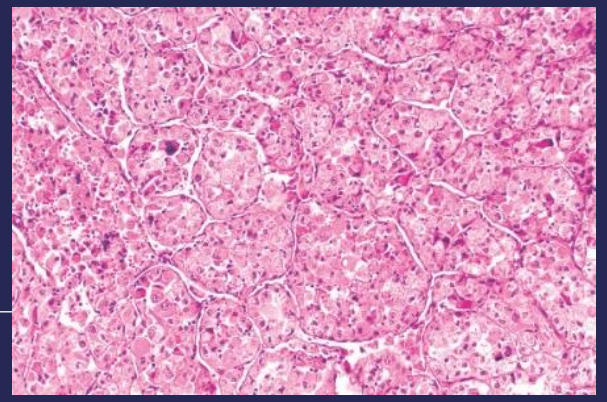
Pleomorphic pattern

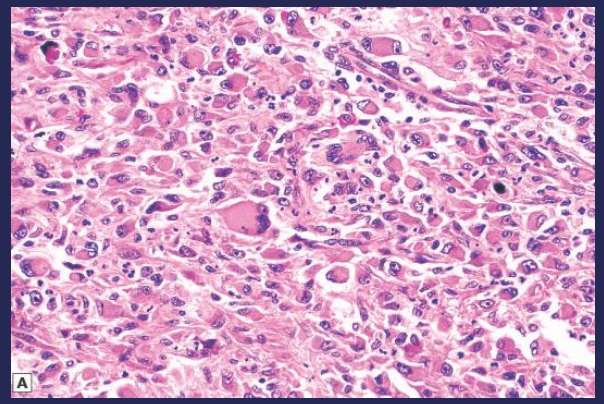
Primitive (round) cell pattern

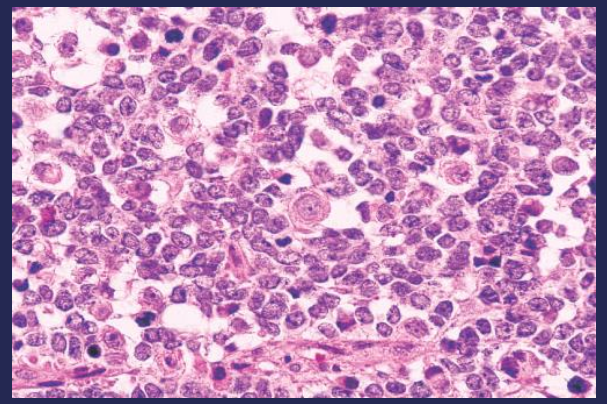
Biphasic or mixed patterns

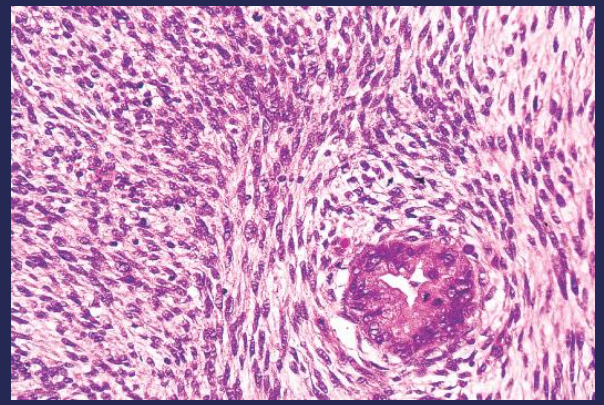
Myxoid pattern

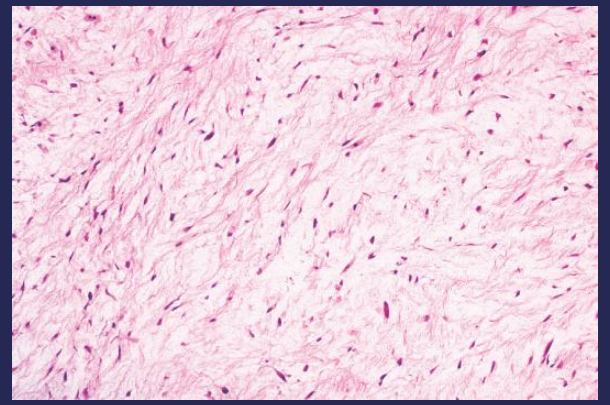




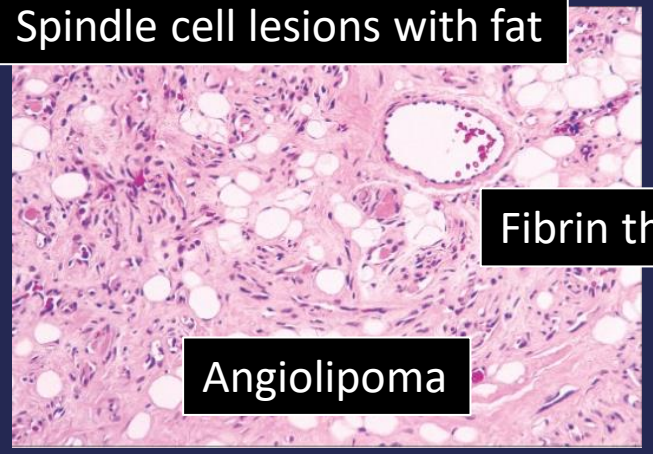








Spindle cell lesions with fat

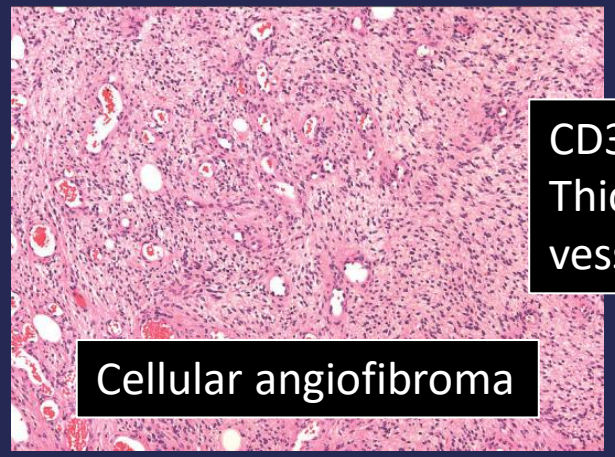


Fibrin thrombi

Angiolipoma

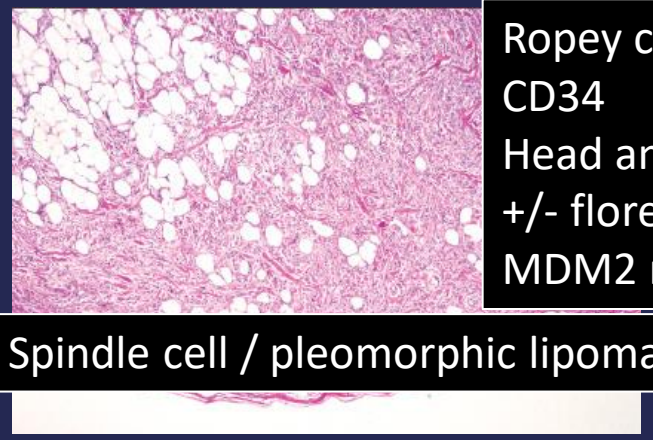
CD34
Desmin

Mammary type myofibroblastoma



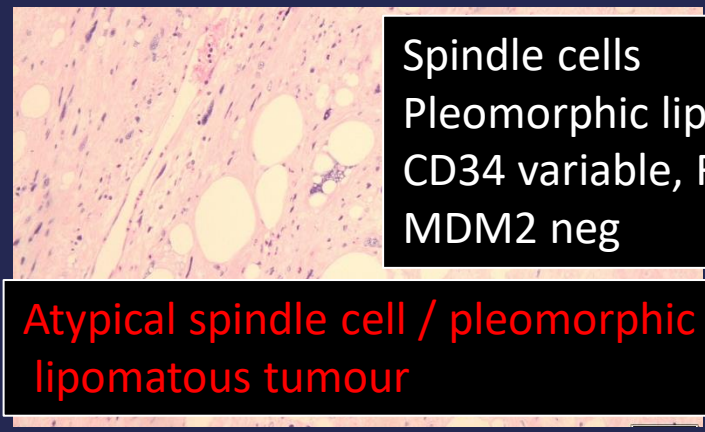
CD34
Thick vessels

Cellular angiofibroma



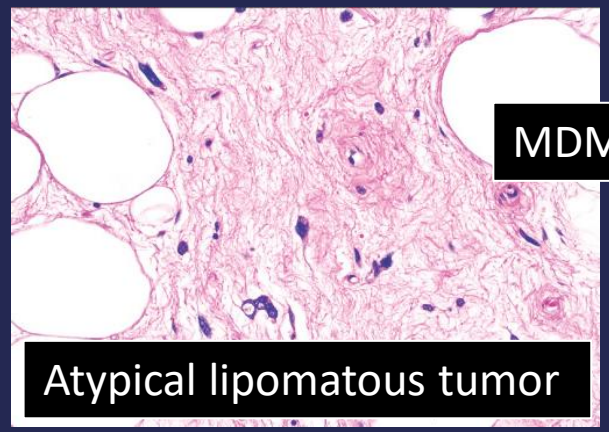
Ropey collagen
CD34
Head and neck
+/- floret cells
MDM2 neg

Spindle cell / pleomorphic lipoma



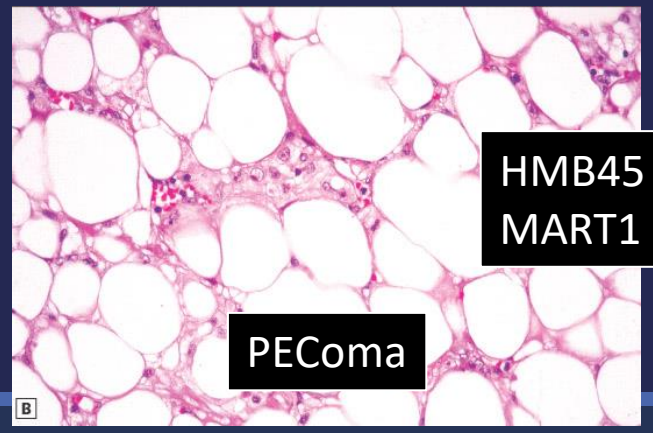
Spindle cells
Pleomorphic lipoblasts
CD34 variable, RB loss
MDM2 neg

Atypical spindle cell / pleomorphic lipomatous tumour



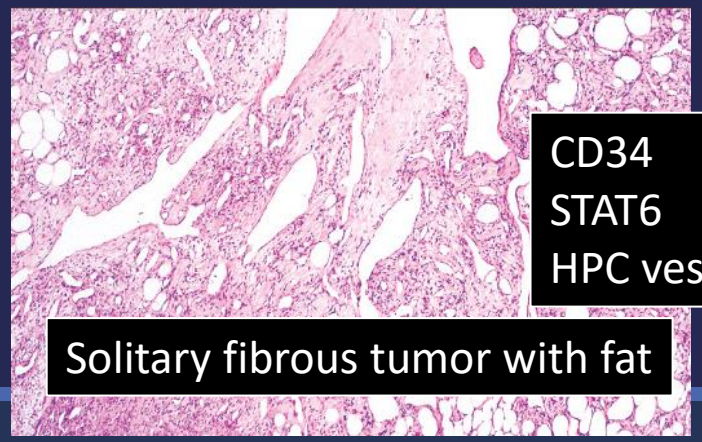
MDM2 pos

Atypical lipomatous tumor



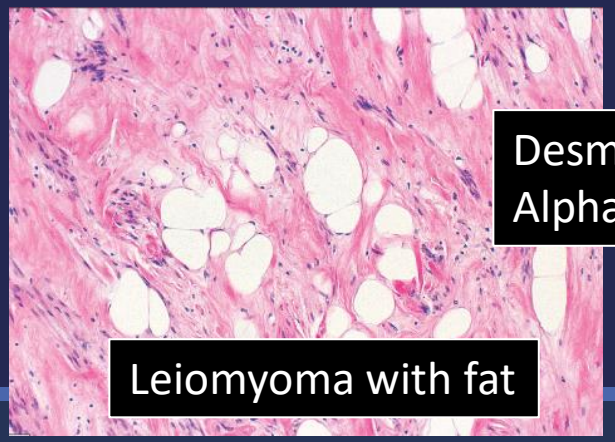
HMB45
MART1

PEComa



CD34
STAT6
HPC vessels

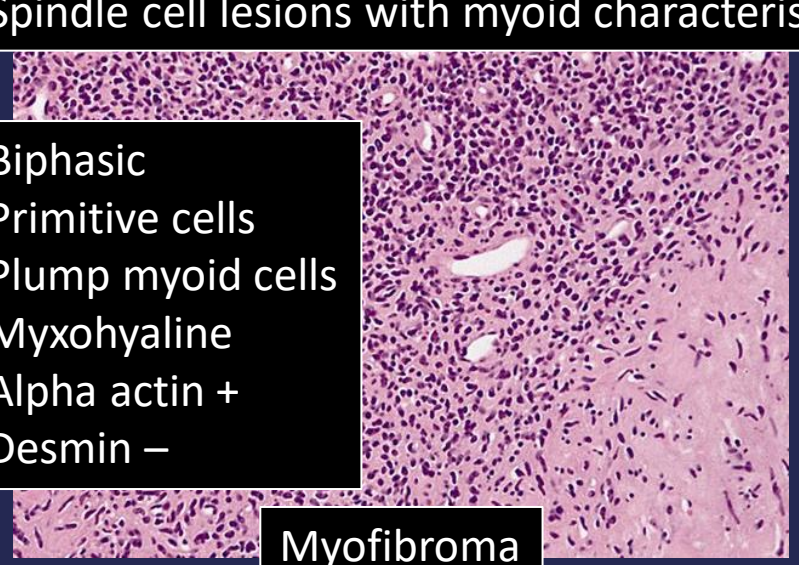
Solitary fibrous tumor with fat



Desmin
Alpha actin

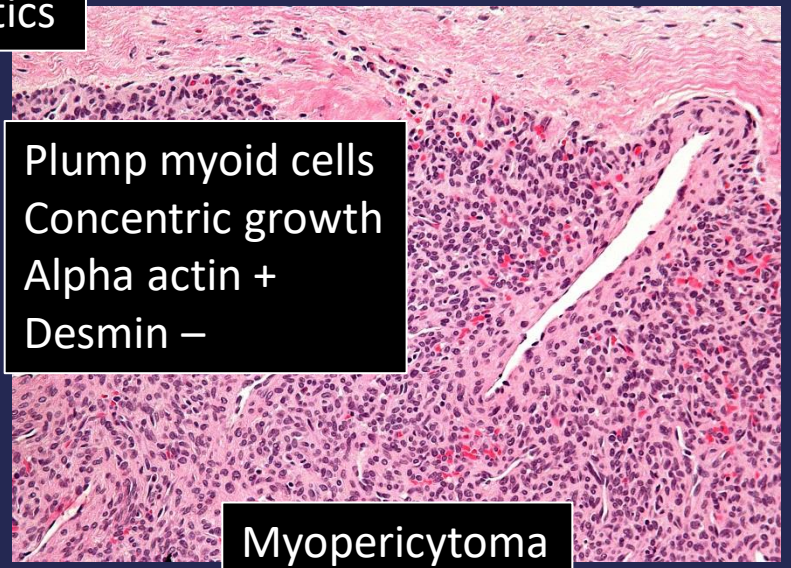
Leiomyoma with fat

Spindle cell lesions with myoid characteristics



Biphasic
Primitive cells
Plump myoid cells
Myxohyaline
Alpha actin +
Desmin –

Myofibroma

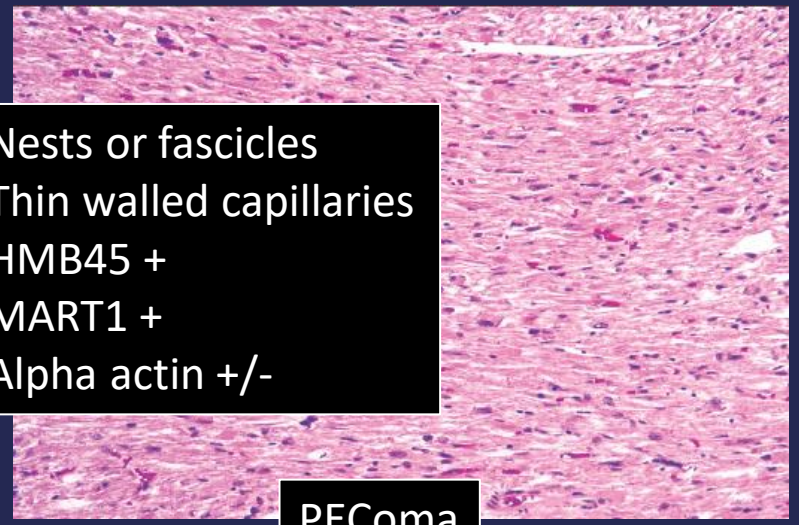


Plump myoid cells
Concentric growth
Alpha actin +
Desmin –

Myopericytoma

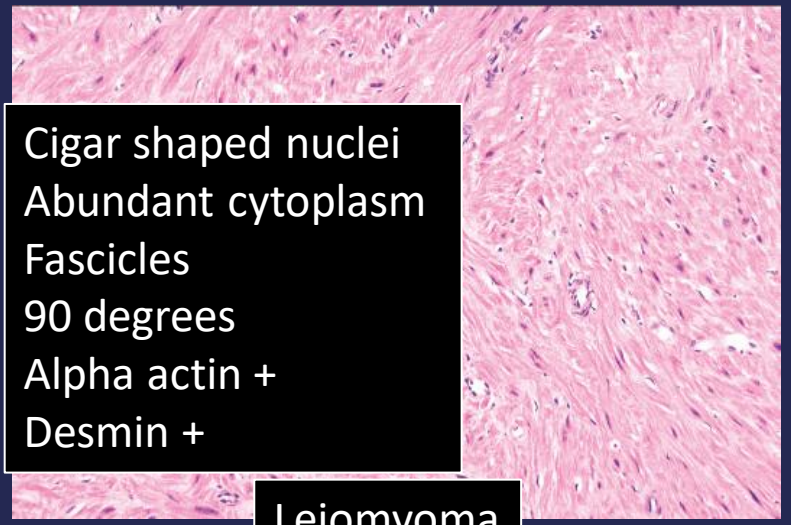
Smooth muscle
Fascicles
Slit like vessels
Alpha actin +
Desmin +

Angiomyoma



Nests or fascicles
Thin walled capillaries
HMB45 +
MART1 +
Alpha actin +/-

PEComa



Cigar shaped nuclei
Abundant cytoplasm
Fascicles
90 degrees
Alpha actin +
Desmin +

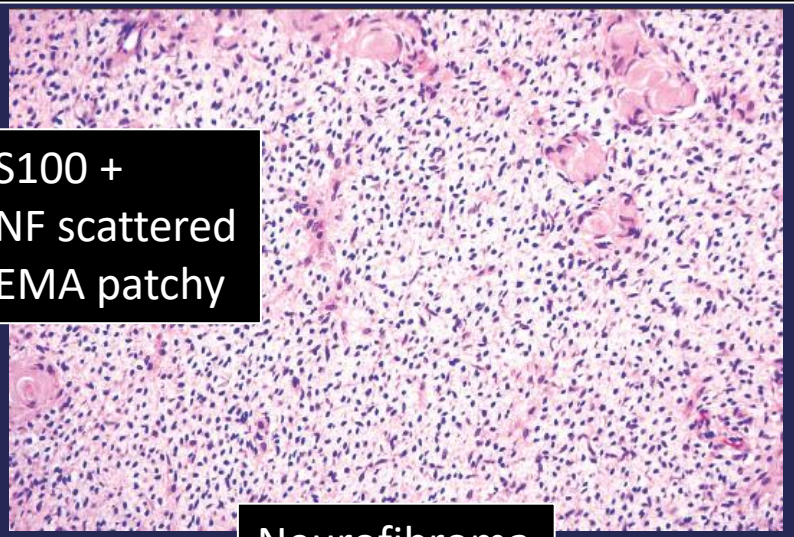
Leiomyoma

Atypia
Mitotic activity

Leiomyosarcoma

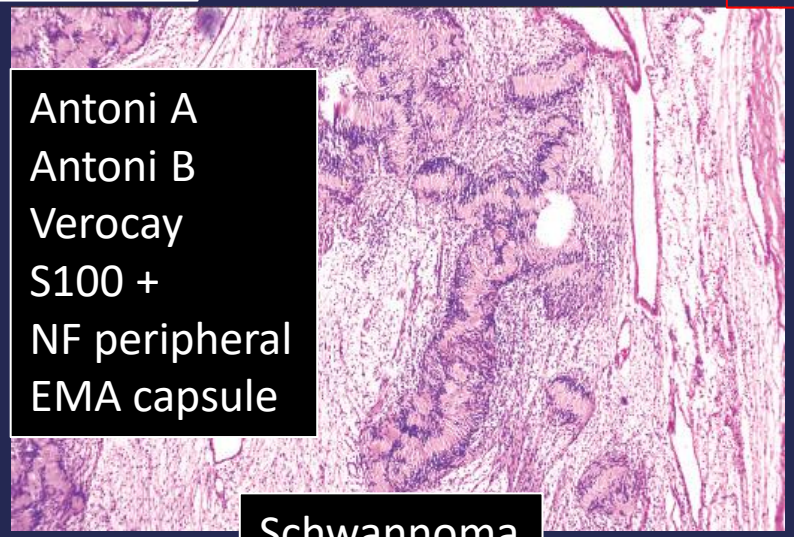
Spindle cell lesions with fibrous and myxoid stroma

Also consider EWSR1-SMAD3-positive fibroblastic tumour if small and acral



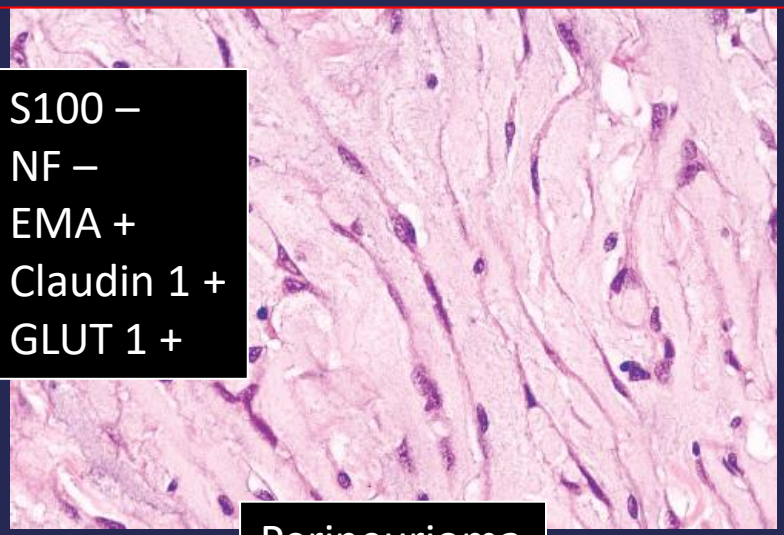
S100 +
NF scattered
EMA patchy

Neurofibroma



Antoni A
Antoni B
Verocay
S100 +
NF peripheral
EMA capsule

Schwannoma



S100 –
NF –
EMA +
Claudin 1 +
GLUT 1 +

Perineurioma

Tissue culture
Extravasated RBCs
Alpha actin patchy
Desmin rare

Nodular fasciitis

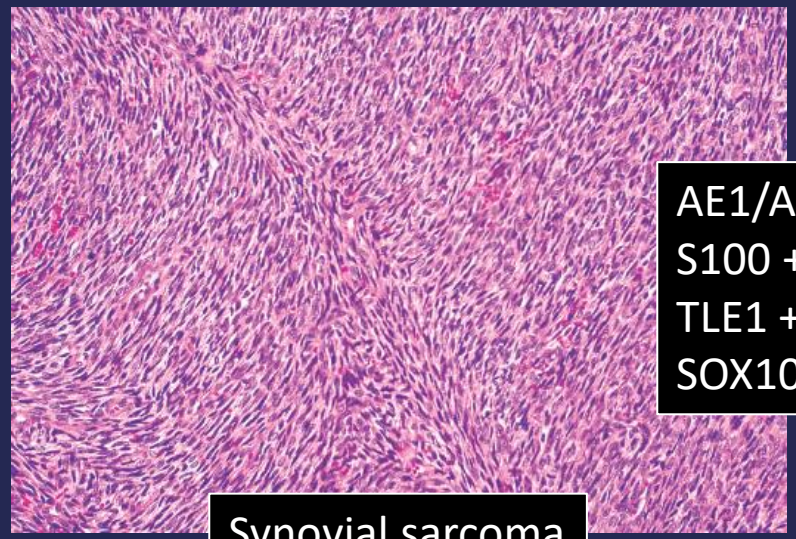
Alpha actin patchy
Tram track pattern
Desmin rare
Beta catenin nuclear

Fibromatosis

Uniform bland spindle cells
Alternating fibrous/myxoid
MUC4 +

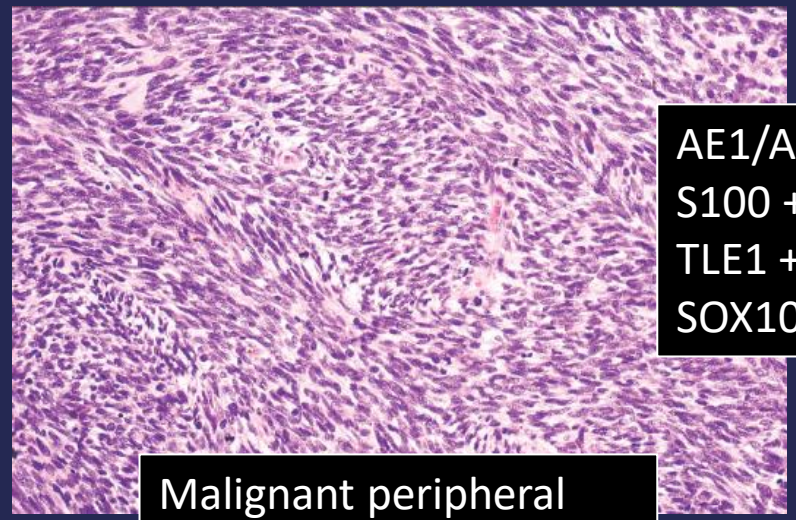
Low grade fibromyxoid sarcoma

Spindle cell lesion with fibrosarcomatous pattern



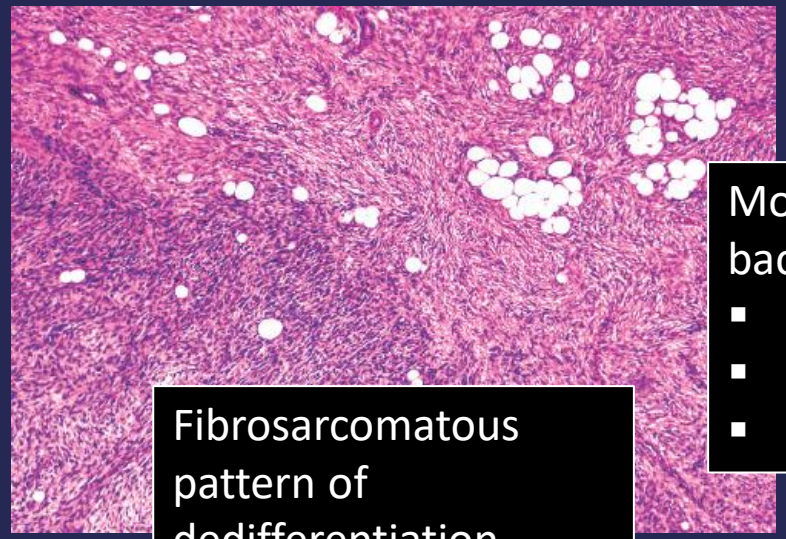
AE1/AE3 +/-
S100 +/-
TLE1 +
SOX10 -

Synovial sarcoma



AE1/AE3 +/-
S100 +/-
TLE1 +/-
SOX10 +/-

Malignant peripheral nerve sheath tumor



Fibrosarcomatous pattern of dedifferentiation

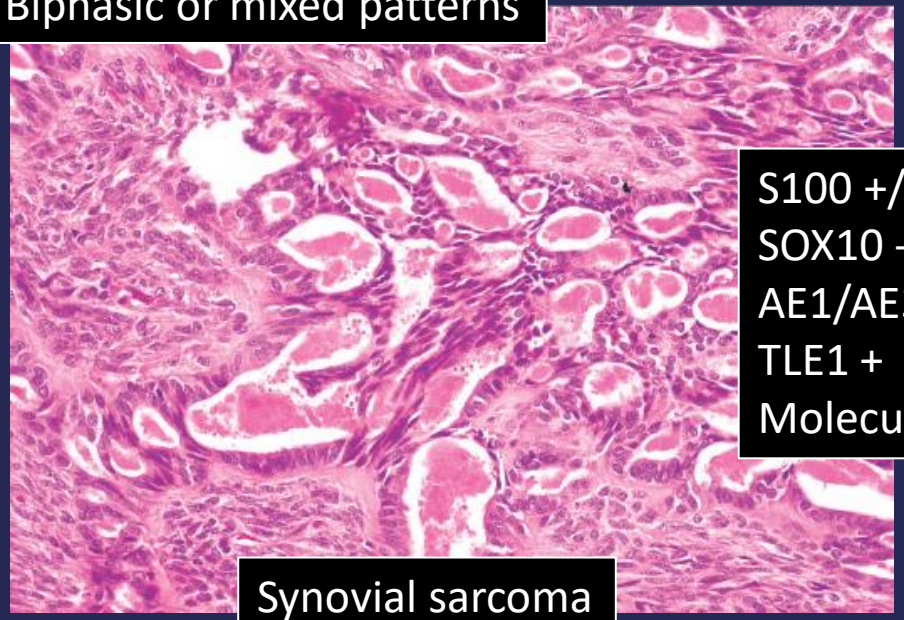
More sections to find background lesion

- DFSP
- Chondrosarcoma
- Liposarcoma

Consider NTRK, EWSR1-non-ETS, CIC, and BCOR rearranged tumors

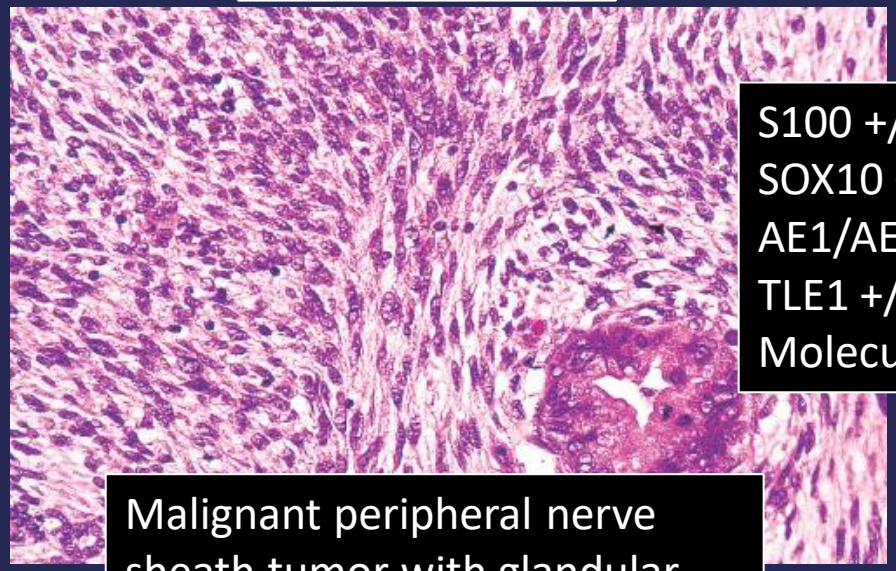
Molecular …

Biphasic or mixed patterns



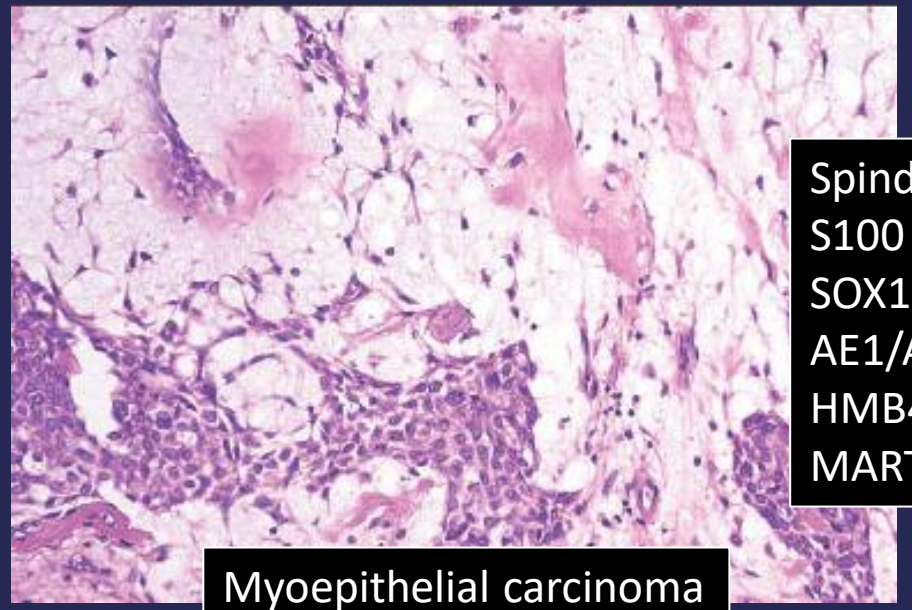
S100 +/-
SOX10 -
AE1/AE3 +
TLE1 +
Molecular

Synovial sarcoma



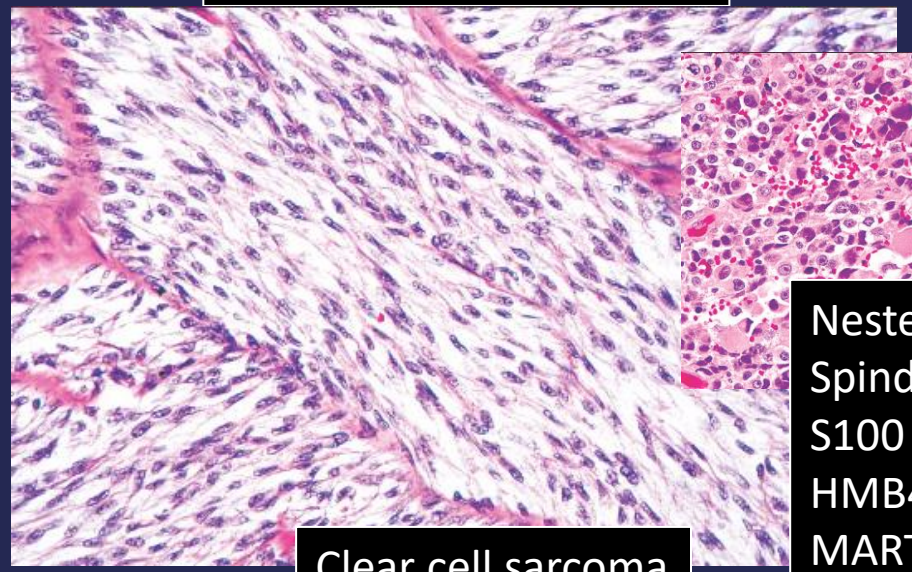
S100 +/-
SOX10 +/-
AE1/AE3 +
TLE1 +/-
Molecular

Malignant peripheral nerve sheath tumor with glandular differentiation



Spindled and epithelioid
S100 +
SOX10 +
AE1/AE3 +/-
HMB45 –
MART1 -

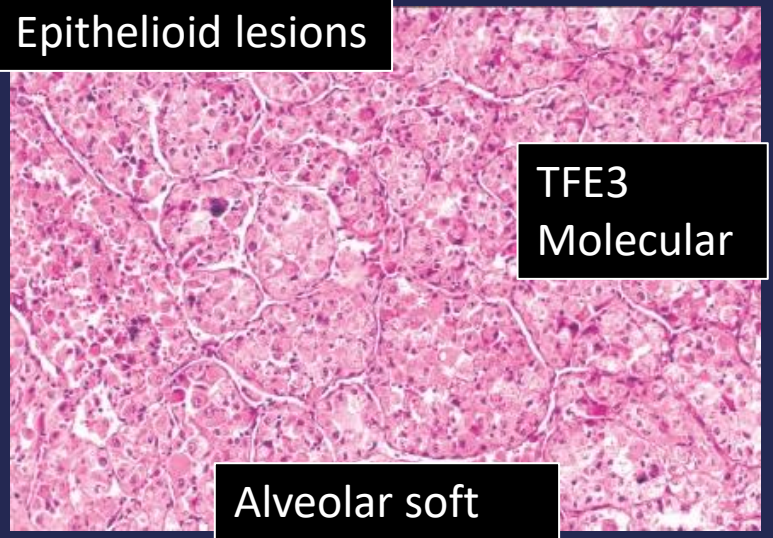
Myoepithelial carcinoma



Nested with fibrous bands
Spindled and epithelioid
S100 +
HMB45 +
MART1 +
Melanin

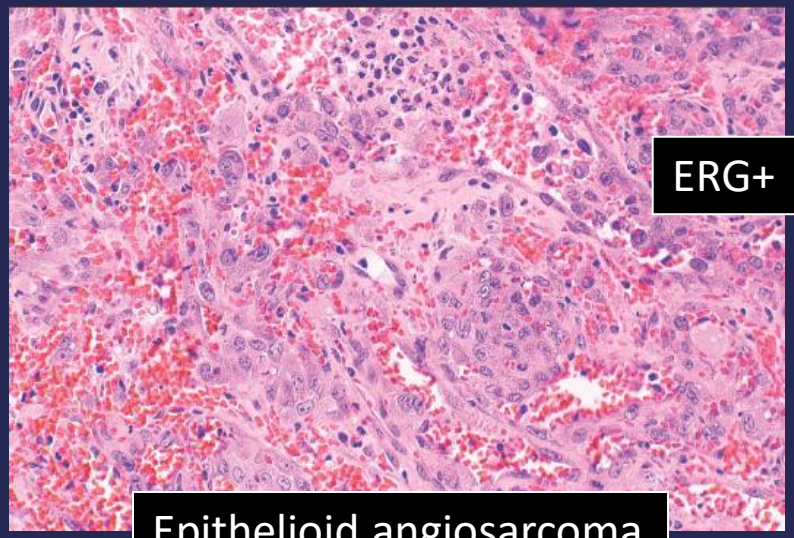
Clear cell sarcoma

Epithelioid lesions



TFE3
Molecular

Alveolar soft part sarcoma



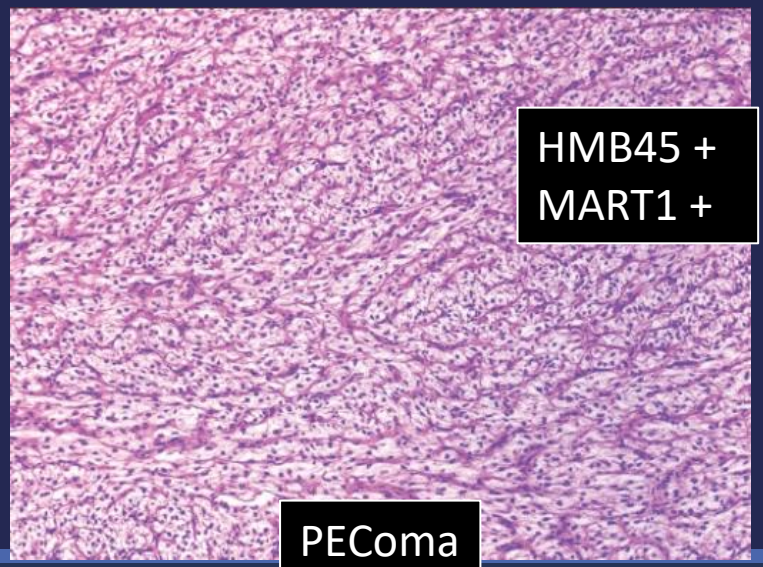
ERG+

Epithelioid angiosarcoma

Blister cells
Myxochondroid
Vessel
ERG+

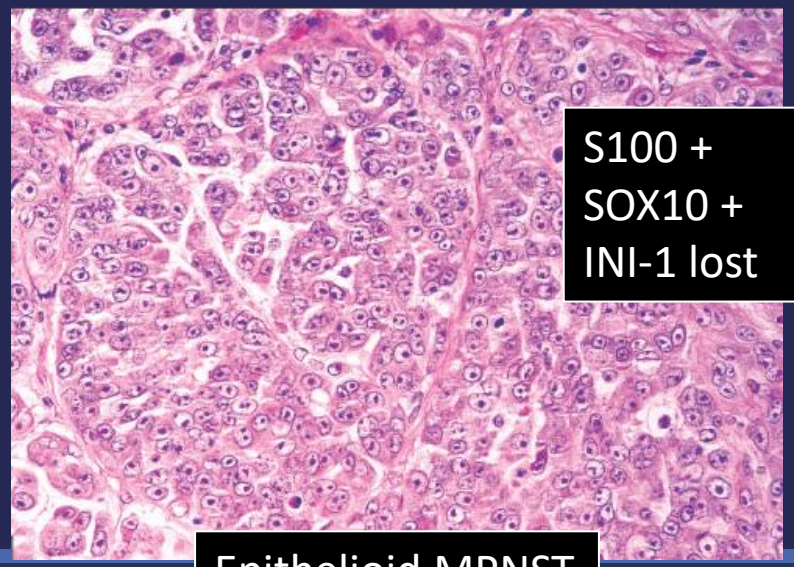
Epithelioid hemangioendothioma

Also: Extrarenal rhabdoid tumor, myoepithelial carcinoma, sclerosing epithelioid fibrosarcoma



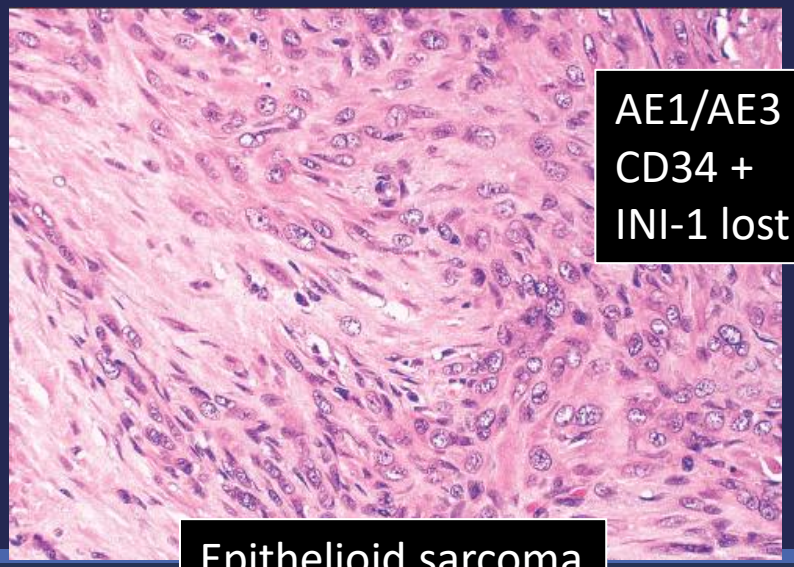
HMB45 +
MART1 +

PEComa



S100 +
SOX10 +
INI-1 lost

Epithelioid MPNST



AE1/AE3 +
CD34 +
INI-1 lost

Epithelioid sarcoma

INI-1 (SMARCB1) deficient tumors

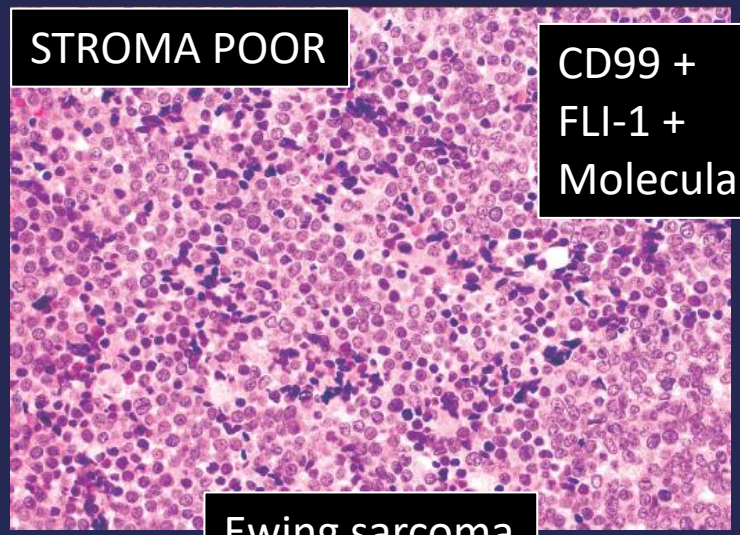
INI-1 deficient tumors

◦ Malignant rhabdoid tumor of infancy	98%
◦ Renal medullary carcinoma	100% (limited # tested)
◦ Epithelioid sarcoma	85-90%
◦ Epithelioid MPNST	50%
◦ Myoepithelial carcinoma of soft tissue	40%
◦ Extraskeletal myxoid chondrosarcoma	17%

Epithelioid sarcoma

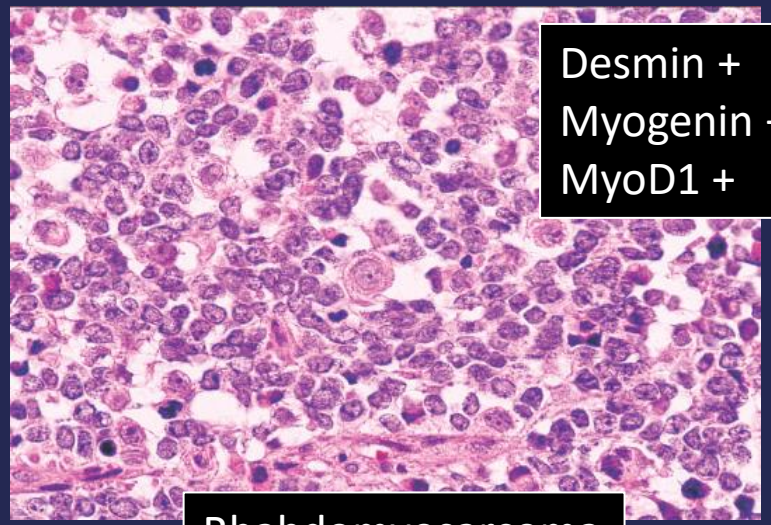
- Rearrangements of 8q, 18q11, 22q11
- Deletions of 22q
- Inactivations of 22q
- Cases can have loss of INI-1 on IHC and molecular alterations that cannot be detect by routine testing of the SMARCB-1 / INI-1 gene

STROMA POOR



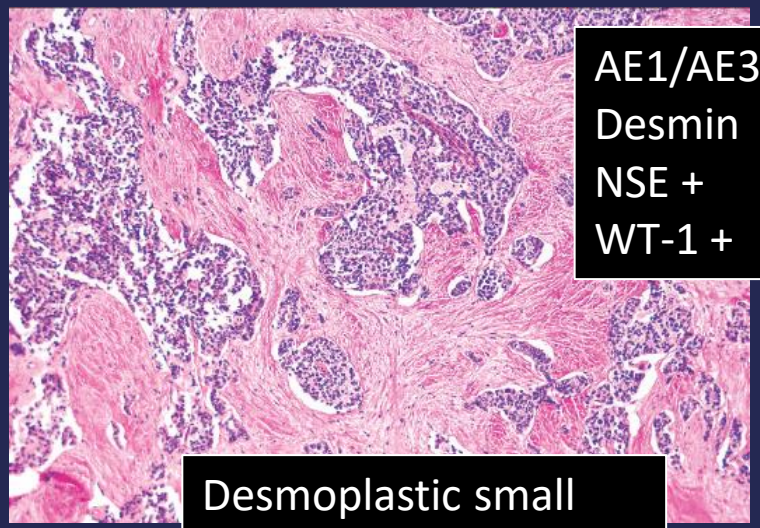
CD99 +
FLI-1 +
Molecular

Ewing sarcoma



Desmin +
Myogenin +
MyoD1 +

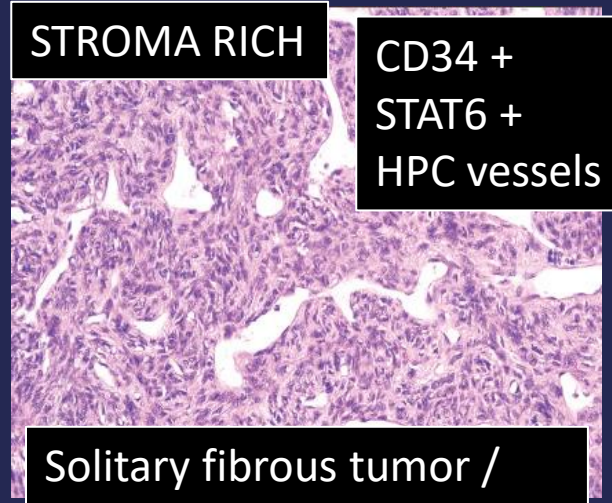
Rhabdomyosarcoma



AE1/AE3 +
Desmin +
NSE +
WT-1 +

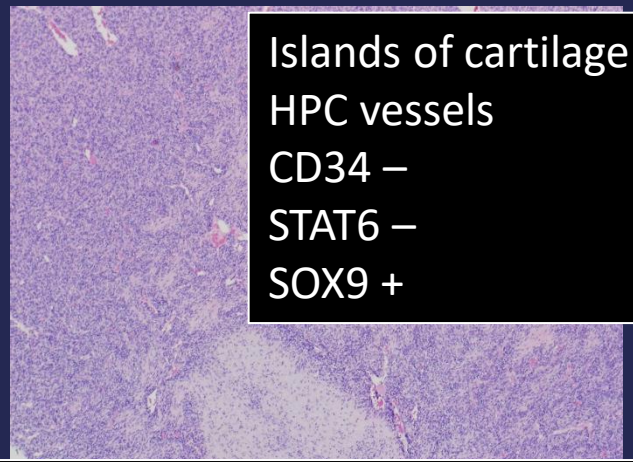
Desmoplastic small round cell tumor

STROMA RICH



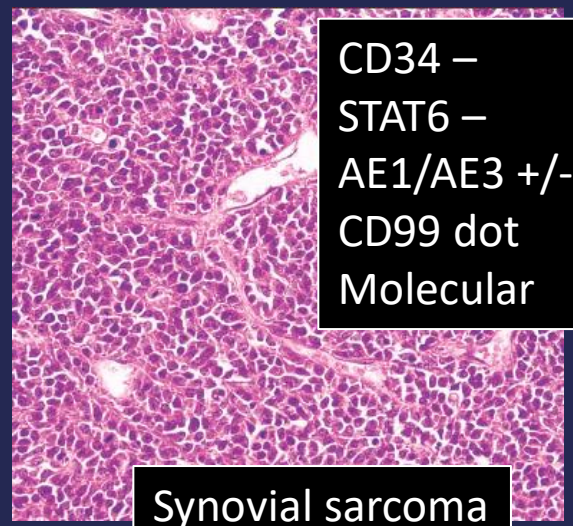
CD34 +
STAT6 +
HPC vessels

Solitary fibrous tumor / hemangiopericytoma



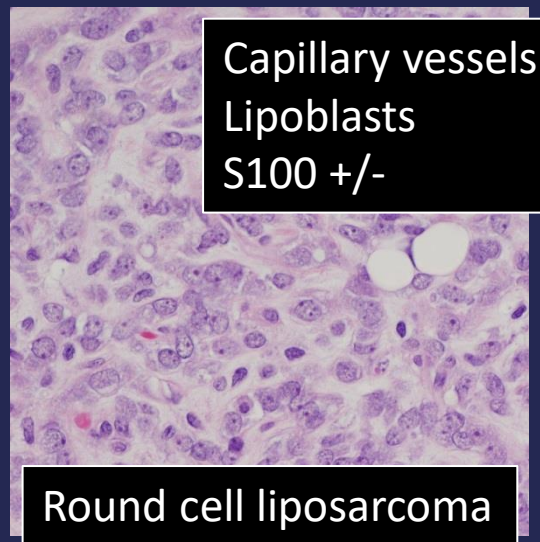
Islands of cartilage
HPC vessels
CD34 –
STAT6 –
SOX9 +

Mesenchymal chondrosarcoma



CD34 –
STAT6 –
AE1/AE3 +/-
CD99 dot
Molecular

Synovial sarcoma

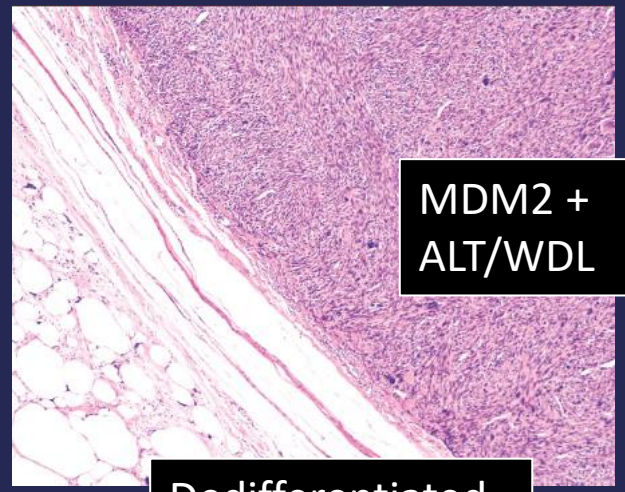


Capillary vessels
Lipoblasts
S100 +/-

Round cell liposarcoma

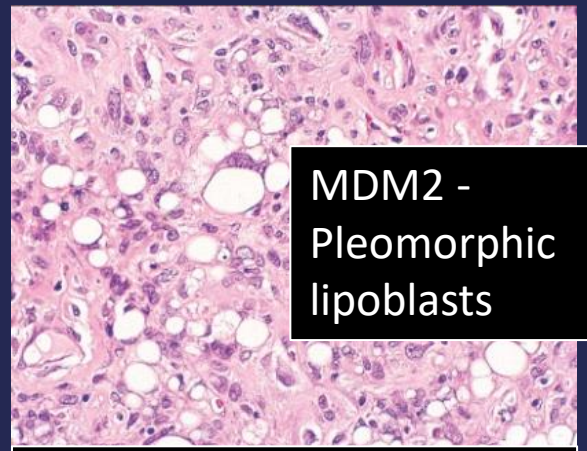
Primitive (round) cell lesions

Consider NTRK, EWSR1-non-ETS, CIC, and BCOR rearranged tumors



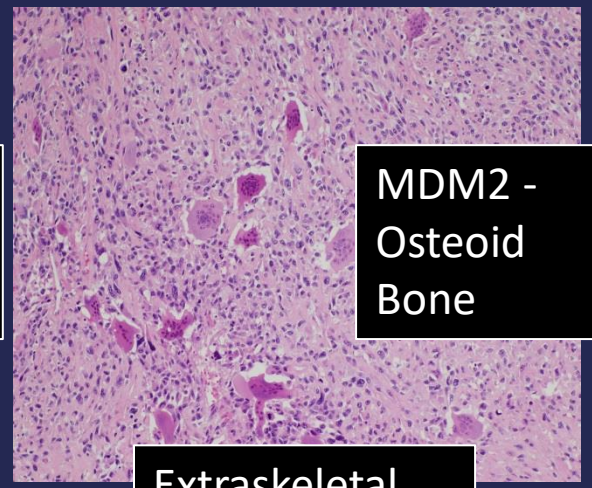
MDM2 +
ALT/WDL

Dedifferentiated liposarcoma



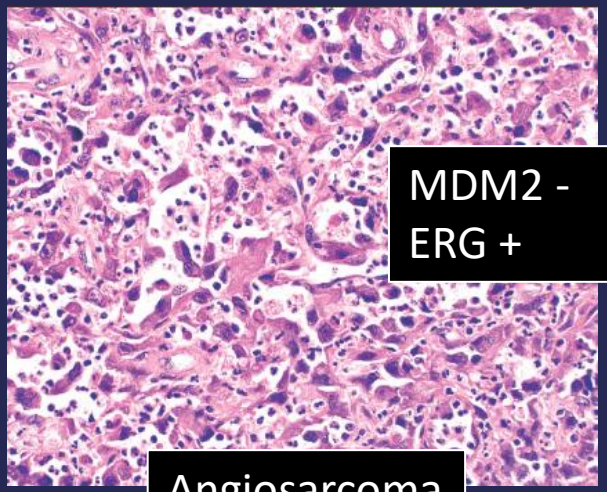
MDM2 -
Pleomorphic lipoblasts

Pleomorphic liposarcoma and Pleomorphic myxoid liposarcoma



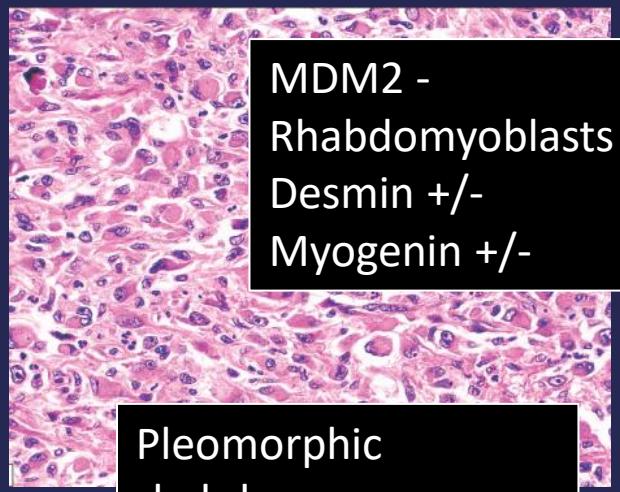
MDM2 -
Osteoid
Bone

Extraskeletal osteosarcoma



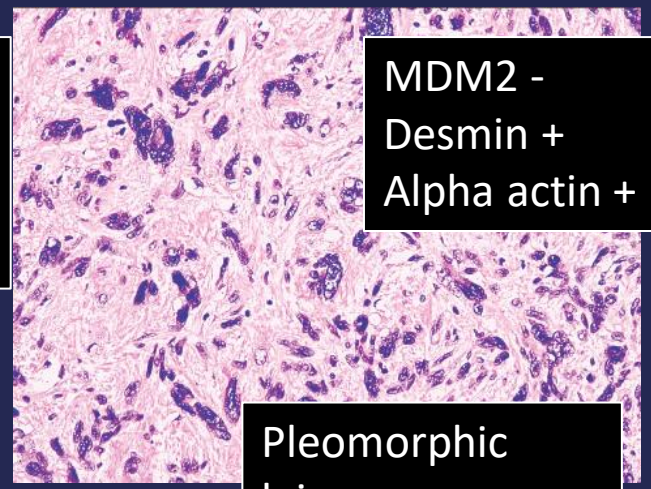
MDM2 -
ERG +

Angiosarcoma



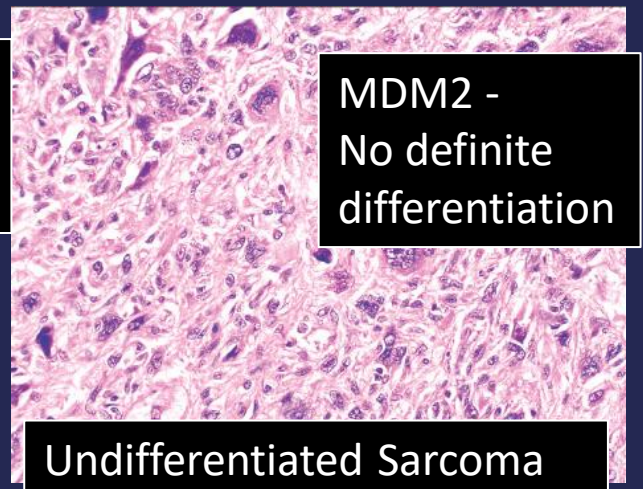
MDM2 -
Rhabdomyoblasts
Desmin +/-
Myogenin +/-

Pleomorphic rhabdomyosarcoma



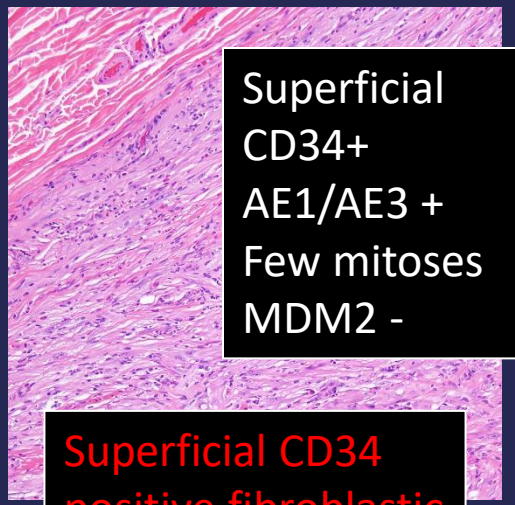
MDM2 -
Desmin +
Alpha actin +

Pleomorphic leiomyosarcoma



MDM2 -
No definite differentiation

Undifferentiated Sarcoma



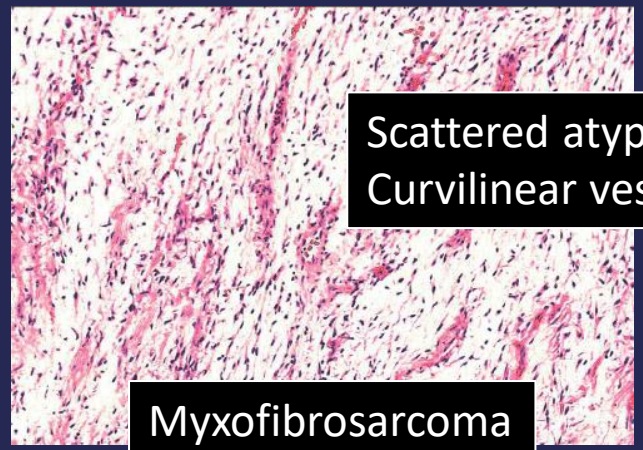
Superficial
CD34+
AE1/AE3 +
Few mitoses
MDM2 -

Superficial CD34 positive fibroblastic tumour

Pleomorphic lesions

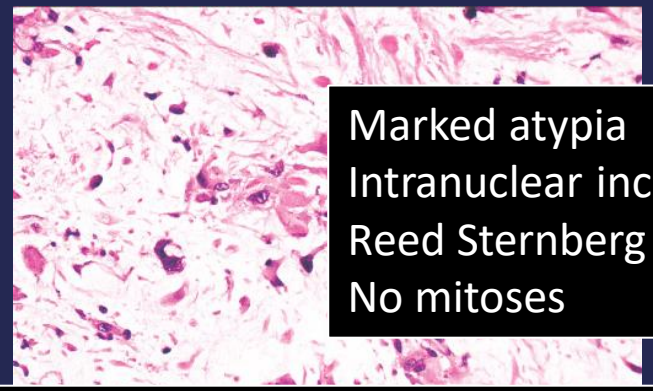
Hypocellular
Uniform bland
Hypovascular

Intramuscular myxoma



Scattered atypia
Curvilinear vessels

Myxofibrosarcoma

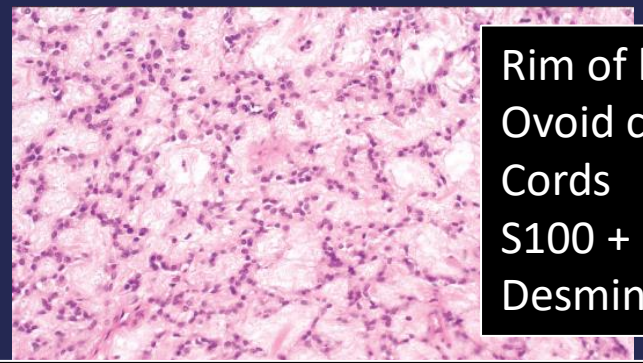


Marked atypia
Intranuclear inclusions
Reed Sternberg like cells
No mitoses

Myxoinflammatory fibroblastic sarcoma

Myxoid microcysts
Arborizing capillaries
Lipoblasts

Myxoid liposarcoma and
Pleomorphic myxoid liposarcoma



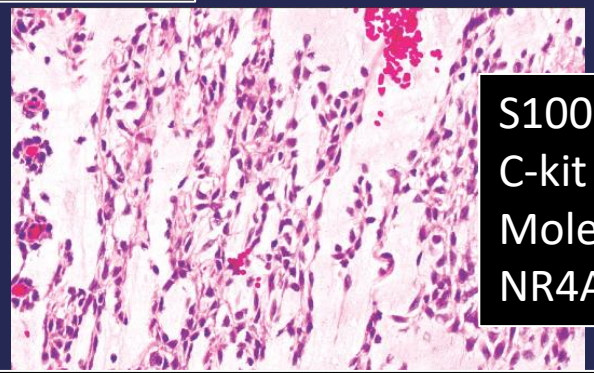
Rim of bone
Ovoid cells
Cords
S100 +
Desmin +/-

Ossifying fibromyxoid tumor of soft tissue

Uniform bland spindle cells
Fibrous and myxoid stroma
MUC4 +

Low grade fibromyxoid sarcoma

Myxoid lesions



S100 +
C-kit +
Molecular
NR4A3

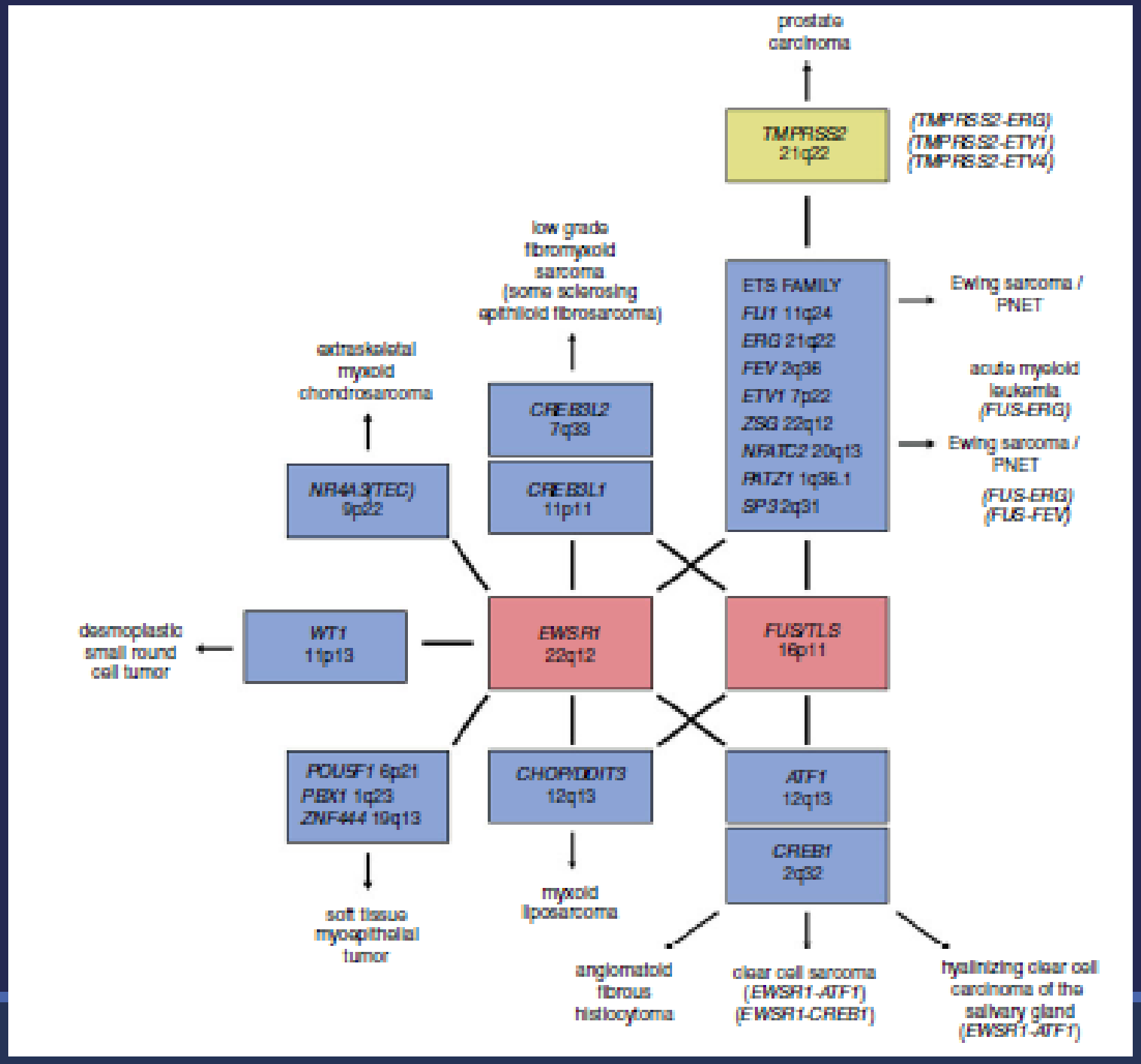
Extraskeletal myxoid chondrosarcoma

AE1/AE3 +/-
S100 +
SOX10 +

Myoepithelial carcinoma

Indications for Molecular Testing

1. To distinguish between benign and malignant lesions which have significant morphological and immunohistochemical overlap
2. Unusual clinical presentation
3. Unusual morphology
4. Unusual immunohistochemical profile
5. Significant impact on clinical management
6. To resolve conflicting opinions
7. Becoming essential for the diagnosis of newer entities



- Some chimeric genes are tumor specific
- Some chimeric genes are not tumor specific
- Some tumors are (thus far associated with only one genetic abnormality
- Some tumors are associated with multiple possible variant translocations
- EWS and FUS can substitute for one another in gene fusions

Histopathology 2014; 64; 119-133

Tumor Syndromes

Angiosarcoma
- Maffuci syndrome

Chondrosarcoma
- Maffuci syndrome
- Ollier syndrome
- Multiple osteochondromas

Enchondroma
- Maffucci syndrome
- Ollier syndrome

Fibromatosis
- Hereditary desmoid disease(Gardner syndrome)
- Myofibromatosis
- Juvenile hyaline fibromatosis

Fibroma
- Basal cell nevus syndrome (cardiac fibromas)
- Beckwith-Wiedemann syndrome
- Familial adenomatous polyposis 1 (Gardner fibroma)
- Jaffe-Campanacci syndrome (non-ossifying fibroma)
- Tuberous sclerosis 1 and 2

Fibrous dysplasia
- McCune-Albright syndrome (polyostotic)
- Mazabraud syndrome (polyostotic

Giant cell lesions
- Cardiofaciocutaneous syndrome (central GCRG)
- Cherubism (central GCRG)
- Noonan syndrome 1 and 4 (central GCRG and PVNS)

Tumor Syndromes

Hemangioma
- Bannayan-Riley-Ruval caba syndrome
- Cowden disease
- Maffucci syndrome
- Klippel-Trenauny-Weber syndrome
- Rubinstein-Taybi syndrome 1
- Multiple cutaneous and mucosal venous malformations

Granular cell tumor
- LEOPARD syndrome 1
- Noonan syndrome 1 and 4

Leiomyoma
- Hereditary leiomyomatosis and renal cell cancer

Leiomyosarcoma
- Hereditary leiomyomatosis and renal cell cancer
- Rubinstein-Taybi syndrome 1

Lipoma
- Bannayan-Riley-Ruval caba syndrome
- Cowen disease
- Lipomatosis
- MEN type 1
- Proteus syndrome

Myxoma
- Beckwith-Wiedemann syndrome
- Carney complex type 1
- Mazabraud syndrome (intramuscular myxoma)

Myositis ossificans
- Fibrodysplasia ossificans progressiva

Neurofibroma / MPNST
- NF1

Osteochondroma
- Fibrodysplasia ossificans progressive
- Metachondromatosis
- Multiple osteochondromas
- Tricho-rhino-phalangeal syndrome type 2
- Potocki-Shaffer syndrome

Tumor Syndromes

Osteosarcoma
- Baller-Gerold syndrome
- Bloom syndrome
- Li-Fraumeni syndrome 1 and 2
- McCune-Albright syndrome
- OSLAM syndrome
- Paget disease of bone
- Polyostotic osteolytic dysplasia
- Retinoblastoma
- Rothmund-Thomson syndrome
- Werner syndrome

Osteoma
- Familial adenomatous polyposis

PEComa
- Tuberous sclerosis

Rhabdoid tumor
- Rhabdoid predisposition syndrome 1 and 2

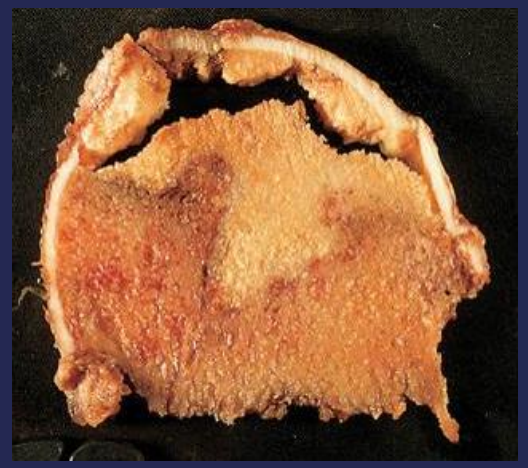
Rhabdomyoma (fetal)
- Basal cell nevus syndrome

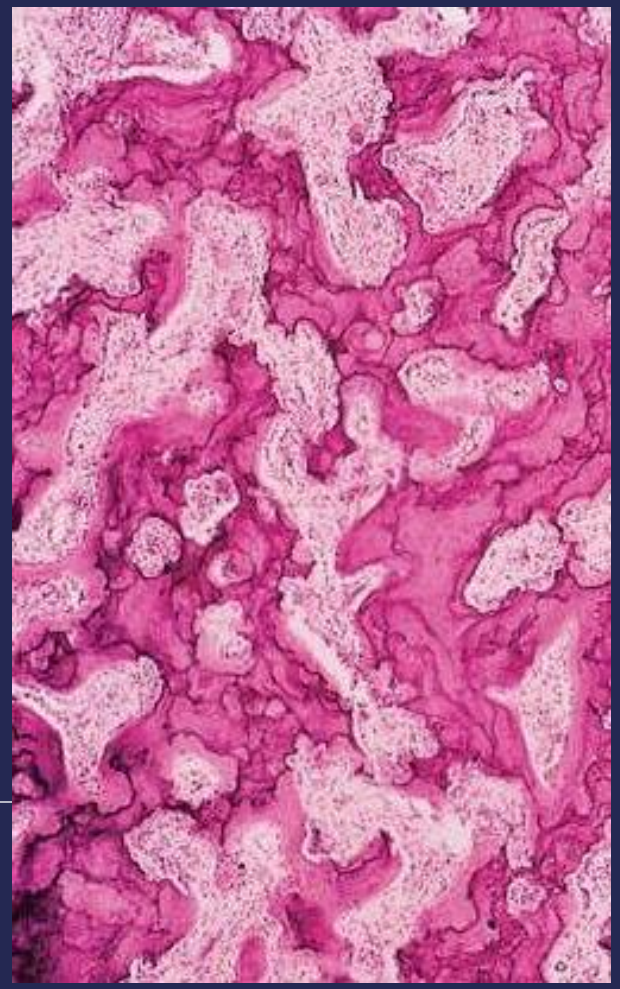
Rhabdomyosaroma
- Basal cell nevus syndrome
- Beckwith-Wiedemann syndrome (embryonal)
- Costello syndrome (embryonal)
- DICER1 syndrome (embryonal)
- Noonan syndrome 4 (embryonal)
- Li-Fraumeni syndrome 1 and 2
- Mismatch repair cancer syndrome
- NF1
- Rubinstein-Taybi syndrome 1

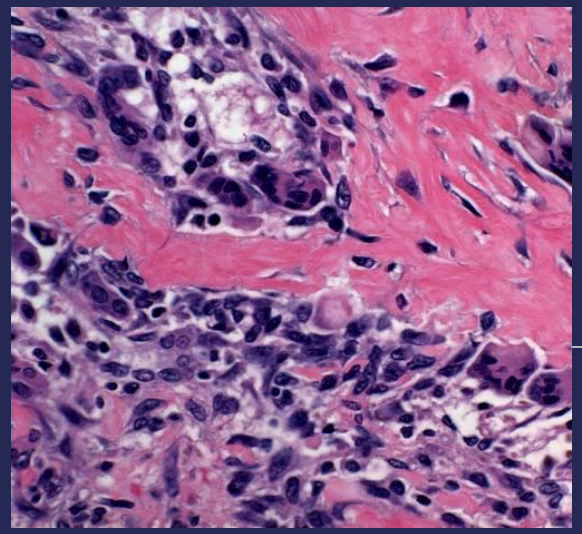
Schwannoma
- Carney complex type 1
- NF2

Synovial chondromatosis
- Synovial chondromatosis with dwarfism

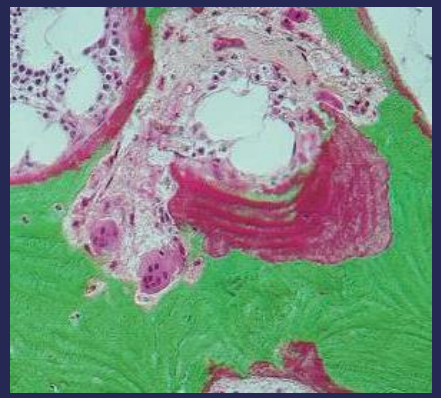
Undifferentiated pleomorphic sarcoma of bone
- Diaphyseal medullary stenosis with UPS

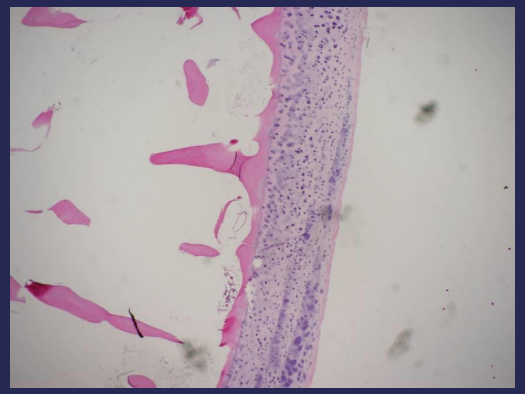






Non-Neoplastic Bone and Joint Disease

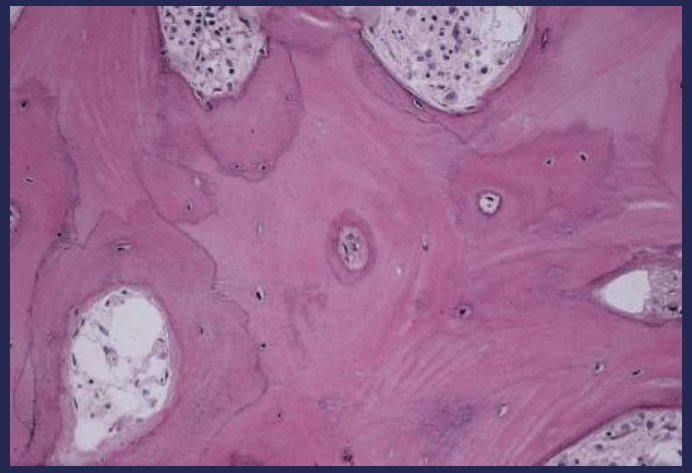


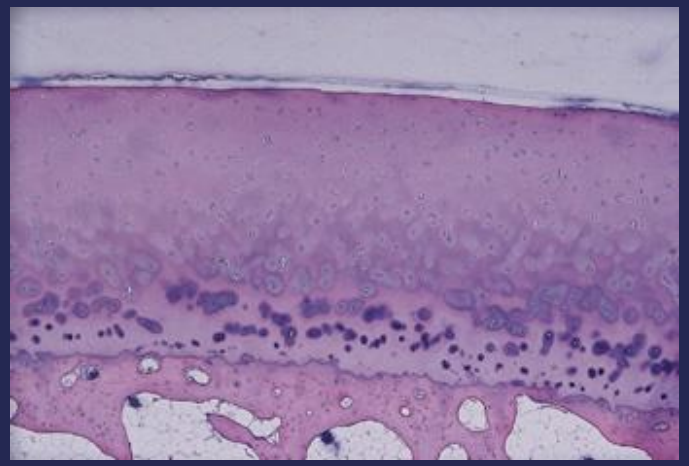


Normal Bone and Cartilage

Normal bone structure

Normal articular cartilage structure





Bone Composition

Components

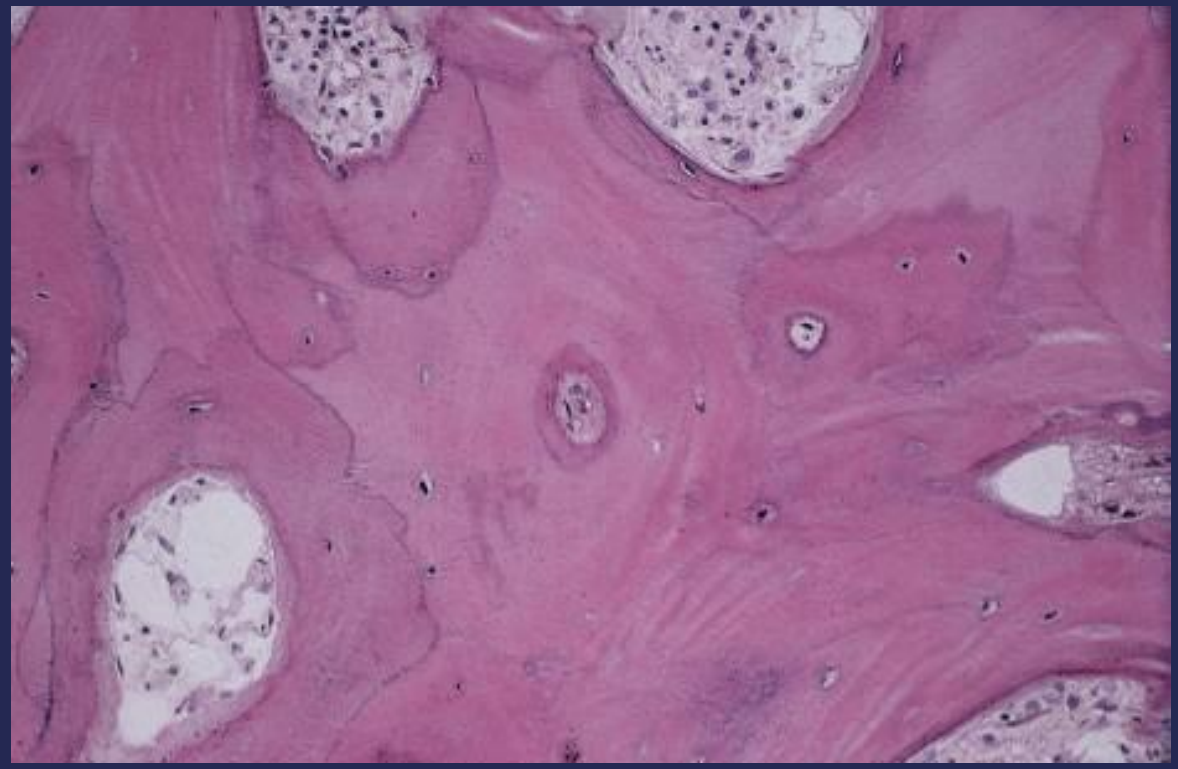
- Minerals (65-70% skeletal weight)
  - Bone mineral is called apatite or hydroxyapatite ($Ca_5(PO_4)_3OH$)
- Organic matrix (30-34% skeletal weight)
  - Osteoid is composed of type I collagen that is produced by osteoblasts
- Water (5-10% skeletal weight)
- Fat (<3% skeletal weight)
- Cells

<u>Hematopoietic derived cells</u>

- Osteoclasts
- Bone marrow

<u>Mesenchymal stem cell derived cells</u>

- Marrow stromal cell
- Osteoblast
- Osteocyte



Bone Structure

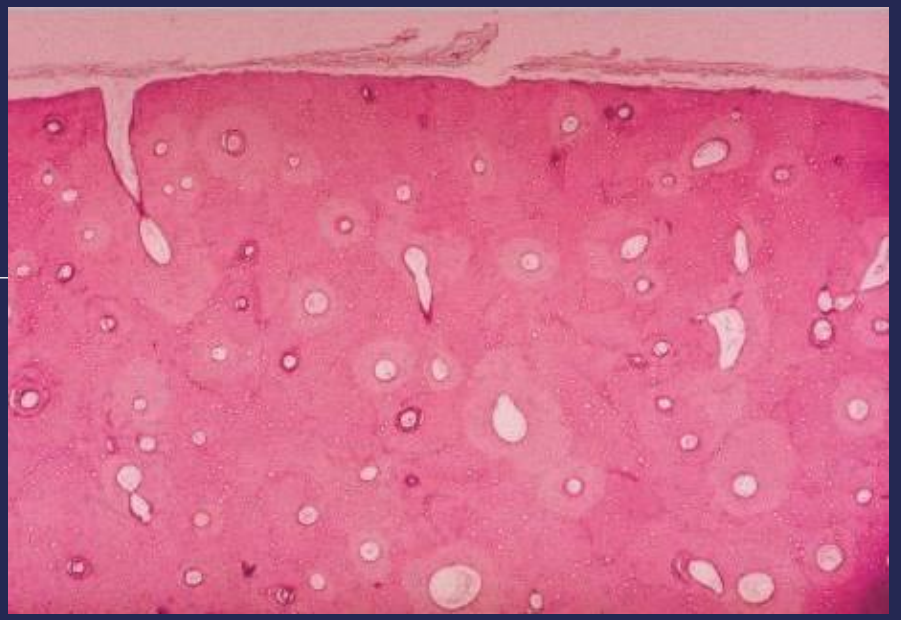
Cortical (Compact, Haversian) Bone

Trabecular (Spongy, Cancellous) Bone

Structural Forms of Bone

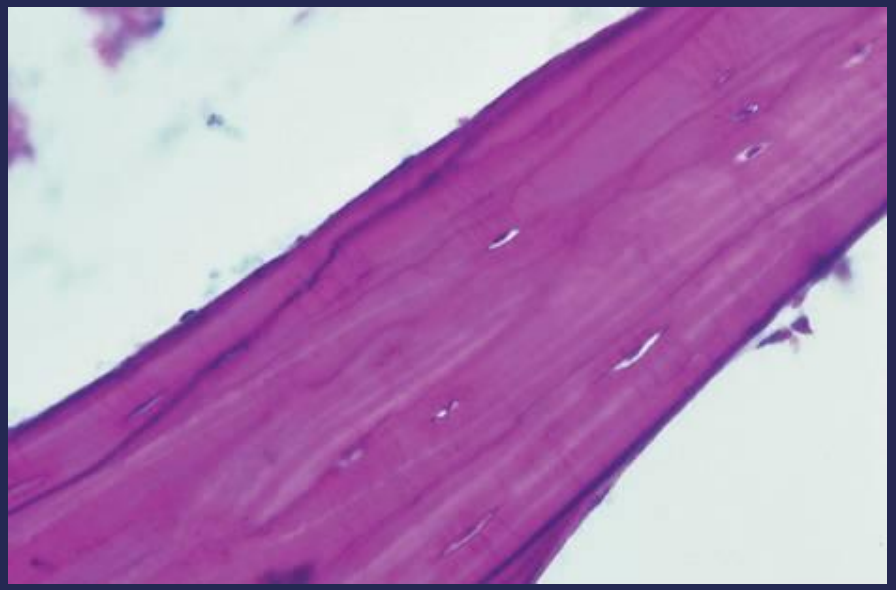
Cortical (Compact, Haversian) bone

- Thick bone that makes up the outer shell of the bone and provides structural integrity of bone
- Haversian systems necessary for nutrient arteries

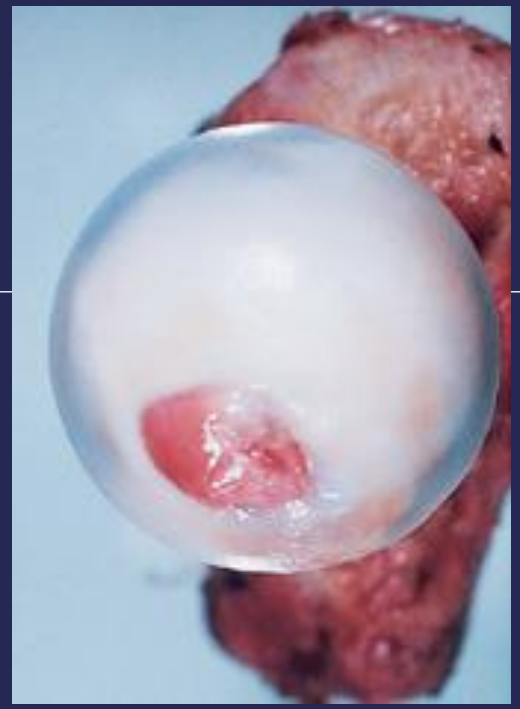


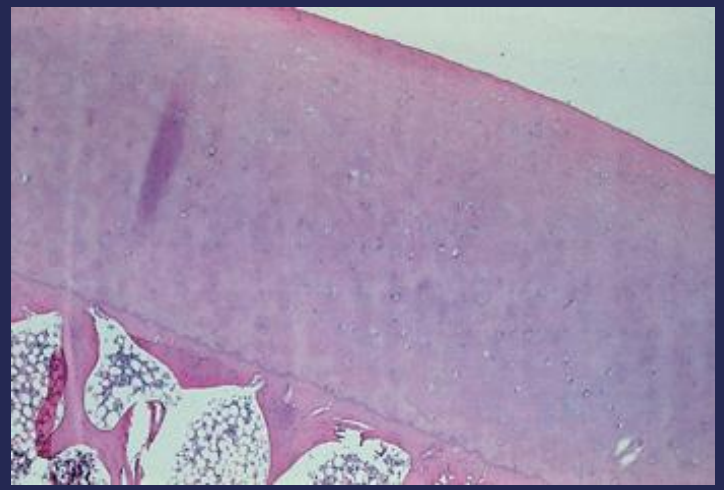
Trabecular (Spongy, Cancellous) bone

- Trabecular bone makes up the bony tissue within the marrow cavity
- Trabecular bone is an extensive interconnecting network of plate-like structures
- Nutritients obtained from well vascularized fatty and hematopoietic tissue



Articular Cartilage





Cells (10%)

- Chondrocytes

Extracellular matrix (90%)

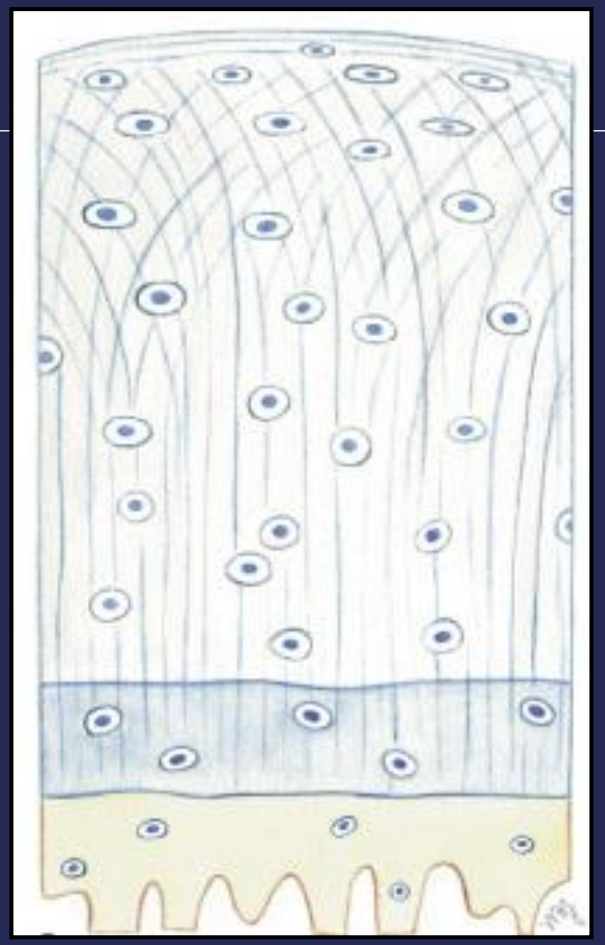
- Proteins and proteoglycan (10-25%)
  - Collagen (Type II, Type IX, Type XI)
  - Aggregating and non-aggregating proteoglycans
  - Small amounts of collagen Type VI on surface and Type X at ossifying zone
- Glycosaminoglycans
  - Hyaluronic acid
  - Sulfated mucins: keratin sulfate, chondroitin sulfate, heparin sulfate
- Water (65-80%)

- Intact surface
- Chondrocytes evenly spaced
- Homogeneous staining of matrix
- Single tidemark

Articular Cartilage

- Zones are based on orientation of collagen fibers, amount of proteoglycan and appearance of chondrocytes
- The various zones can be appreciated by LM with polarization

- Zones:
  - Gliding zone (superficial or tangential zone)
  - Intermediate zone (transitional zone)
  - Basal zone (radial zone)
  - Tidemark
  - Zone of calcified cartilage
  - Subchondral plate



Degenerative Joint Disease (Osteoarthrosis)

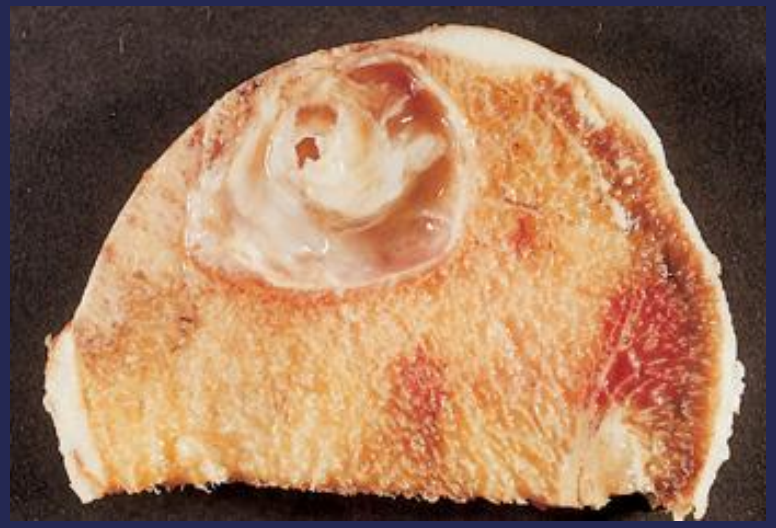
Definition:

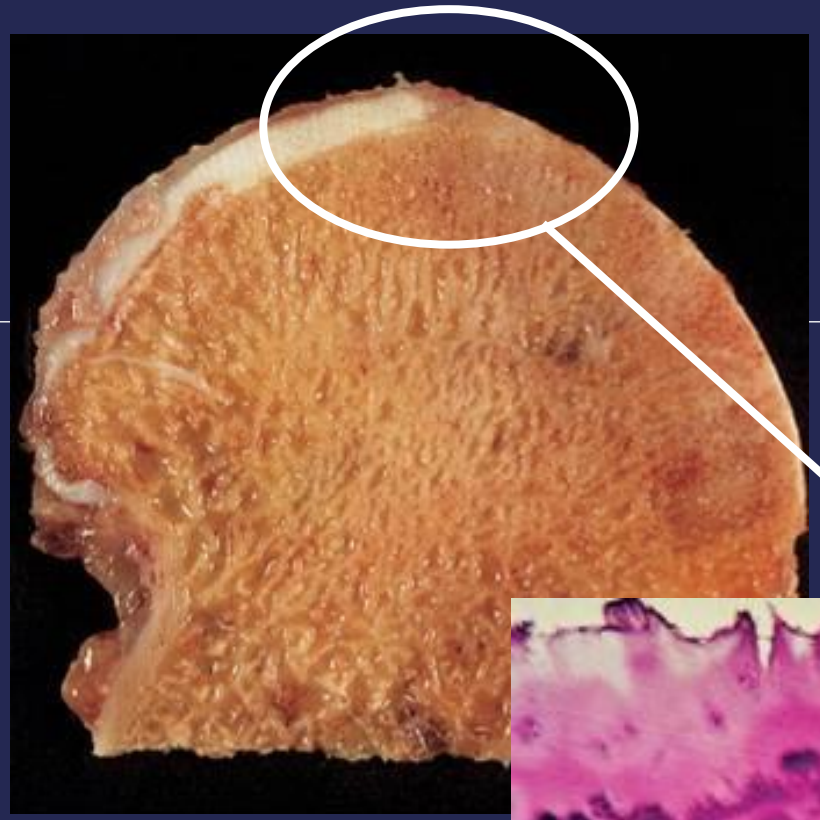
- A primary or secondary non-inflammatory process involving diarthrodal joints that leads to subtle synovial changes, alteration of articular cartilage, destruction of articular cartilage, narrowing of the joint space, and remodeling of the bone

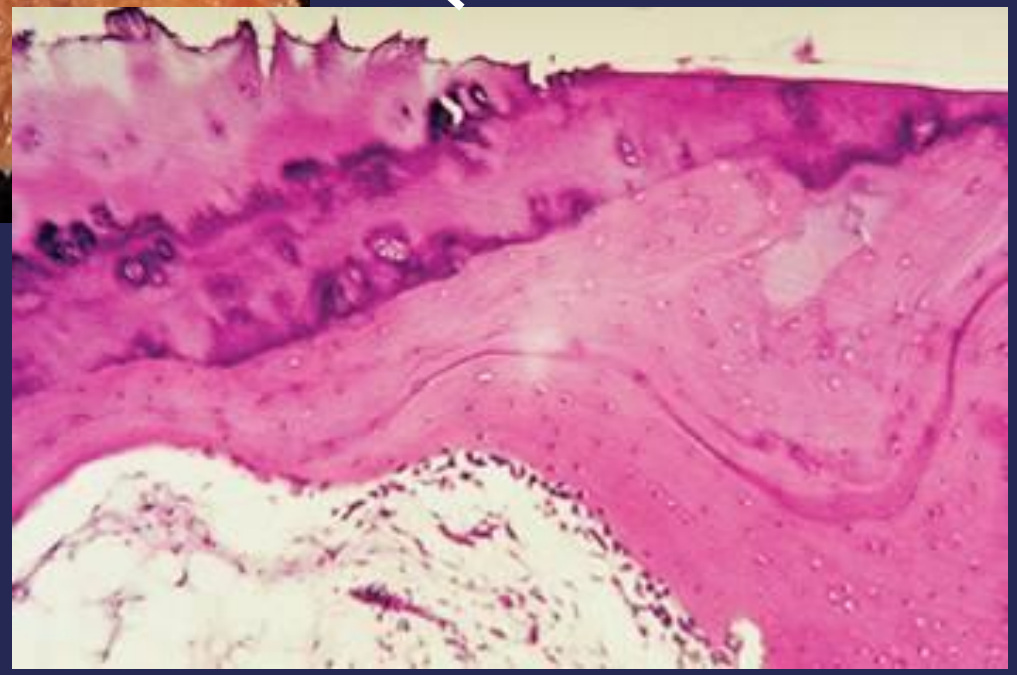
Population:

- Primary: diarthrodial joints, most commonly > 55 years, increased incidence with age
- Secondary: mechanical asymmetry, metabolic disease, endocrine disease, obesity, crystal arthropathy, neuropathic disease, crystal arthropathy, inflammatory arthropathy, trauma, metabolic disease

Osteoarthrosis

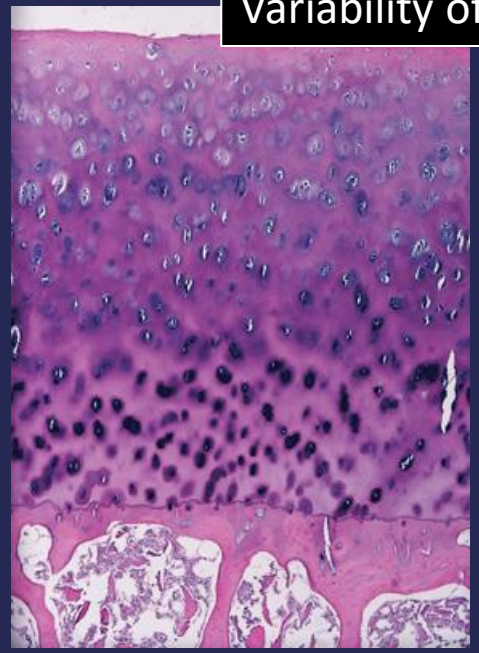






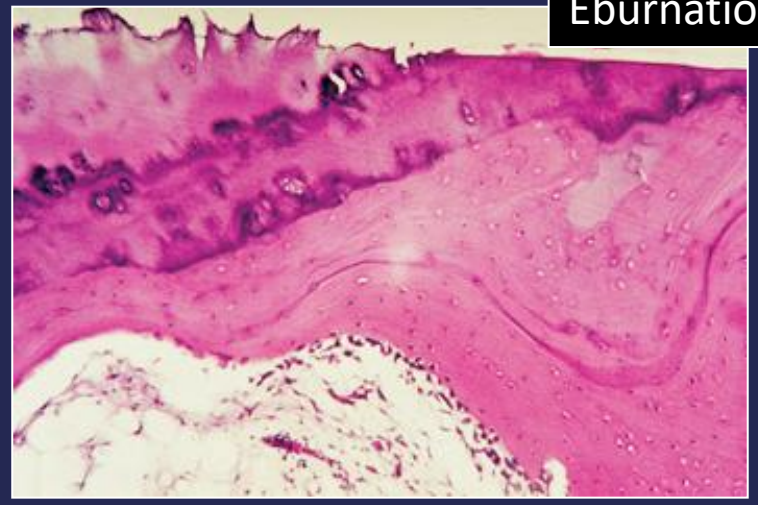
Definition: Osteoarthrosis refers to a degenerative disease in which there is loss of articular cartilage on the surface of bones in a diarthrodal joint resulting in joint space narrowing, joint pain, and impaired mobility

Variability of matrix staining

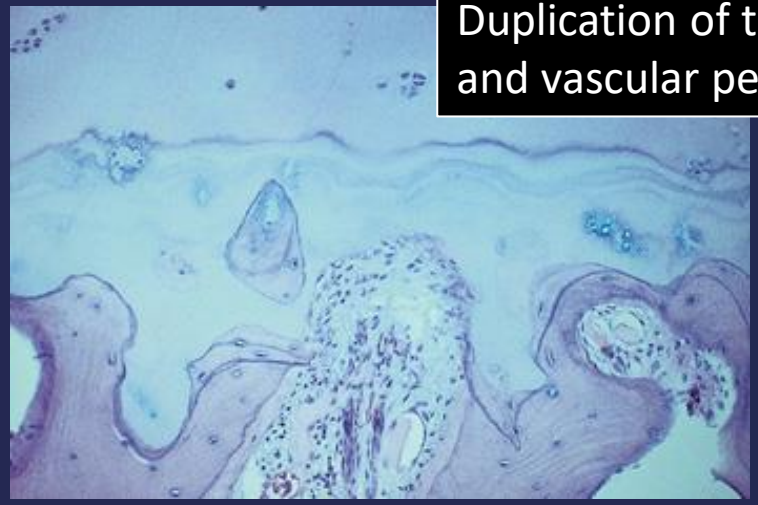


Surface fibrillation and “cartilage clones”

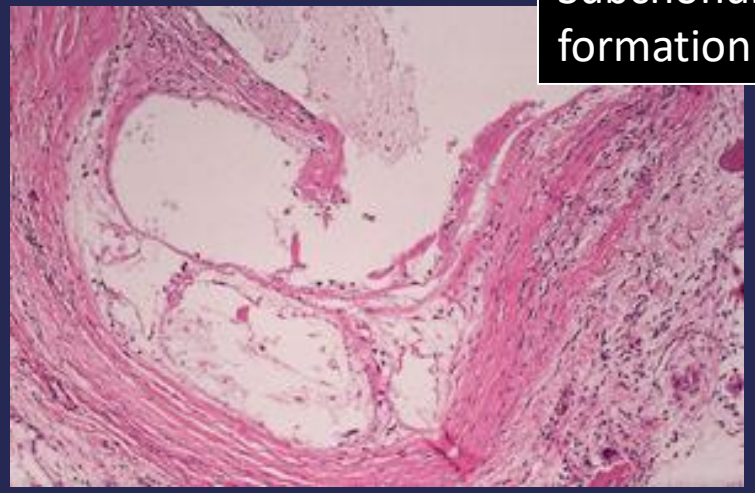
Eburnation



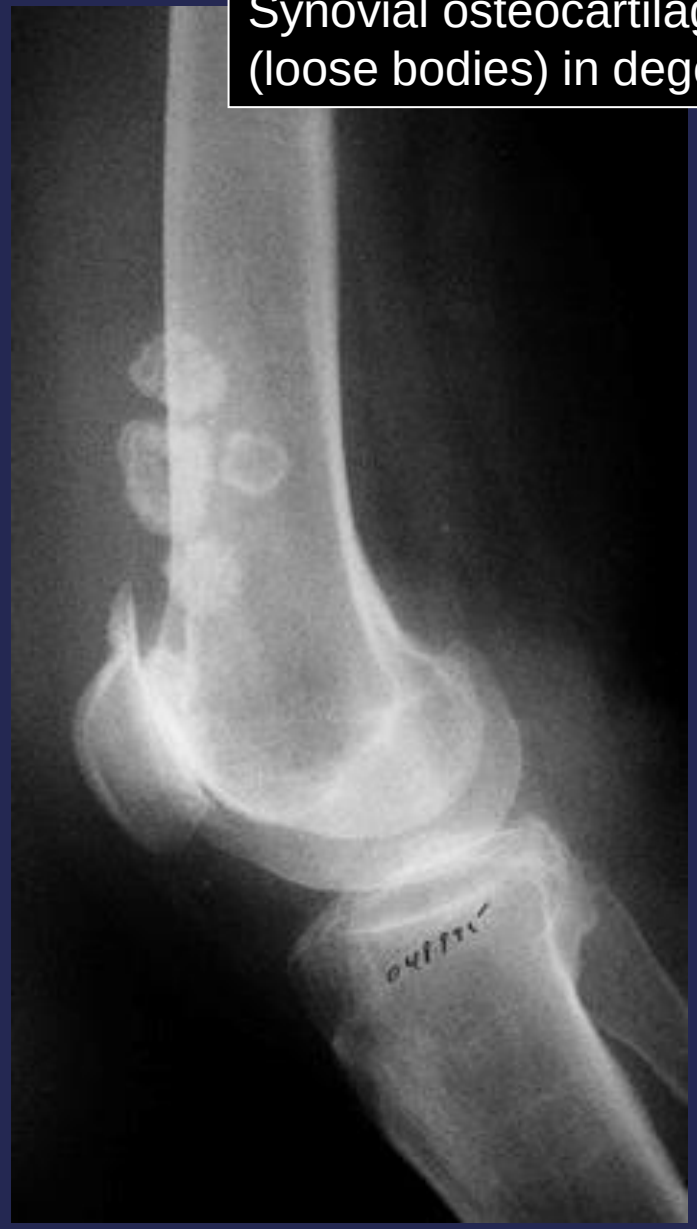
Duplication of tidemark and vascular penetration

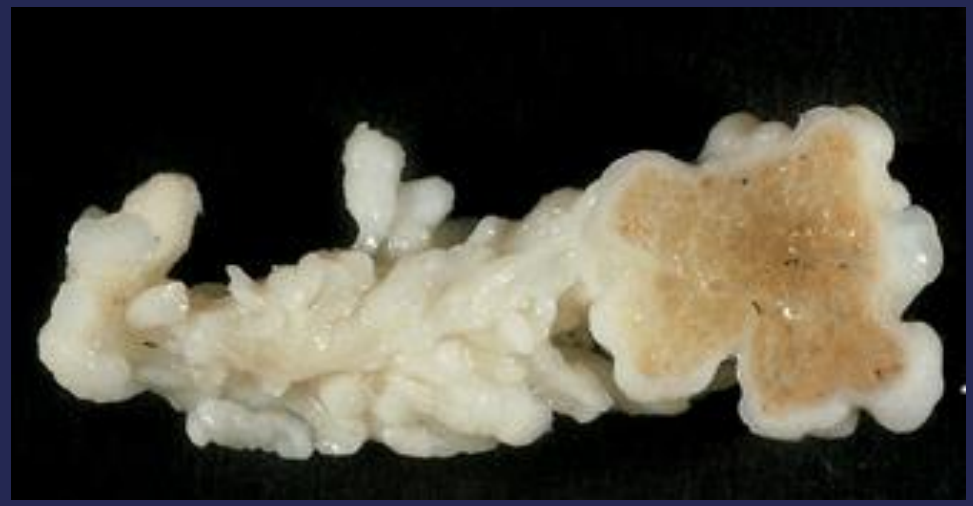


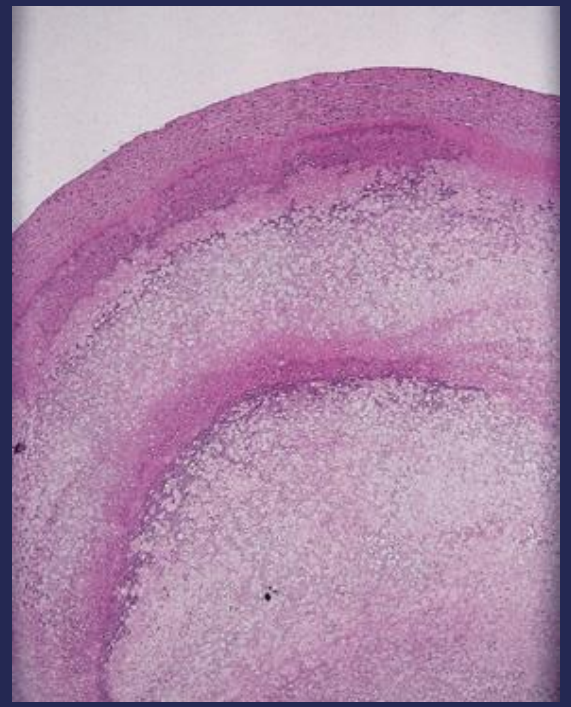
Subchondral cyst formation

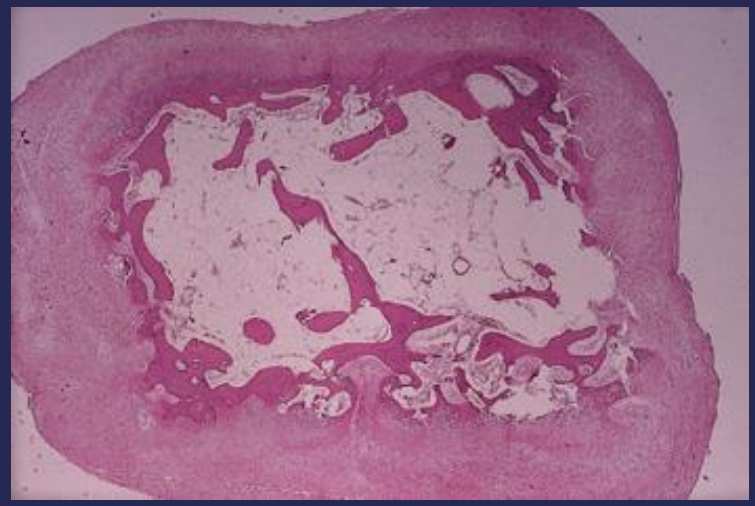


Synovial osteocartilaginous metaplasia (loose bodies) in degenerative joint disease









Rheumatoid Arthritis

Definition:

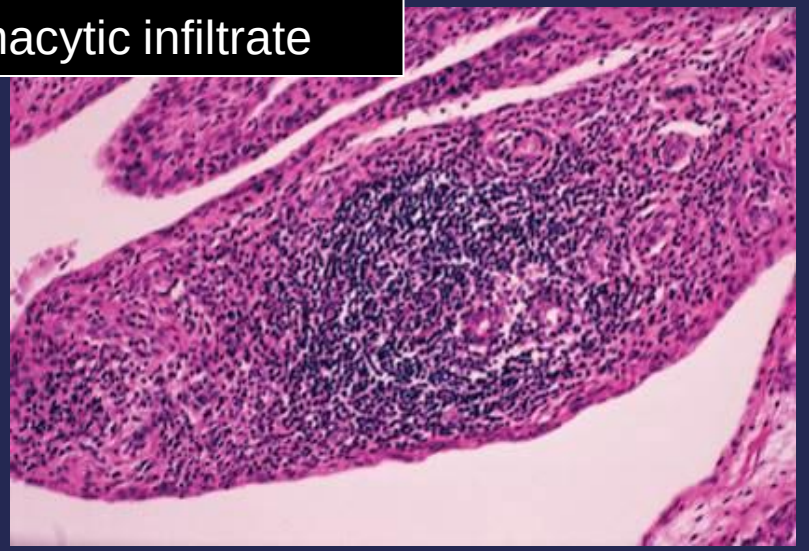
- Inflammatory disease that results in the degeneration of a joint with loss of articular cartilage destruction of joint structures
- The disease causes joint pain, impaired mobility, and deformation of the joints and bones

Early pathology:

- Proliferation of synovial lining
- Perivascular proliferation of lymphocytes and other mononuclear cells
- Dense inflammatory infiltrate that organizes into germinal center-like aggregates with peri-central plasma cells

Hyperplastic and edematous synovial villi fill the joint space

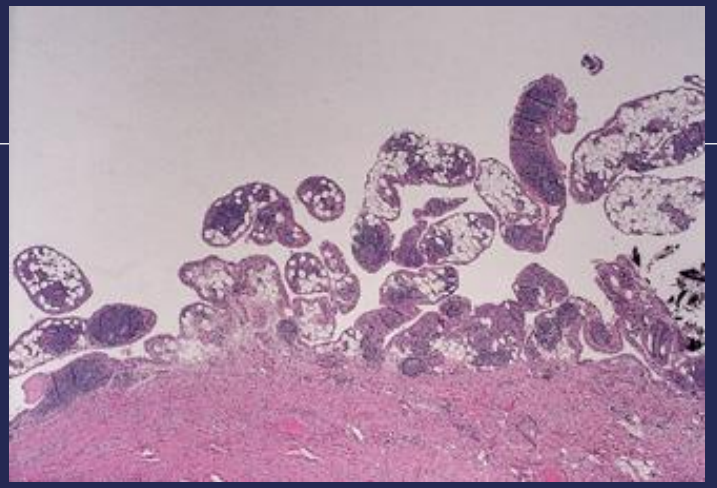
Synovial villous with lymphoplasmacytic infiltrate

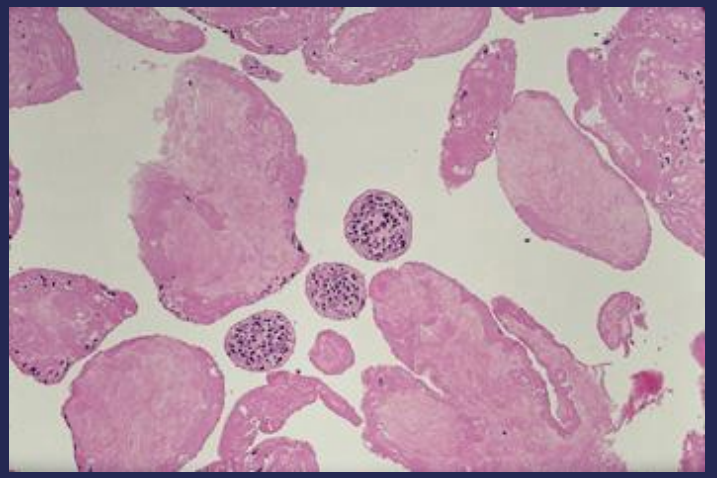


Rheumatoid Arthritis

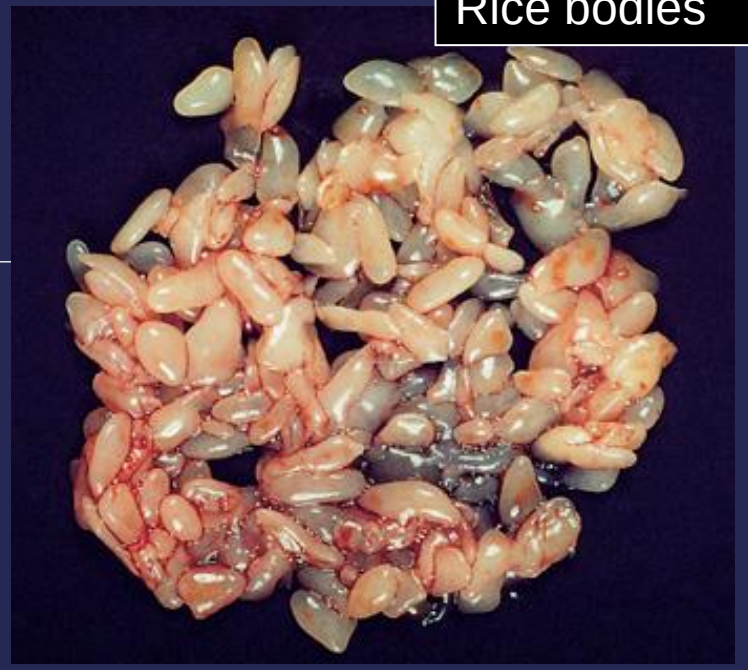
Intermediate pathology:

- Fibrin deposition and stromal edema cause subsynovium to thicken and it protrudes into the joint as hypertrophic villi
- The stroma of the villi is filled with lymphoplasmacytic infiltrate
- The synovium becomes hyperplastic consists of more than 10 layers
- Cells become hypertrophic cells and some form peculiar giant cells (Grimly-Sokoloff)
- Rice bodies are fibrinous aggregates of synovial exudate that accumulate in the joint space

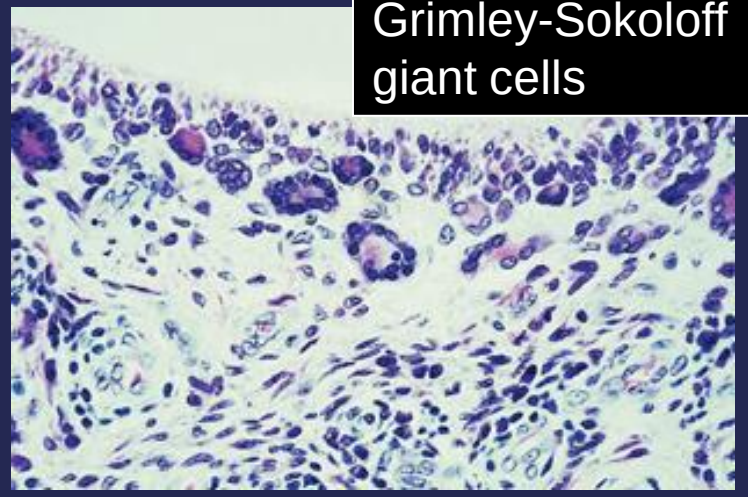




Rice bodies



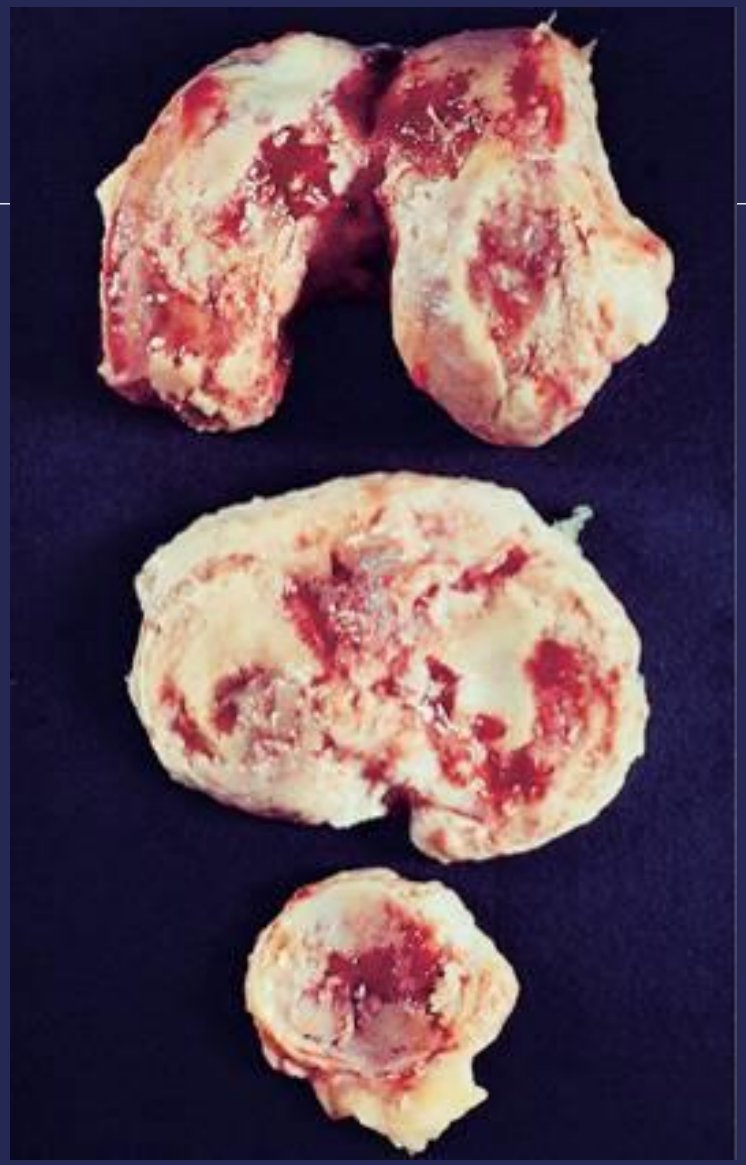
Grimley-Sokoloff giant cells

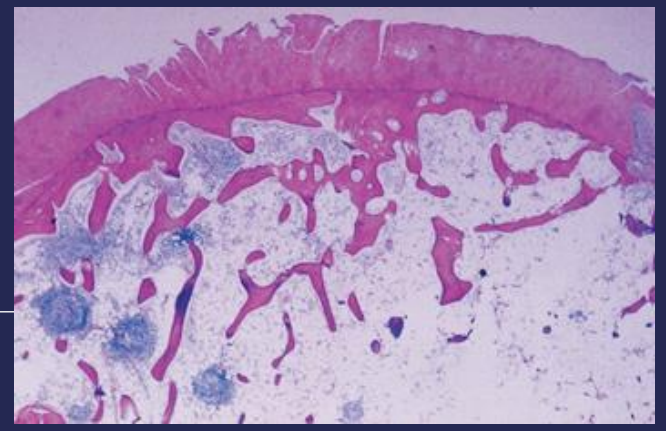


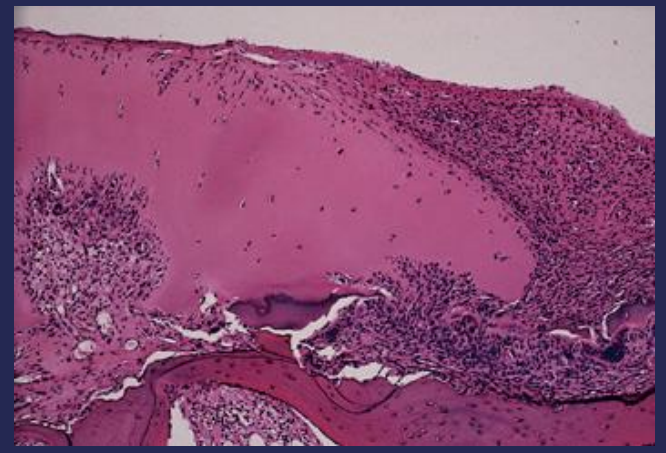
Rheumatoid Arthritis

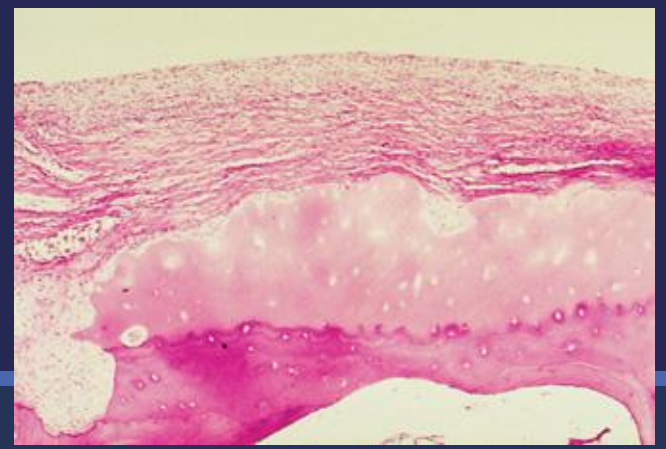
Late pathology:

- Synovial pannus invades the joint structures
- Synovial cells, macrophages, and inflammatory cells release various destructive substances:
  - Proteinases (collagenase and streptolysin)
  - Prostaglandins and leukotrienes
  - Oxygen radicals
  - Hydrolases
- Osteoclasts are activated and contribute to bone resorption
- The result is destruction of:
  - Articular cartilage and fibrocartilage (meniscus)
  - Ligaments, tendons and soft tissue
  - Subchondral bone



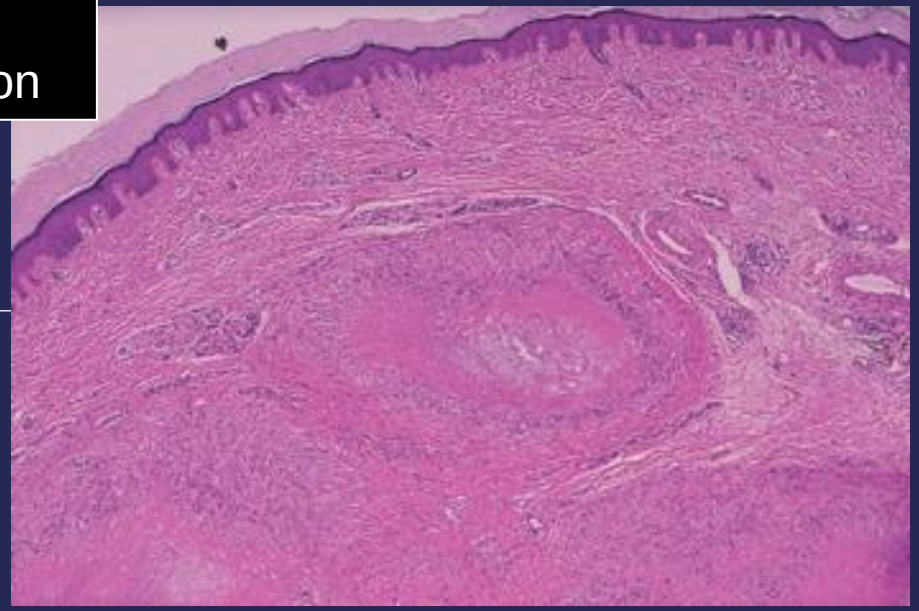


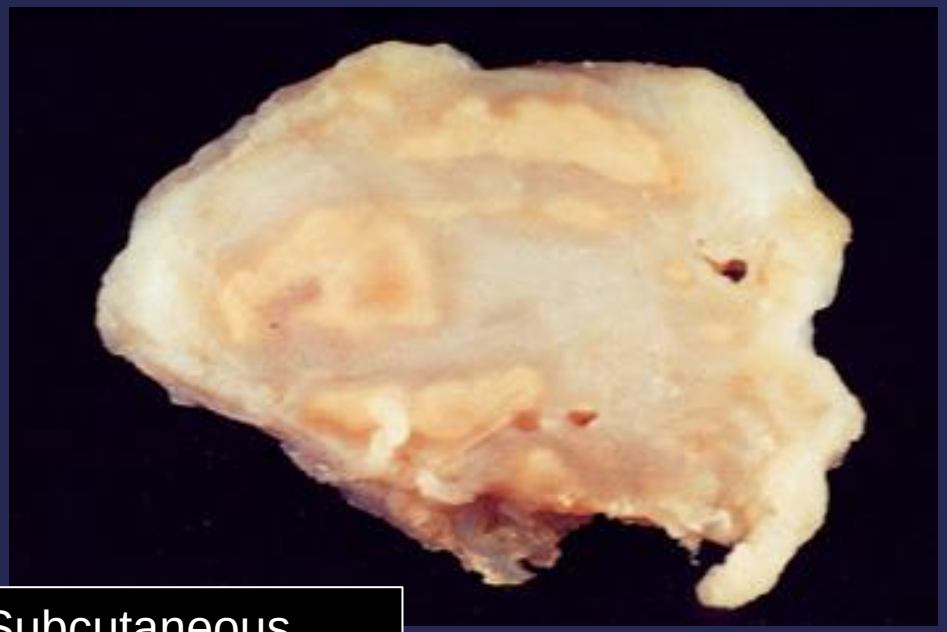




Rheumatoid Arthritis

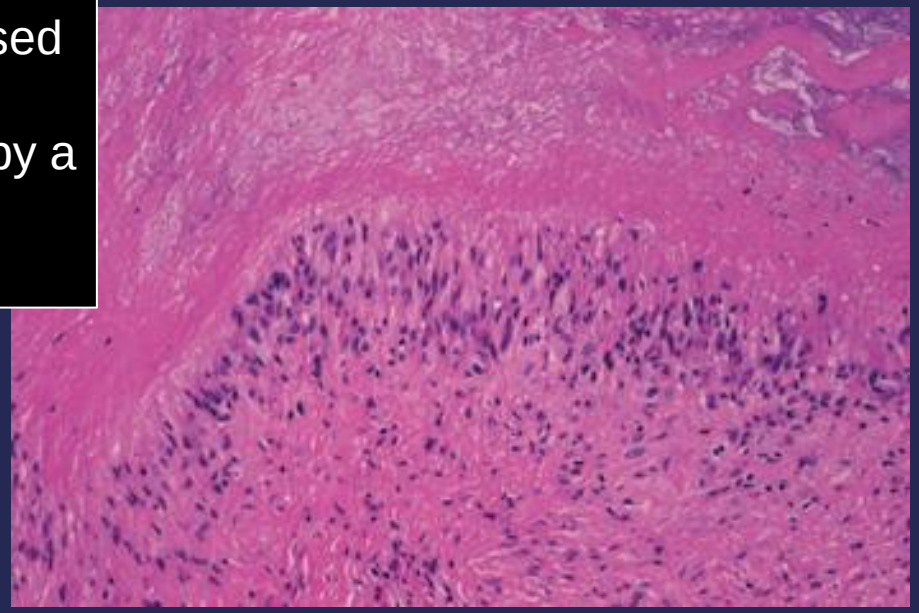
Skin with palisading granulomatous reaction





Subcutaneous rheumatoid nodule

The nodule is composed of a central zone of necrosis surrounded by a palisaded rim of epithelioid histiocytes



Revision Arthroplasty

Main causes of loosening

Biological

- Osteolysis
- Infection
- Immunological reaction to prosthetic wear debris

Mechanical

- Excessive patient activity
- Material failure
- Mismatch between implant size and bone or joint

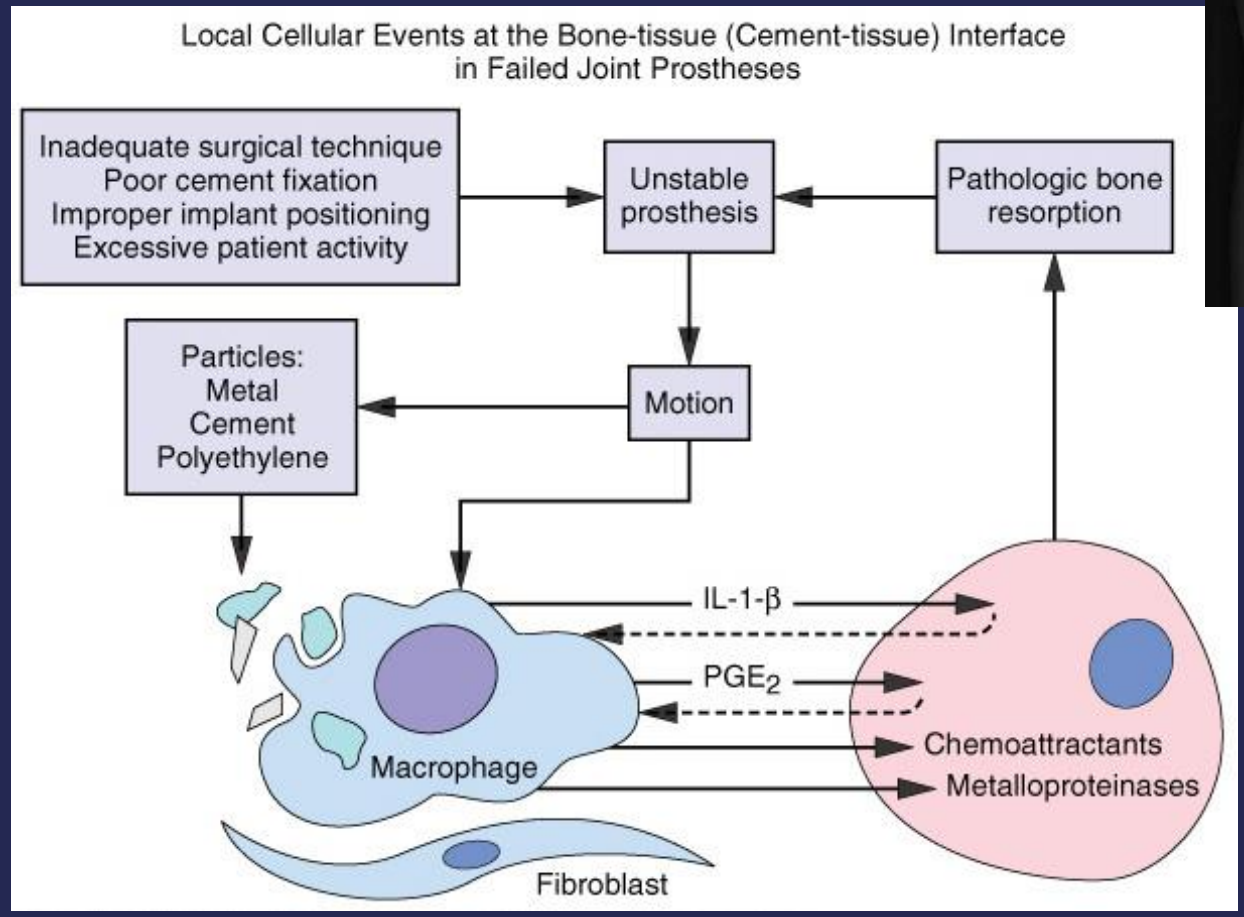
Reason	0 prior revisions	1 prior revision	2 prior revisions	>2 prior revisions	total
Aseptic loosening	76%	64.4%	61.3%	46.8%	74%
Infection	7.2%	11.1%	12.3%	20.6%	8%
Dislocation	6.6%	11.4%	13.3%	21.4%	7%
Periprosthetic fracture	5.4%	7.8%	7.3%	1.6%	6%
Technical	2.5%	2.5%	3.3%	1.6%	2.5%
Implant fracture	1.5%	1.6%	1.3%	2.4%	1.5%
Miscellaneous	0.5%	0.8%	1.0%	4.8%	0.5%
Pain	0.3%	0.3%	0.2%	0.8%	0.5%

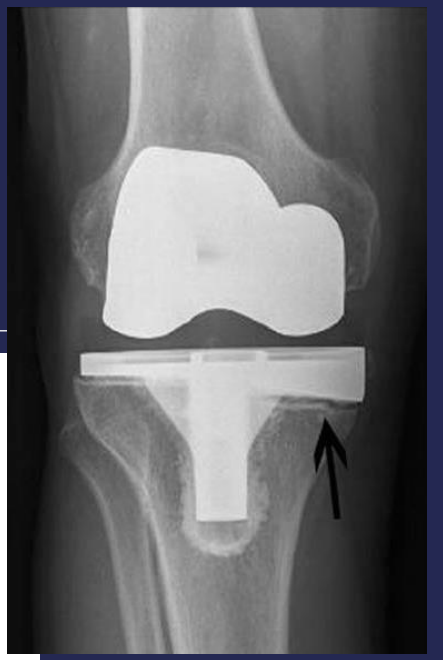
Aseptic Loosening

Micromotion and subsequent loosening of the prosthesis is the most frequent complication of joint replacement

Aseptic loosening accounts for about 74% of revision surgeries

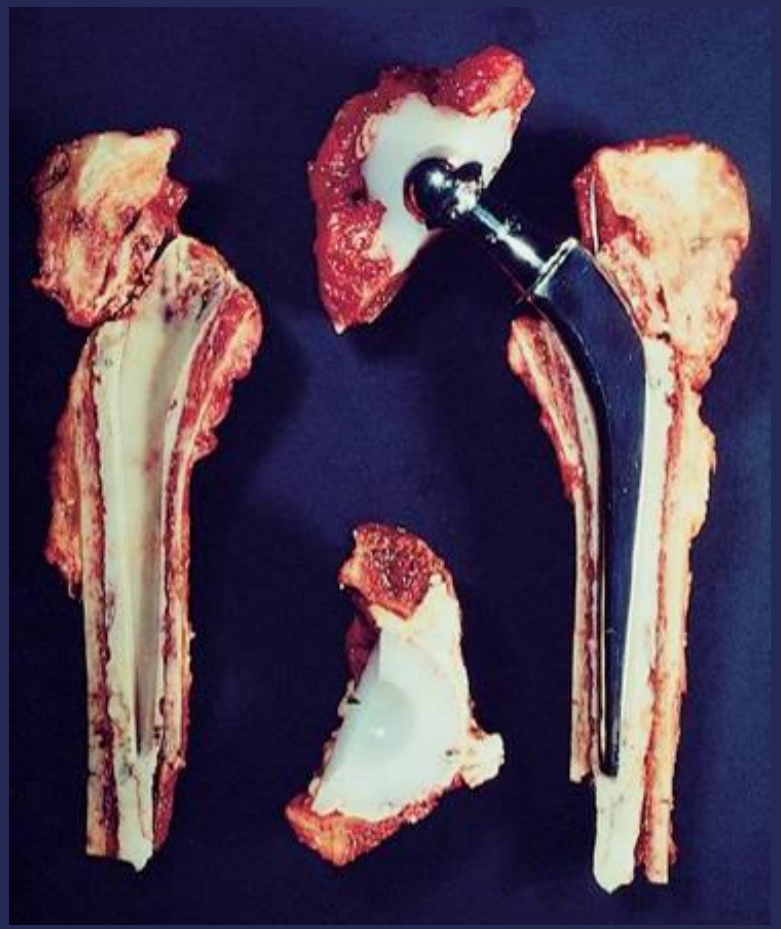
Loosening usually occurs about 4 years after surgery and progresses at a rate of 0.89mm/year

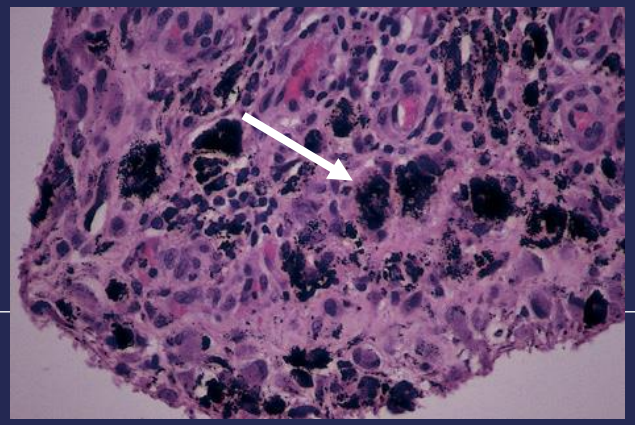


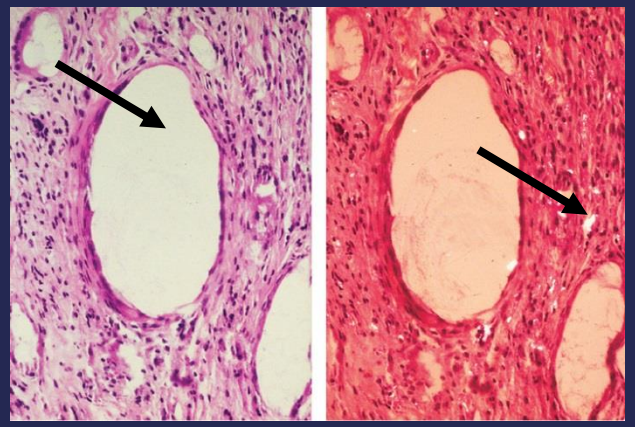


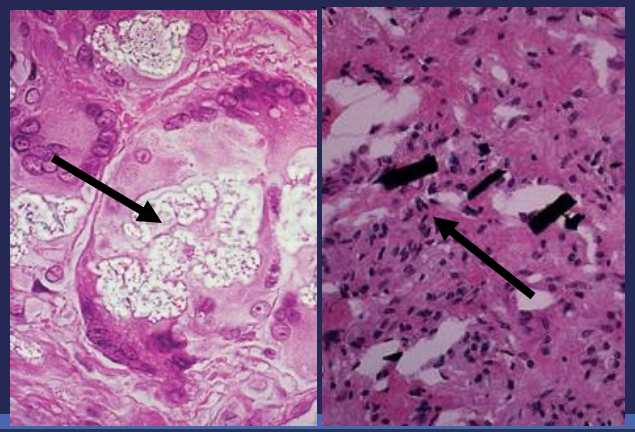
Detritic synovitis

Implant Related Materials









- Metal wear debris
  - Irregularly shaped black specks
  - Refractile and polarizable
  - Histiocytic and giant cell reaction
- Polyethylene shards
  - Clear and colorless shards of material
  - Brightly refractile
  - Polarizable
  - Histiocytic and giant cell reaction
- Methylmethacrylate (cement)
  - Empty holes in tissue since dissolved in processing solvents
  - Histiocytic and giant cell reaction around empty holes
- Carbon
  - Black rectangular and block-like fragments
  - Not refractile
  - Histiocytic reaction and mild chronic inflammation
- Silicon
  - Clear and colorless glassy or granular material
  - Brightly refractile
  - Histiocytic reaction and mild chronic inflammation

Prosthetic Joint Infections

Definition:

- Infection associated with a prosthetic joint
- Diagnosis is based on the clinical (pain, warmth, swelling, erythema), radiographic, and laboratory (ESR, CRP) findings

Four Types of infections:

1. Positive intraoperative infection

   Infection noted at time of surgery

2. Early positive infection

   Occurs within 4 weeks of joint replacement and is associated with fever, inflammation, fluid, or pus

   Coagulase negative or positive staphylococcus or gram(-) bacilli

3. Acute hematogenous

   Occurs after 4 weeks from joint replacement and is associated with fever, inflammation, fluid, or pus

   Coagulase positive staphylococcus or streptococcus

4. Late chronic

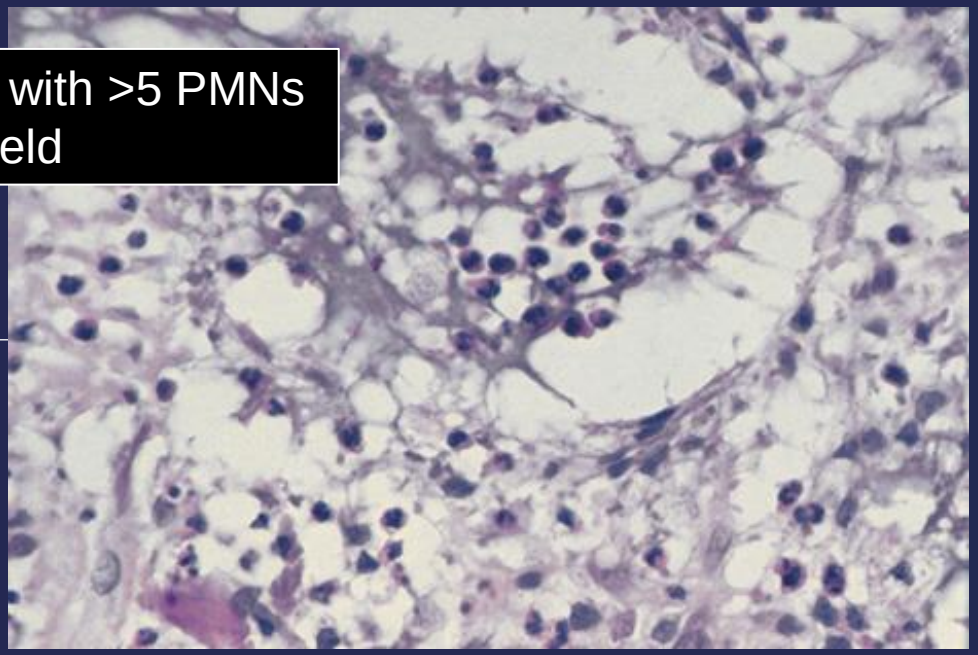
   Months after joint replacement and is associated with fever, fluid, or pus

   A sinus tract may be present

Prosthetic Joint Infections

Frozen section:

- Ideal sample is obtained from the periprosthetic fibrous membrane not the superficial fibrin or exudate
- Multiple samples from different sites should be sampled to reduce the possibility of sampling error (false negative result)
- Neutrophils must be located in the tissue below the periprosthetic membrane and not in the fibrin
- Five or more neutrophils in each of 3 high power fields is suggestive of periprosthetic joint infection



High power view with >5 PMNs per high power field

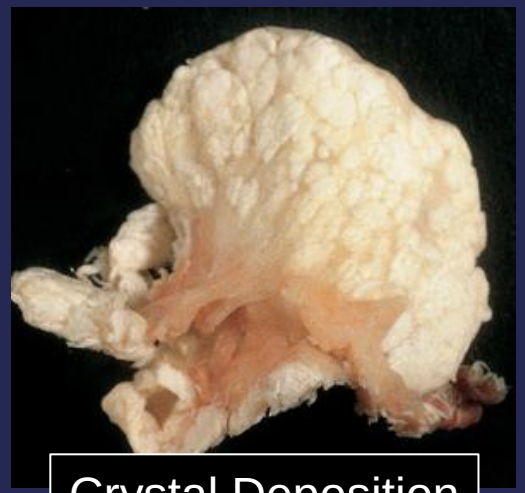
Significance of periprosthetic neutrophils

- Presence of neutrophils does not confirm infection – other inflammatory processes (crystal arthropathies and rheumatoid arthritis) may have neutrophils in the absence of infection
- High neutrophil counts may be due to inflammation or infection (poor positive predictive value)
- Low neutrophil counts are unlikely to be infection (good negative predictive value)

Changes in Synovium

Villous Transformation Reaction to Foreign Material or Trauma

Rusty Brown Iron Related Changes



Crystal Deposition Gout or CPPD

Gray Discoloration Implant Related Changes (Metal Deposition)

Dull, thick opaque synovium
- Inflammation (mechanical, infection or systemic disease)

Rusty brown or reddish synovium
- Iron (metabolic or bleeding)

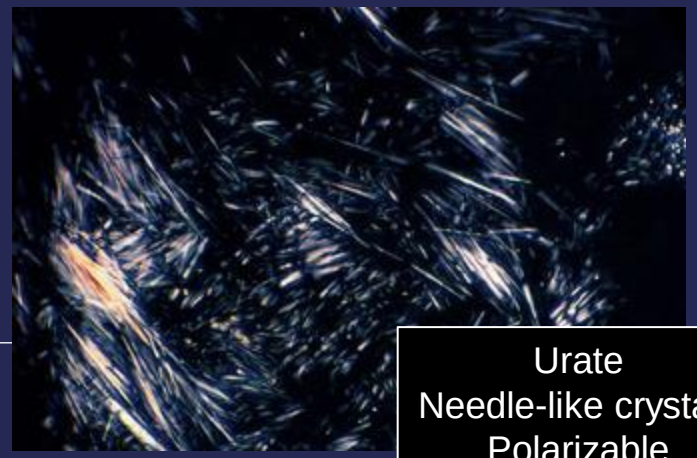
Dull gray synovium
- Implant related changes (metal wear debris)

Black synovium
- Ochronosis (alkaptonuria)

White patches
- Urate
- CPPD
- Hydroxyapatite
- Calcium phosphate

Yellow / Brown synovium
- Xanthomatous disease (yellow)
- PVNS (yellow and brown)

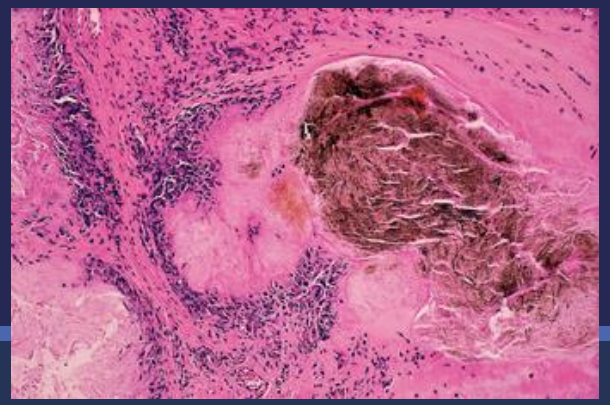
Gout



Urate
Needle-like crystals
Polarizable

Crystal properties of urate:

- Refractile and polarizable needle shaped crystals
- Brown color (alcohol fixation)
- Amorphous areas with rim of inflammation (aqueous formalin)
- Negative birefringence with polarized light
  - Urate crystals parallel to red filter are yellow
  - Urate crystals perpendicular to red filter are blue

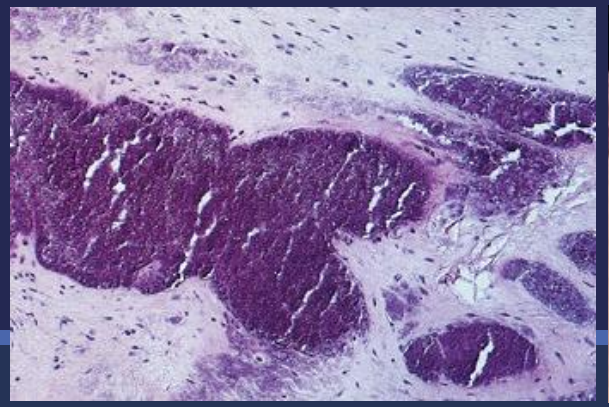


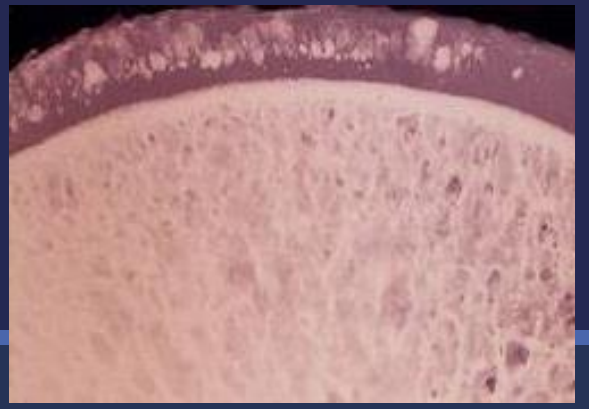
CPPD

Calcium pyrophosphate
Rhomboid crystals
Polarizable

Crystal properties of calcium pyrophosphate:

- Refractile and polarizable rhomboid shaped crystals
- Purple color on H&E (alcohol fixation)
- Amorphous areas without inflammation (aqueous formalin)
- Positive birefringence with polarized light
  - CPPD crystals parallel to red filter are blue
  - CPPD crystals perpendicular to red filter are yellow





Developmental Abnormalities

Localized Abnormality

- Dysostoses (problem forming primitive mesenchymal condensations / cartilage template of skeleton)
  - absent or extra digits

Generalized Abnormality

- Dysplasias (abnormal growth resulting from gene mutations affecting transcription factors, signalling pathways, structural proteins, metabolic enzymes and transporters)
  - Brachydactyly types D and E (HOXD13 gene - transcription factor) = short broad thumbs and big toes
  - Achondroplasia (FGFR3 gene - signalling pathway) = inhibition of endochondral growth of limbs
  - Osteopetrosis (RANKL gene - signalling pathway) = osteoclastic dysfunction, symmetric bone sclerosis
  - Osteogenesis imperfecta (COL1A1, COL1A2 genes - too little type 1 collagen - osteoid) = bone fragility
  - Osteopetrosis (CA2 gene - carbonic anhydrase defect) = ↑bone density, fragility, renal tubular acidosis
  - Osteopetrosis late onset type 2 (CLCN7 gene - chloride channel defect) = ↑bone density, fragility, flask deformity

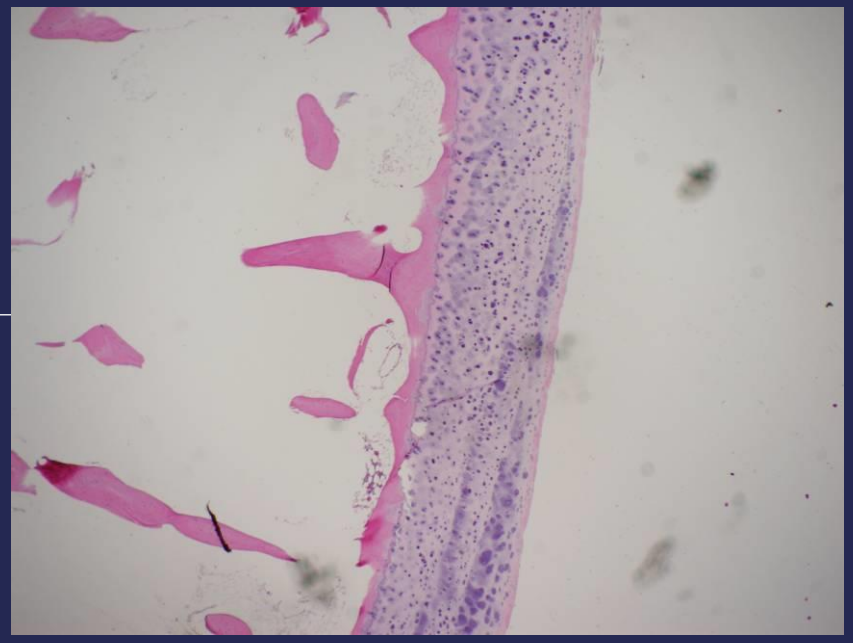
Osteoporosis

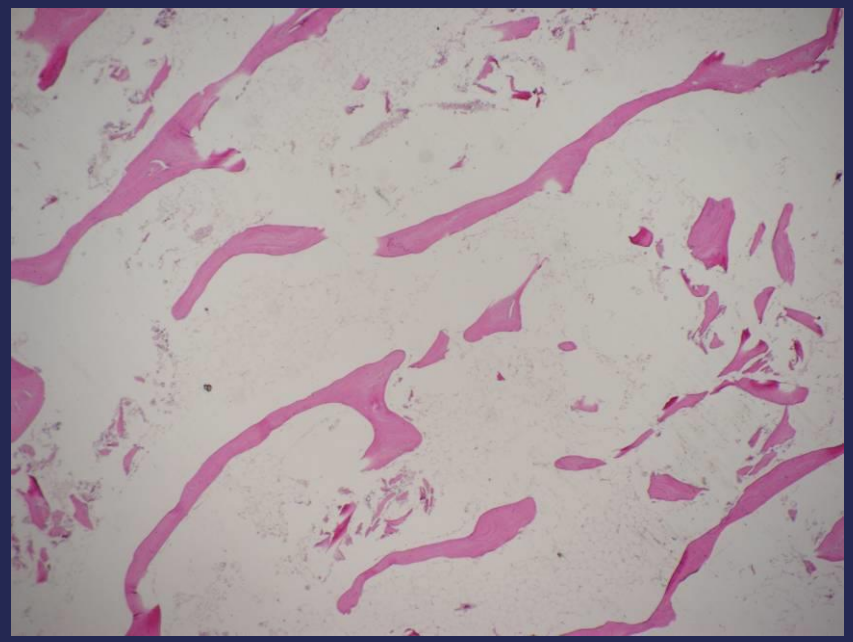
Definition:
•Decreased bone mass that is severe enough to significantly increase the risk of fracture

•Senile osteoporosis – osteoblasts have reduced proliferative and biosynthetic potential.

•Post-menopausal osteoporosis – decreased estrogen will cause disproportionate increase in osteoclastic and osteoblastic activity (resorption > formation) = high turnover osteoporosis

•Micro:
•Thin cortex, wide Haversian systems, thin trabeculae, and loss of supportive horizontal connections between trabeculae (floating spicules).

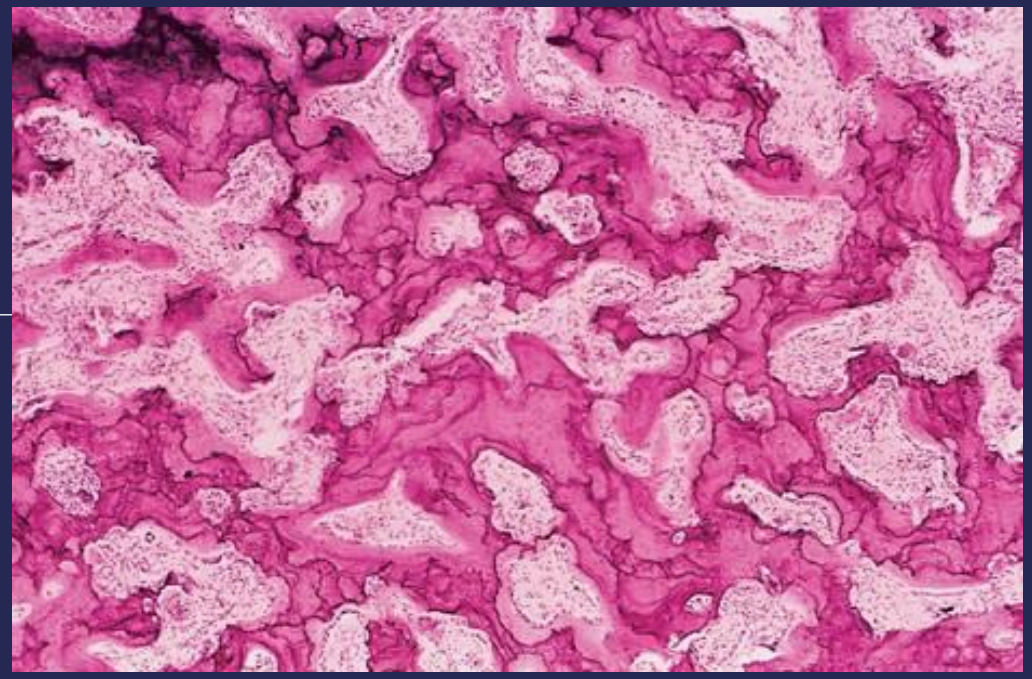


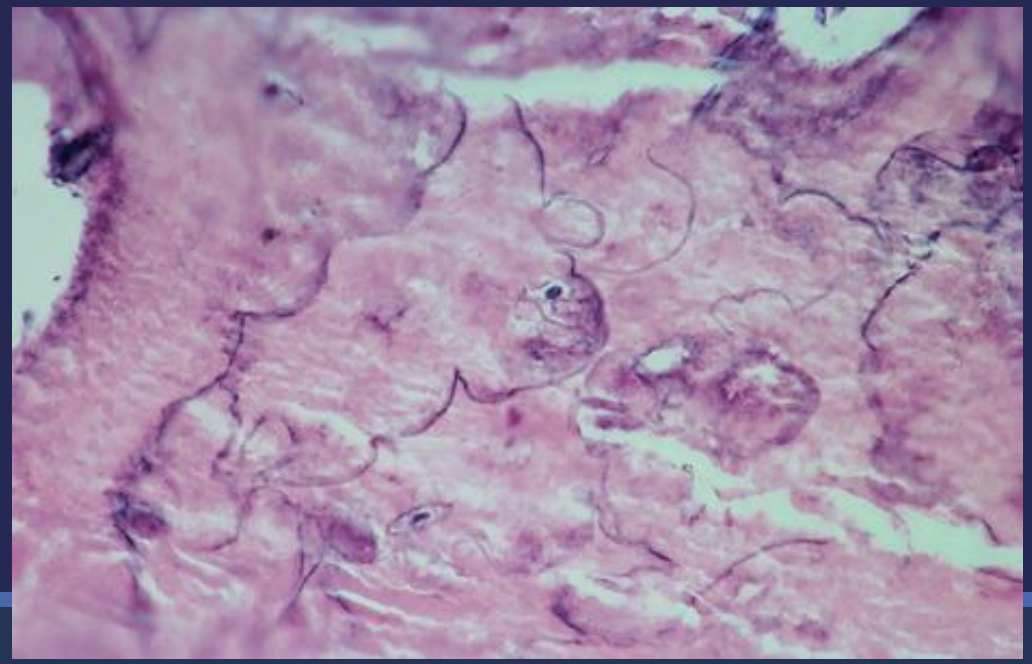


Paget Disease

Definition:
•A disease of bone characterized increased bone that is disordered and structurally unsound.
1.Osteolytic stage
2.Mixed osteoclastic-osteoblastic stage (resorption <formation)
3.Burned-out sclerotic stage

Micro:
- Increased numbers of osteoclasts (1, 2)
- Large osteoclasts with increased numbers of nuclei (1, 2)
- Increased osteoblastic activity (2)
- Marrow stromal fibrosis with increased vascularity (2)
- Thickened trabeculae of woven bone (3)
- Prominent irregular cement lines (3)





Rickets and Osteomalacia

Rickets and Osteomalacia – impaired mineralization of bone and accumulation of unmineralized bone resulting from vitamin D deficiency

Rickets – refers to disorder in children which interfere with deposition of bone in growth plates

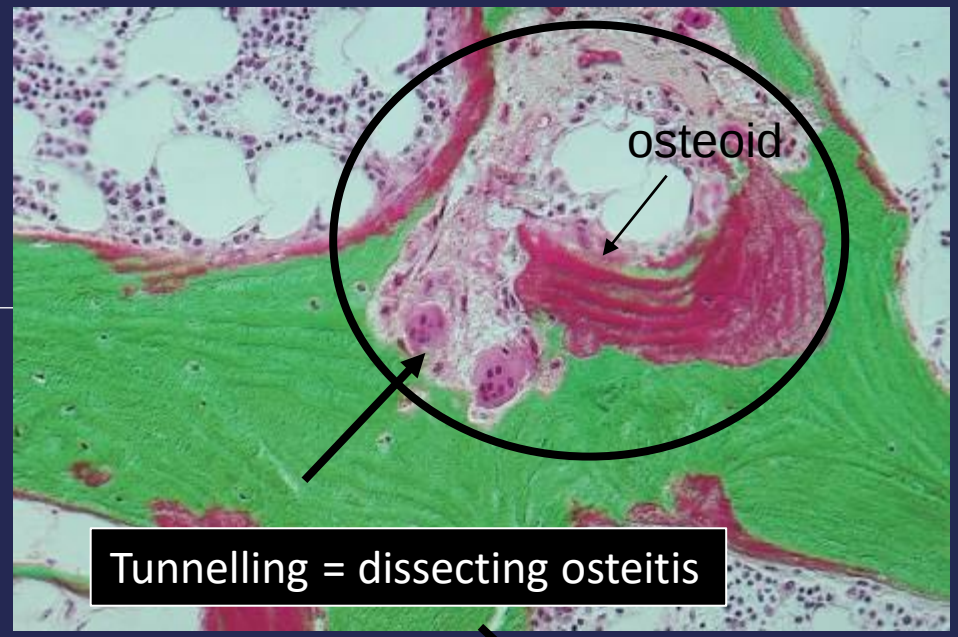
Osteomalacia – refers to disorder in adults in which the osteoid deposited during remodelling is undermineralized

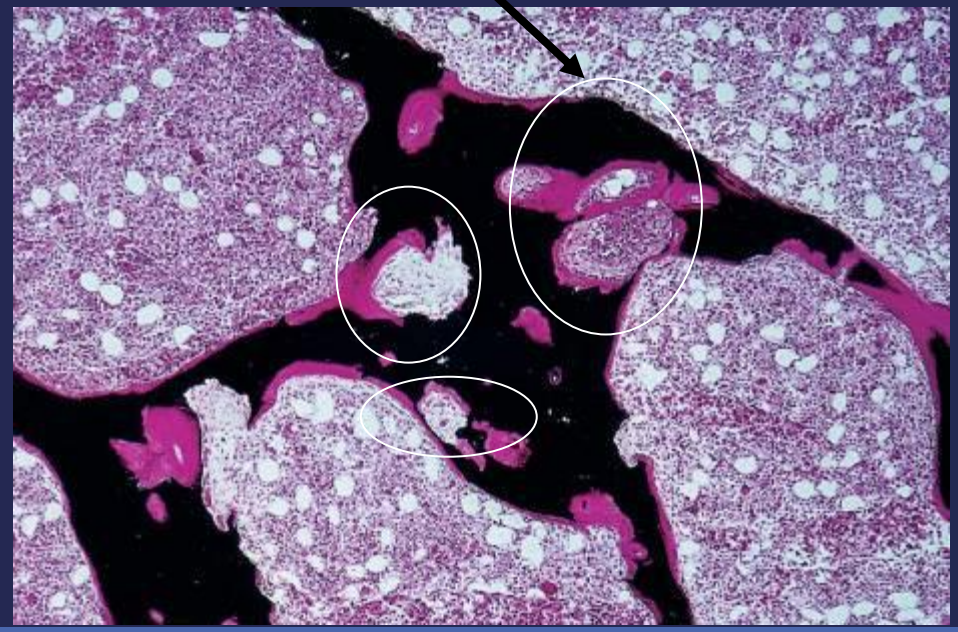
Hyperparathyroidism

Definition:
Primary
- Increased PTH production from parathyroid glands stimulates bone resorption (activates osteoclasts)
- Osteoporosis, Brown tumor, Osteitis fibrosis cystica

Secondary (CRF)
- Decreased renal synthesis of vitamin D (causes osteomalacia) and decreases GI absorption of Ca and secondary increase in PTH (activates osteoclastic activity)

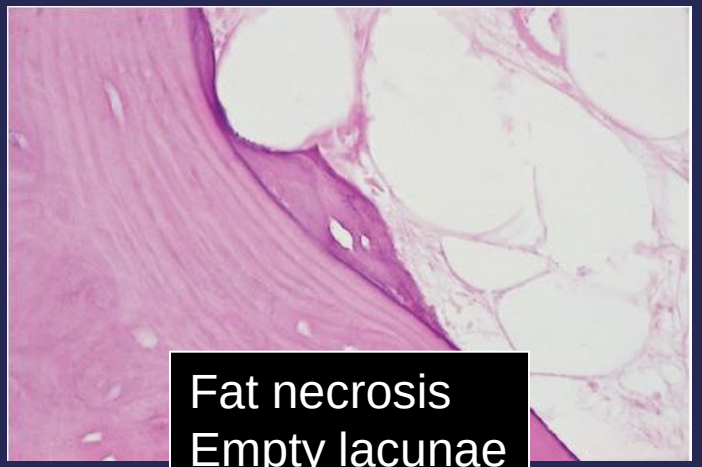
Renal osteodystrophy
- Osteoporosis
- Osteomalacia
- Secondary hyperparathyroidism
- Growth retardation





Osteonecrosis

- Bone dies due to disrupted vascular supply
- Fat necrosis and death of hematopoietic cells (loss of fat cell nuclei and hematopoietic cell nuclei) are the earliest changes of osteonecrosis
- Loss of osteocytes may not occur for up to 2 weeks following osteonecrosis so do not rely on empty lacunae
- Dead bone is pale on H&E with empty ghostlike lacunae
- Outcomes:
  - Poorly vascularized areas undergo bone resorption and fat saponification (liberation of free fatty acids that react with calcium to form fatty acid salts)
  - Vascularized areas undergo repair (granulation tissue, cartilage formation, bone formation, creeping substitution)

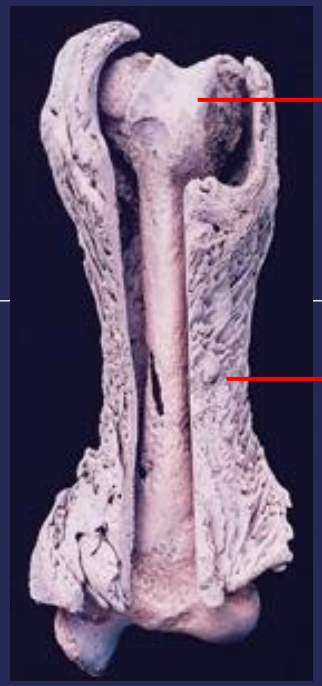


Causes of Osteonecrosis

- Traumatic
- Non-traumatic
  - Vascular
    - Pregnancy induced vascular compromise
    - Hemoglobinopathy
      - Sickle cell disease
    - Thrombosis
      - Factor V Leiden
      - ATIII gene defect
      - Prothrombin gene defect
      - Protein S and Protein C
      - Lupus and antiphospholipid antibodies
    - Embolism
      - Dysbarism
      - Fat embolism
      - Air embolism
      - Foreign material embolism
  - Infectious
    - Septic arthritis
  - Neoplastic
    - Myeloproliferative disorders
    - Hematologic
    - Polycythemia
  - Degenerative
    - Stress of fatigue fractures
    - Age related lesions of the distal femur
    - Gout
  - Systemic disease
    - Inflammatory
      - RA
      - SLE
      - Pancreatitis
    - Storage
      - Gaucher disease
  - Congenital/Genetic/Childhood Disease
    - Legg-Calve-Perthes disease
    - Sever's disease
    - Kohler's disease
    - Blout's disease
    - Panner's disease
  - Autoimmune
    - Vasculitis or arteritis
  - Drug or Therapy related
    - Alcohol
    - Steroids
    - Radiation injury
  - Idiopathic

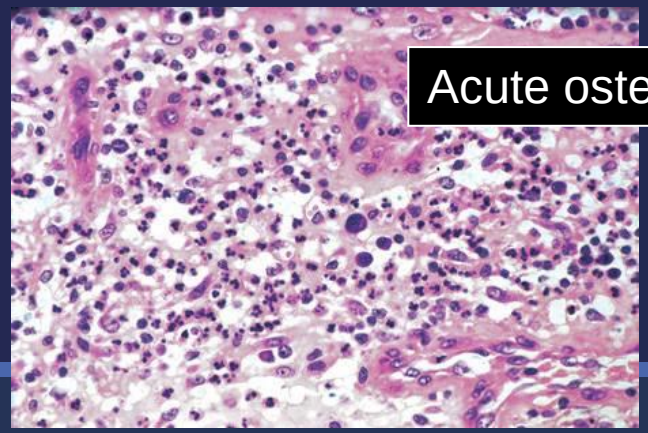
Osteomyelitis

- Infection of a bone characterized by dead bone and inflammation
- Acute osteomyelitis has lots of neutrophils and dead bone
- Chronic osteomyelitis has lots of plasma cells, dead bone, and creeping substitution

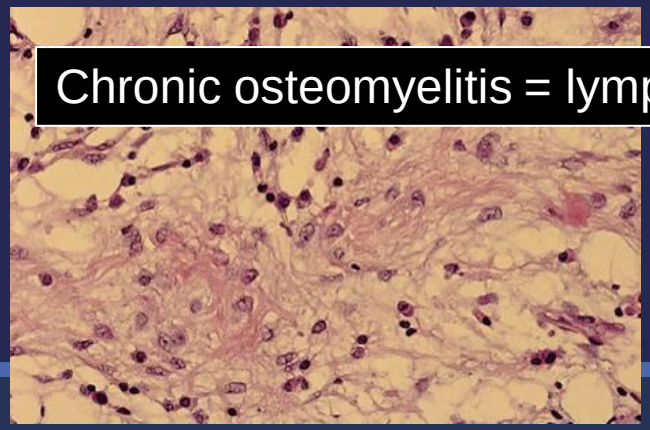


Sequestrum = dead bone

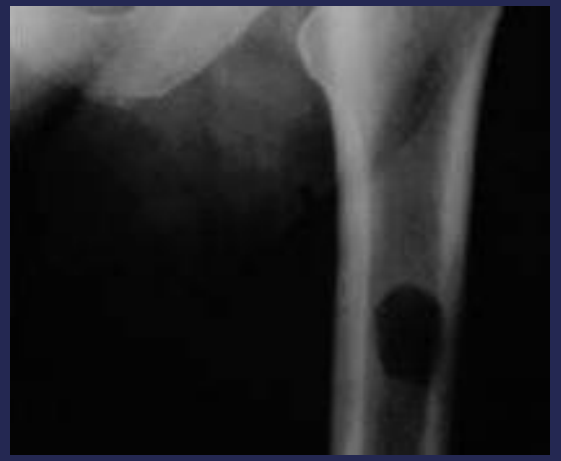
Involucrum = shell of reactive bone formation associated with the periosteum

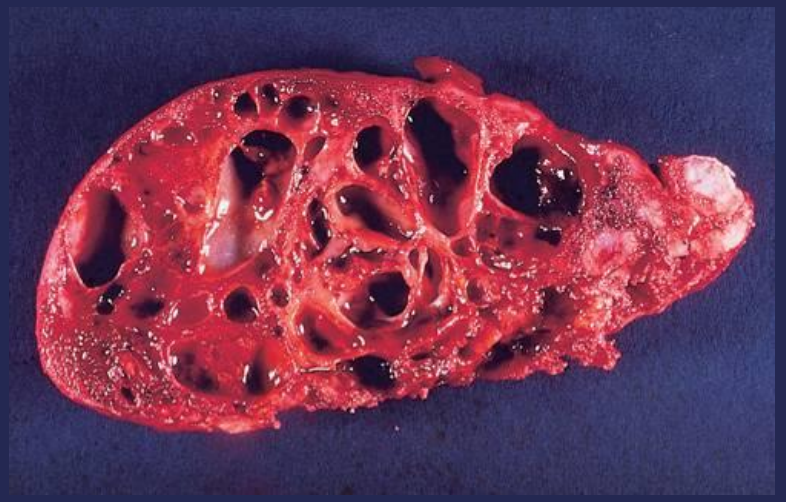


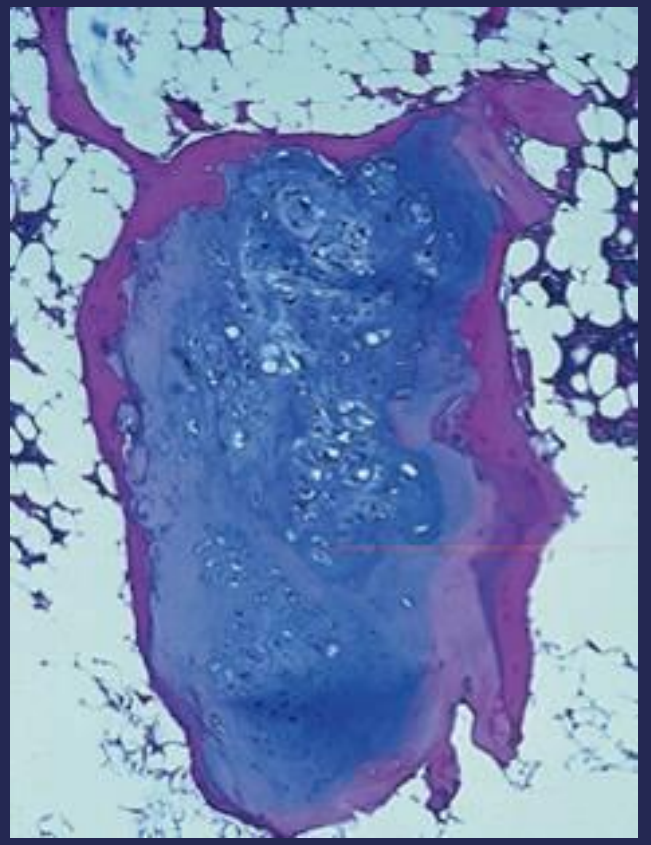
Acute osteomyelitis = neutrophils

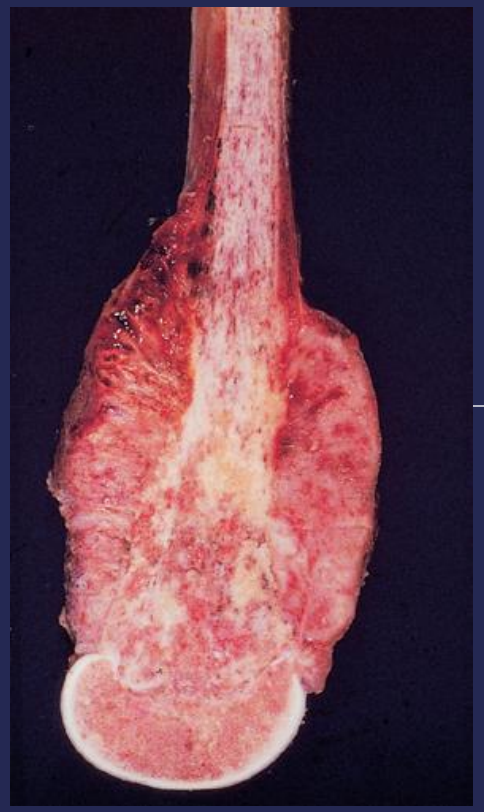


Chronic osteomyelitis = lymphocytes and plasma cells

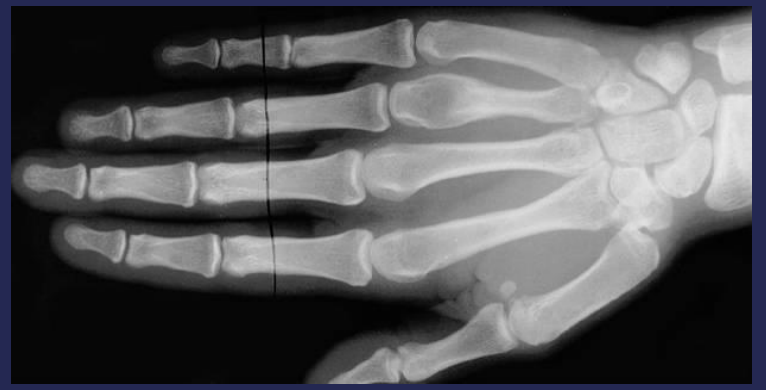








Neoplastic Bone



WHO 2013

Differentiation	Benign	Intermediate	Malignant
Hematopoietic			Plasma cell neoplasm Lymphoma
Fibrogenic			
Fibrohistiocytic			
Chondrogenic	Osteochondroma Enchondroma	Chondromyxoid fibroma Chondroblastoma Atypical cartilaginous tumor / chondrosarcoma grade I	Chondrosarcoma grade II or III Dedifferentiated chondrosarcoma Mesenchymal chondrosarcoma Clear cell chondrosarcoma
Osteogenic	Osteoma Osteoid osteoma	Osteoblastoma	Osteosarcoma
Giant cell rich	Giant cell lesion of the small bones	Giant cell tumor of bone	Malignancy in giant cell tumor of bone
Notochordal	Benign notochordal tumor		Chordoma
Vascular	Hemangioma	Epithelioid hemangioma	Epithelioid hemangioendothelioma Angiosarcoma
Myogenic			Leiomyosarcoma of bone
Lipogenic	Lipoma of bone		Liposarcoma of bone
Uncertain neoplastic nature	Simple bone cyst Fibrous dysplasia Osteofibrous dysplasia Chondromesenchymal hamartoma Rosai Dorfman	Aneurysmal bone cyst Langerhan cell histiocytosis Erdheim Chester disease	
Miscellaneous			Ewing sarcoma Adamantinoma Undifferentiated pleomorphic sarcoma

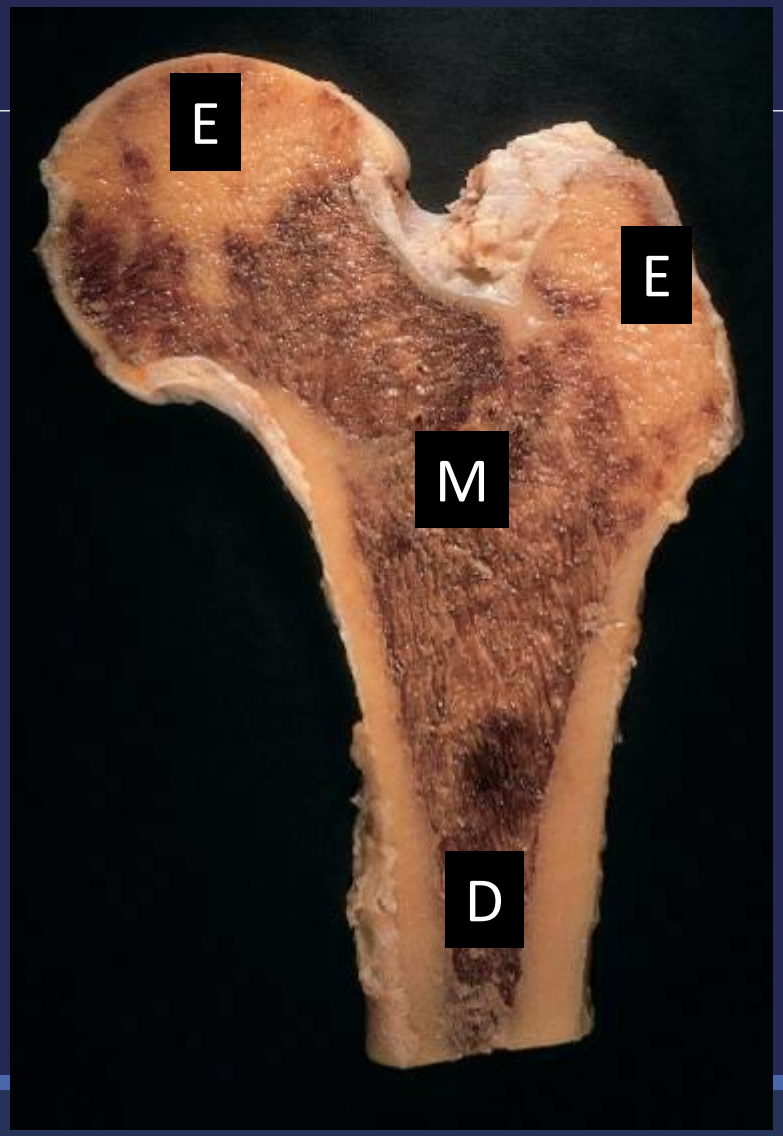
Bone Tumors by Location

Malignant

Epiphysis
- Clear cell chondrosarcoma

Metaphysis
- Osteosarcoma

Diaphysis
- Chondrosarcoma
- Ewing sarcoma
- Lymphoma
- Myeloma



Benign / Intermediate

Epiphysis
- Chondroblastoma
- Giant cell tumor of bone

Metaphysis
- Osteochondroma
- Non-ossifying fibroma
- Osteoid osteoma, osteoma
- Chondromyxoid fibroma
- Osteoblastoma
- Giant cell tumor
- Aneurysmal bone cyst

Diaphysis
- Osteofibrous dysplasia
- Adamantinoma
- Enchondroma
- Fibrous dysplasia

Clinical Presentation of Bone Tumors

Incidental Pain

Not associated with trauma

Persistent

Increasing intensity

Mass

Lesions that expand bone

Lesions that involve the surface of bone

Lesions that infiltrate the cortex and surrounding soft tissue

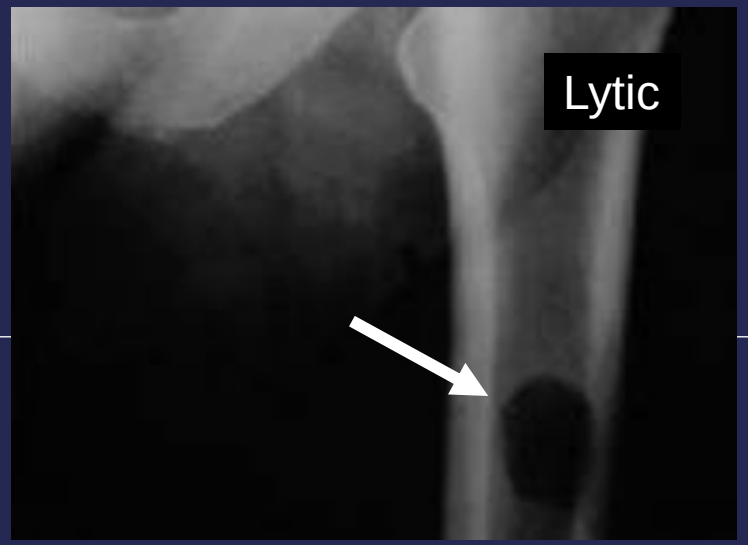
Fracture

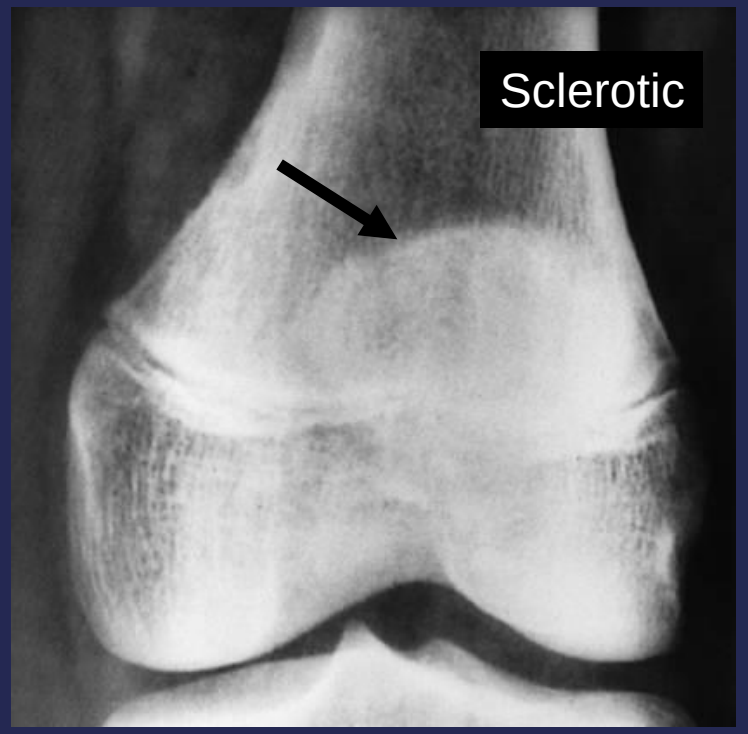
How Bone Reacts to a Neoplasm

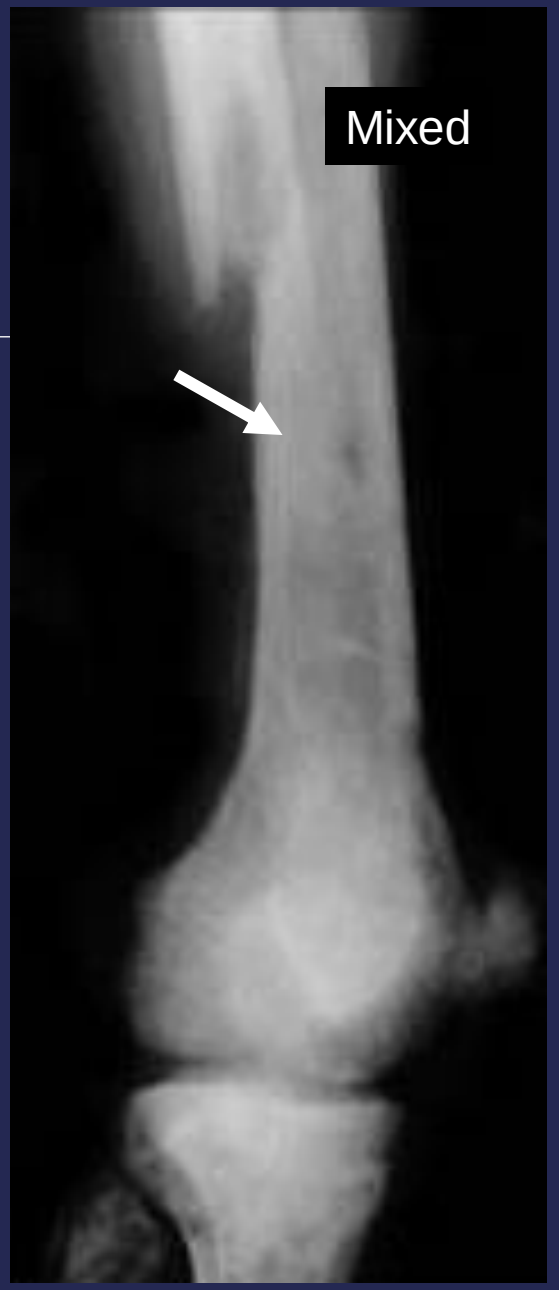
Mainly resorption (lysis) – mediated by reactive osteoclasts.

Mainly new bone formation (blastic or sclerotic lesion) – mediated by reactive osteoblasts.

Mixed lysis and sclerosis – can be thought of as tumor-induced bone remodeling by osteoclasts and osteoblasts.





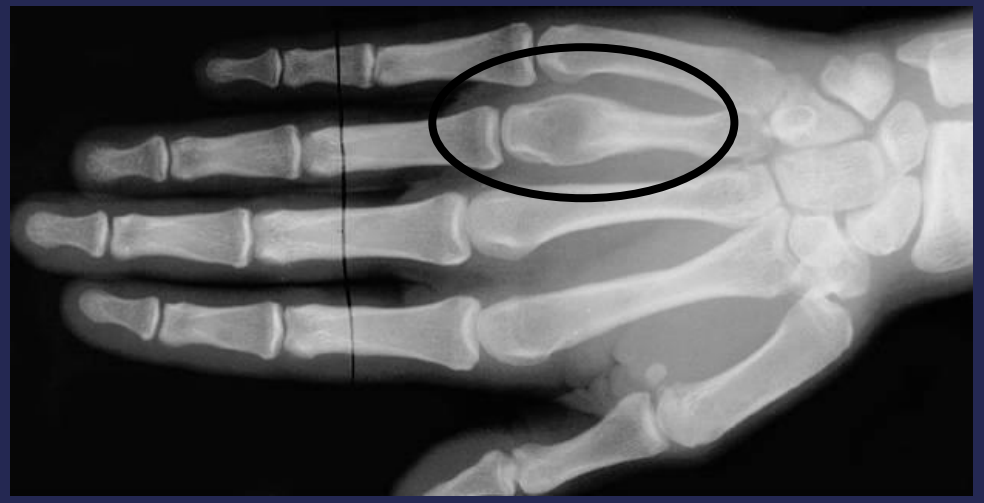


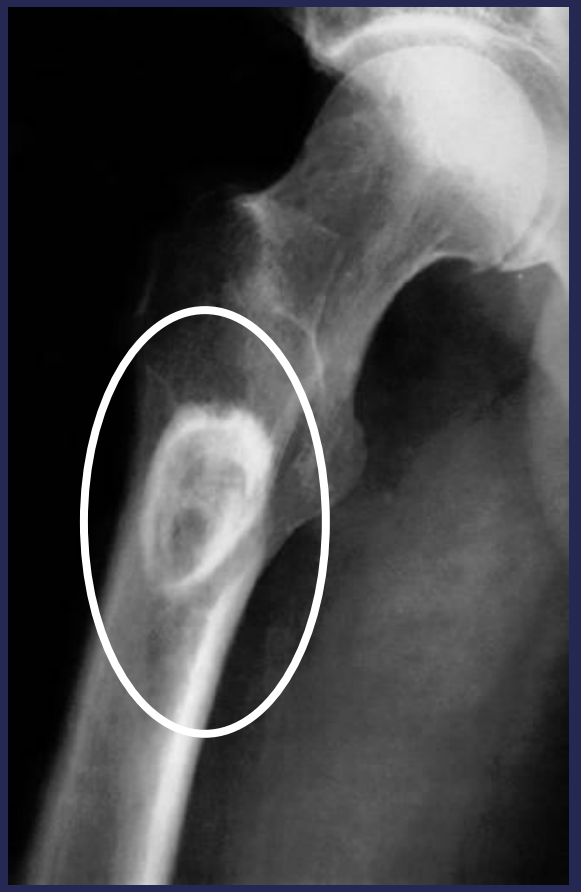
Benign Imaging Features

Circumscribed margins

Sclerotic rim of reactive bone

Expansile growth pattern



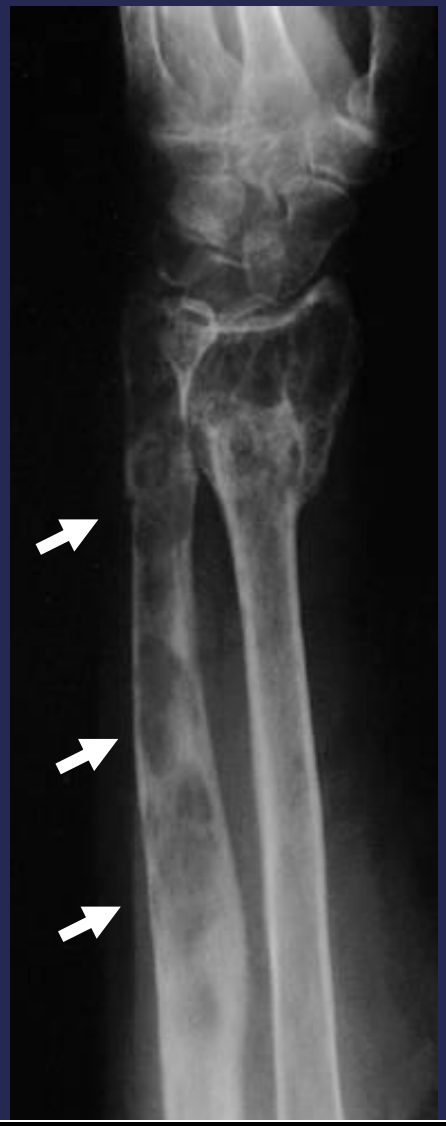


Malignant Bone Tumors: "RED FLAGS"

Poorly Circumscribed
Permeative Growth
Periosteal Reaction
- Onion skin = Ewing sarcoma
- Codman triangle = Osteosarcoma
- Sunburst = Osteosarcoma or Ewing sarcoma

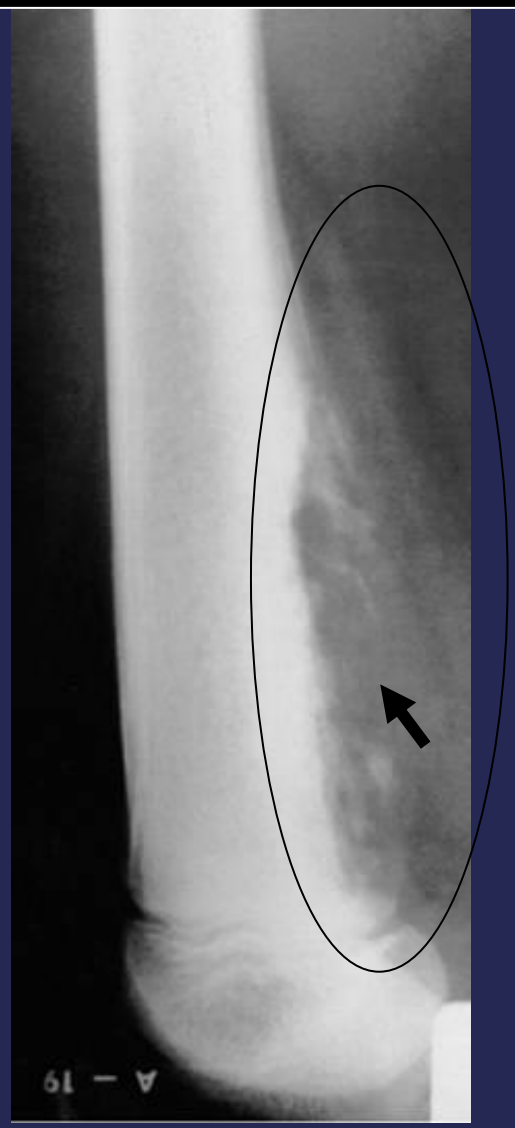
Soft Tissue Extension

Correlation of the biopsy findings with the imaging appearance is essential !

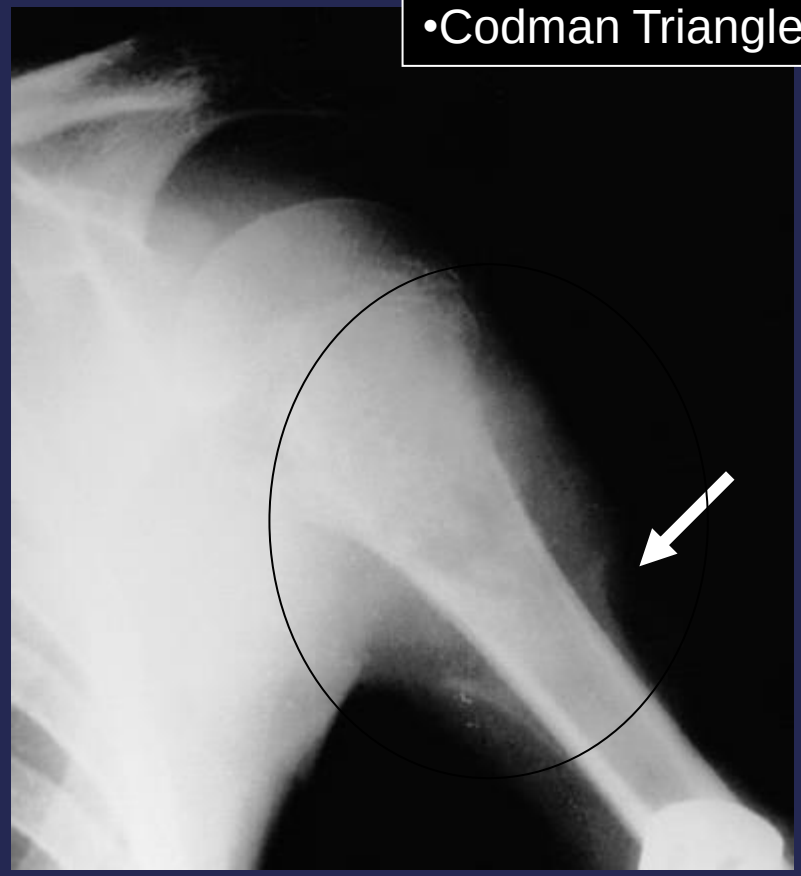


•Permeative Growth
•Poorly Circumscribed
•Multiple Bones Involved

•Poorly Circumscribed Lytic Lesion
• Onion Skin Periosteal Reaction



•Periosteal Reaction
•Codman Triangle



Bone Biopsy

FNA:
- Less accurate
- Sclerotic lesions yield little material and can be especially misleading on FNA
- Generally not used for bone lesions at our institution

Core biopsy
- Image guided procedure performed by radiologist
- Cores of tissue are small
- May not be representative

Open biopsy:
- More tissue
- More accurate
- Four times more costly (OR and anesthesia)

Frozen Section

Indications

Confirm lesional tissue and triage tissue

Green light

- Benign bone lesions (curettage, bone graft)
- Metastasis (implants, stabilization)
- Lymphoma (implants, stabilization)

Red light

- Malignant bone lesions
  - Confirm adequate lesional tissue
  - Close up and await final diagnosis
  - Arrange limb sparing surgery
  - +/- pre-operative chemotherapy

Triage Tissue

- Touch preparation (70% ethanol)
- Formalin (H&E, IHC)
- Flow cytometry (RPMI)
- Molecular studies (normal saline)
- Cytogenetics (RPMI)
- EM (glutaraldehyde)
- Snap freeze (liquid nitrogen)
- Culture (bacteria, fungus, mycobacteria)

Biopsy
For Bone Tumors

Always fix the bone in formalin prior to decalcification !

- Describe the type of specimen (curettings or needle biopsy), size (aggregate, range), color, and consistency of the components (tumor, soft tissue, bone)
- A touch preparation can be used to triage tissue for special studies
- Any obvious tumor can be trimmed away from larger bone fragments and submitted separately to avoid decalcification for IHC studies
- The specimen will be fixed for ~24 hours, and the bone sections will be gently decalcified as required for ~4 hours
- Submit:
  - In toto

Bone Resection for Tumor: Preparation

Always fix the cut bone in formalin prior to decalcification !

- Describe the type of specimen (wide excision, radical excision, amputation, disarticulation)
- List the components and provide measurements
- Take a curetting from the bone resection margin and place it in cassette
- Serially section the soft tissue perpendicular to the bone and determine if there is soft tissue extension of the bone tumor (dimensions, color, consistency, tissues involved, distance to resection margins)
- Take soft tissue sections represent the tissues involved and the margins
- Identify biopsy site and submit sections
- Strip the soft tissue from the bone and bisect the bone with a bone saw.
- Brush the bone dust from the bone surface using a tooth brush and running water (photograph)
- Alcohol can be used on the surface to “brighten” the appearance for photographs
- Use saw to cut a 0.5cm thick parallel section to represent the surface area of the tumor (photograph)
- Use saw to cut appropriate radial sections to examine margins
- Fix bone in formalin prior to decalcification

Bone Resection for Tumor: Description

- Location of tumor:
  - Centred in ____ and extending to involve ____
  - Epiphysis, metaphysis, diaphysis, medullary cavity, cortex, periosteum, soft tissue, joint
- Describe the tumor:
  - Size (three dimensions)
  - Appearance: color, consistency (fleshy, fibrous, gelatinous, gritty, chondroid)
  - Necrosis (%)
- Special features of tumor:
  - bone formation (%), cartilage formation (%), myxoid change (%), aneurysmal change (%), cyst formation (%)
- Relationship to blood vessels and nerves
- Presence of absence of skip metastases
- Relationship to bone margins:
  - Cut bone margin
  - Radial bone margin (anterior, posterior, medial, lateral)
- Relationships to soft tissue margins:
  - Proximal, distal, anterior, deep, medial, lateral

Make a map of the sections for the complete slice to help assess treatment response:
Grade I = no/minimal response
Grade II = < 10% necrosis
Grade III = > 90% necrosis
Grade IV = complete necrosis

WHO 2013

GRADE

TNM Two-Grade	Three-Grade	Four-Grade
Low grade	Grade 1	Grade I Grade II
High grade	Grade 2 Grade 3	Grade III Grade IV

Ewing sarcoma – Always regarded as high grade
Chondrosarcoma – Three-grade system
Osteosarcoma – Two-grade system
Low grade
- Parosteal osteosarcoma
- Low grade central osteosarcoma

High grade
- Virtually all others

AJCC Cancer Staging Manual 8th Edition: Bone

AJCC Cancer Staging Manual 8th Edition recognizes that anatomical site significantly influences outcome and separates the sites for bone sarcoma as:

- Appendicular skeleton, trunk, skull, and facial bones
- Spine
- Pelvis

Appendicular Skeleton, Trunk, Skull, and Facial Bones

T Category	T Criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor ≤ 8 cm
T2	Tumor > 8 cm
T3	Discontinuous tumors in the primary bone site (high grade)

Spine

Vertebral segments are:
- Right vertebral body
- Left vertebral body
- Right pedicle
- Left pedicle
- Posterior element

T Category	T Criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor confined to one vertebral segment or two adjacent vertebral segments
T2	Tumor confined to three adjacent vertebral segments
T3	Tumor confined to four or more adjacent vertebral segments or any nonadjacent vertebral segments
T4 T4a T4b	Extension into the spinal canal or great vessels Extension into the spinal canal Evidence of gross vascular invasion or tumor thrombus in the great vessels

Pelvis

Pelvic segments are:
- Sacrum
- Iliac wing
- Acetabular and periacetabular region
- Pubic rami, symphysis, and ischium

T Category	T Criteria
TX	Primary tumor cannot be assessed
T0	No evidence of tumor
T1 T1a T1b	Tumor confined to one pelvic segment **without** extraosseous extension Tumor ≤ 8 cm Tumor > 8 cm
T2 T2a T2b	Tumor confined to one pelvic segment **with** extraosseous extension or two pelvic segments **without** extraosseous extension Tumor ≤ 8 cm Tumor > 8 cm
T3 T3a T3b	Tumor spanning two pelvic segments **with** extraosseous extension Tumor ≤ 8 cm Tumor > 8 cm
T4 T4a T4b	Tumor spanning three pelvic segments or crossing the sacroiliac joint Tumor involves sacroiliac joints and extends medial to the sacral neuroforamen Tumor encasement of external external iliac vessels or presence of gross tumor thrombus in major pelvic vessels

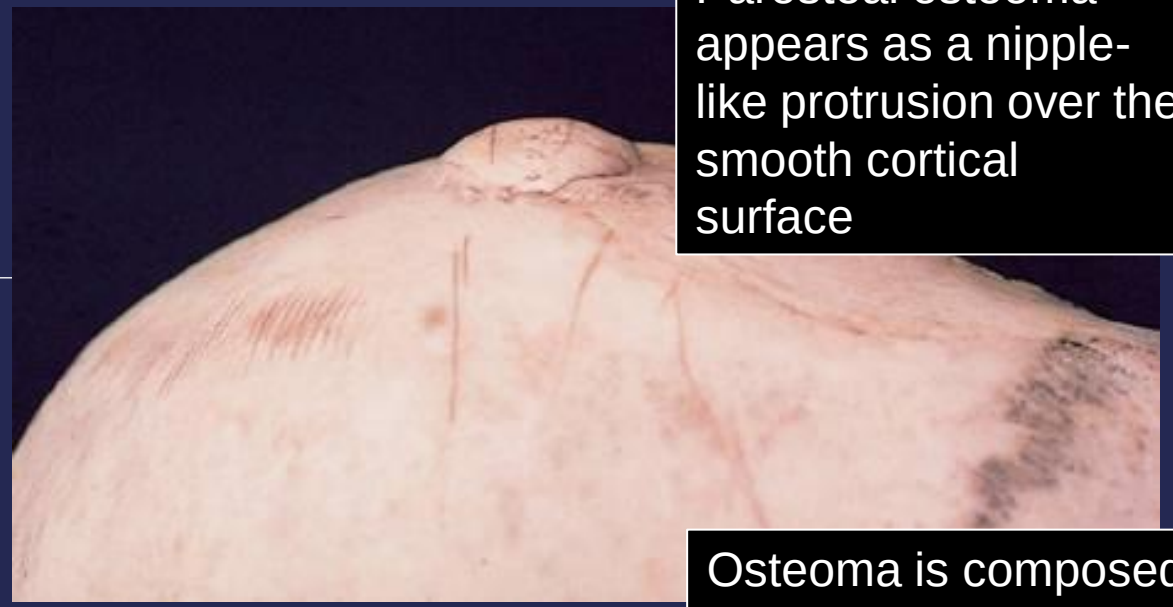
Bone Tumors - Prognostic Factors

Good	Bad
Low grade (G1)	High grade (G2, G3)
Extremity tumors better prognosis	Pelvic and spine tumors worse prognosis
Small size better prognosis for extremity and pelvic tumors	Large size worse prognosis for extremity and pelvic tumors
Fewer anatomic segments involved better prognosis for spine and pelvic tumors	More anatomic segments involved worse prognosis for spine and pelvic tumors
Absence of extraosseous extension better prognosis for pelvic tumors	Presence of extraosseous extension worse prognosis for pelvic tumors
Absence of spinal canal or great vessel involvement good prognosis for spinal and pelvic tumors	Presence of spinal canal or great vessel involvement worse prognosis for spinal or pelvic tumors
Ewing sarcoma ≤ 8 cm	Ewing sarcoma > 8 cm
Osteosarcoma ≤ 9 cm	Osteosarcoma > 9 cm
Chondrosarcoma ≤ 10 cm	Chondrosarcoma > 10 cm

Osteoma

Definition:

- Benign slow growing radiodense tumor-like lesion composed predominantly of lamellar bone with sparse interosseous spaces
- Facial bones, sinuses, skull, jaw
- Slow growing tumor of little clinical significance unless it blocks nasal sinus (sinusitis, nasal discharge, headache, pain, and loss of smell), expands into orbit (exophthalmos, diplopia) or impinges on cranial nerve (visual loss)
- May be associated with Gardner syndrome



Parosteal osteoma appears as a nipple-like protrusion over the smooth cortical surface

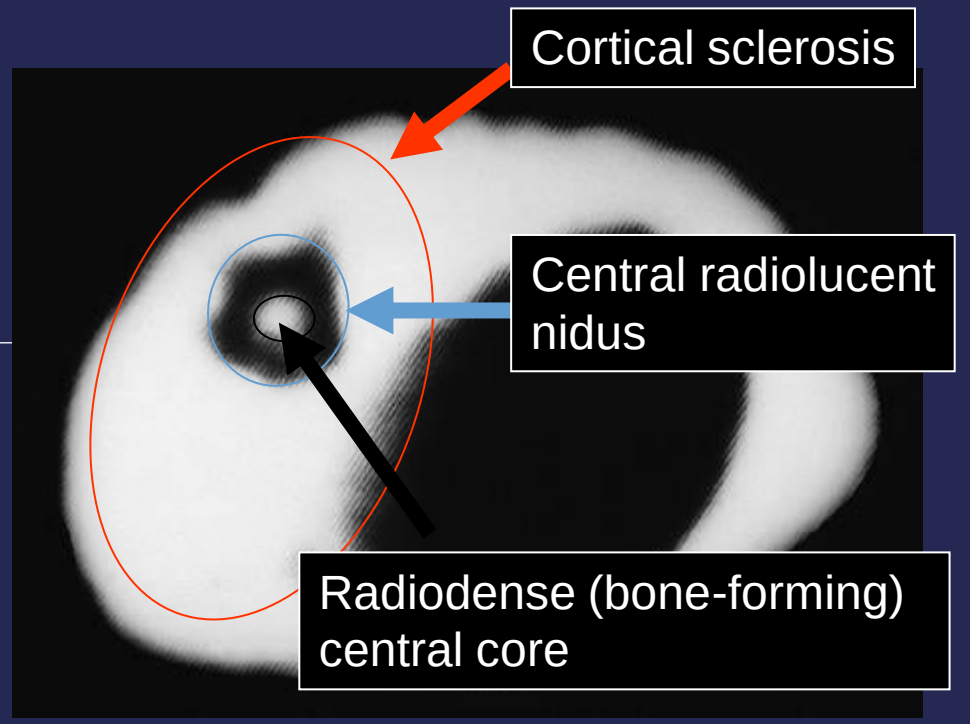
Osteoma is composed of mature cortical bone that blends imperceptibly into the adjacent cortex

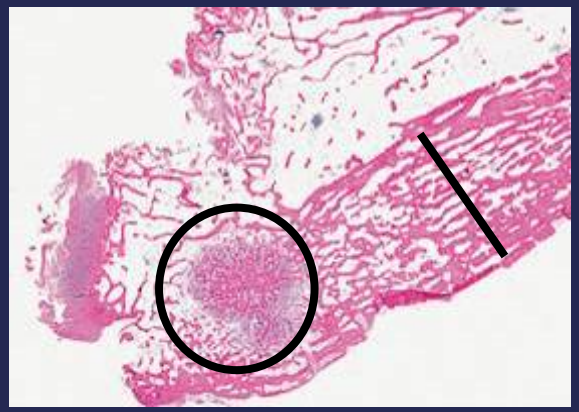
Osteoid Osteoma

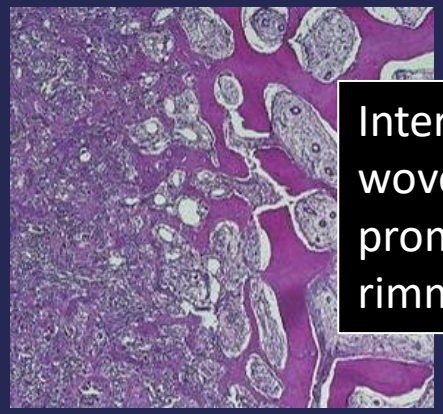
Definition:

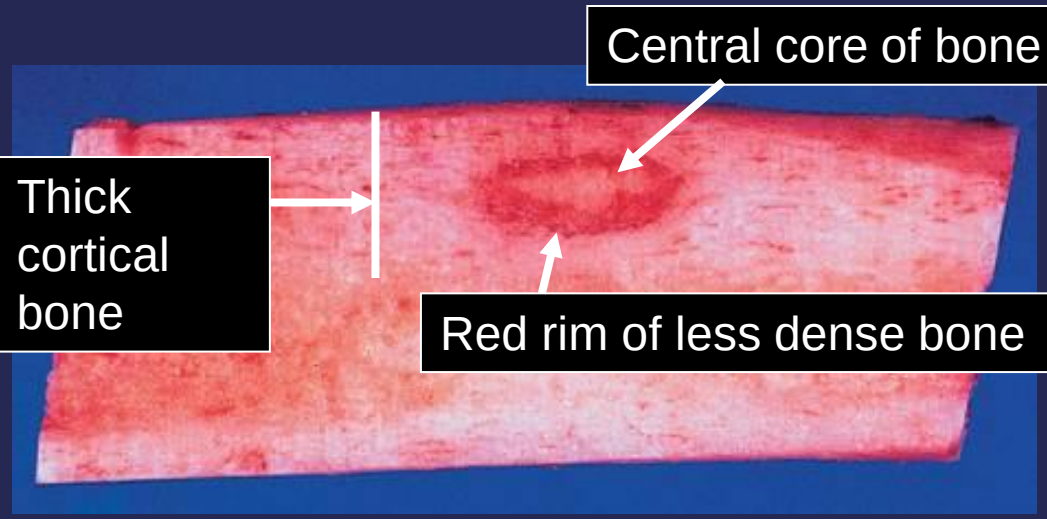
- A small (<2 cm) benign solitary bone forming lesion
- Characterized by pain that is worse at night and relieved by aspirin
- 90% of cases between ages 5 and 30 years
- Male predominance (2:1)
- Cortex of any bone (50% involve femur and tibia)
- Treated by ablation or surgical excision

Imaging:



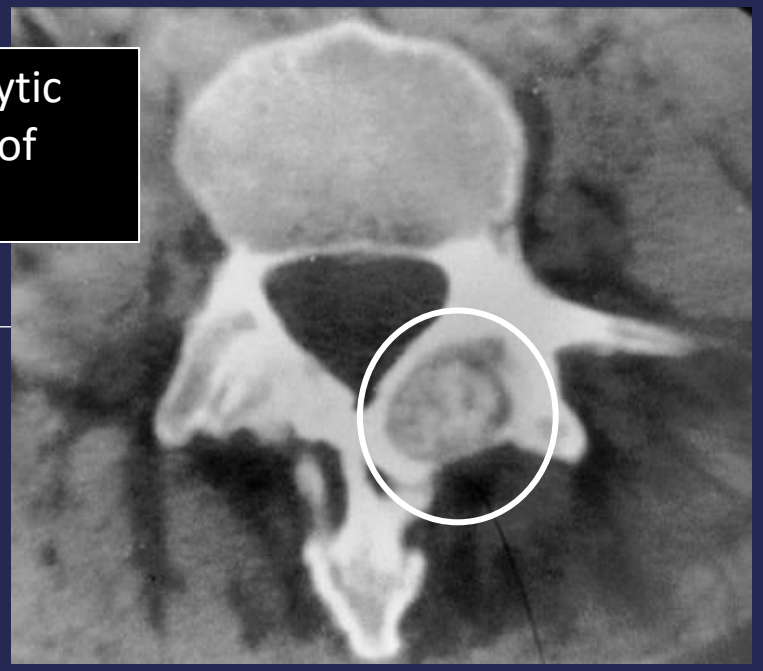






Osteoblastoma

Classic case is painful expansile lytic lesion in the posterior elements of vertebrae in adolescent male



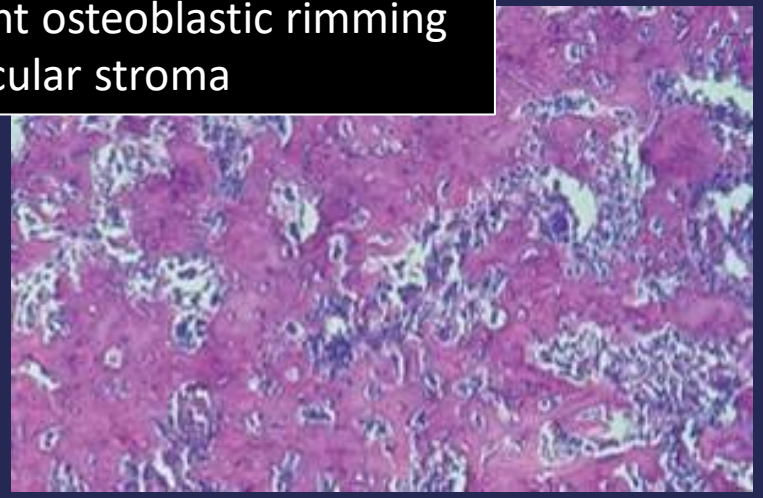
Definition:

- A benign bone forming lesion that similar to osteoid osteoma histological, but differs in the following ways:

1. Pain or tenderness in affected bone not relieved by aspirin
2. Epicenter in medullary bone of the metaphysis or diaphysis (cortical 65%, medullary 30%, surface 5%)
3. Predilection for axial skeleton (40%)
4. Well circumscribed radiolucent lesion with expansile margins
5. Size greater than 2 cm

- Treated by curettage or complete resection of the bone when surgically feasible
- Recurrence rate 21%
- Presence of epithelioid osteoblasts correlates with more aggressive behavior

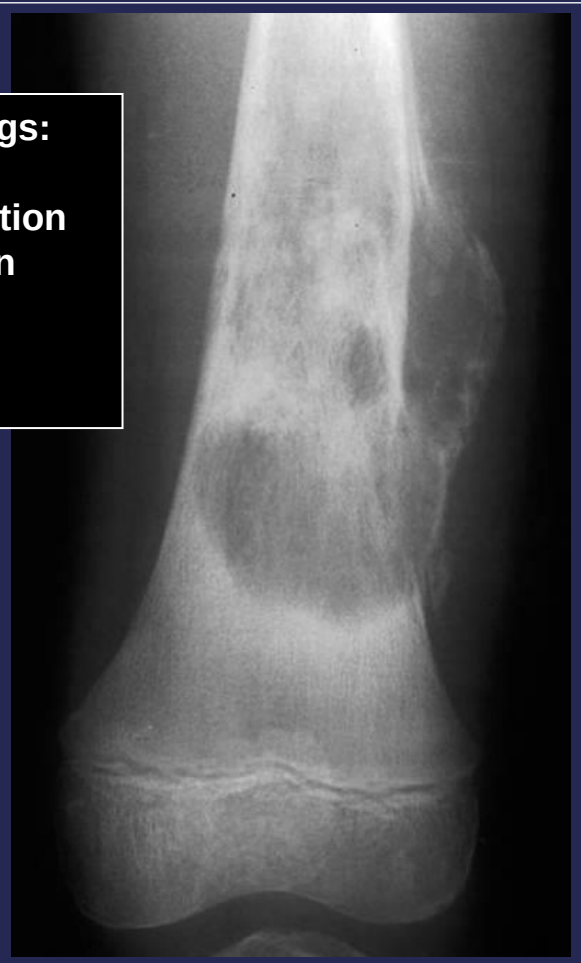
Interlacing spicules of woven bone with prominent osteoblastic rimming and hypervascular stroma



Osteosarcoma

Classic Radiographic Findings:

- **Metaphyseal / diaphyseal location**
- **Mixed sclerotic and lytic lesion**
- **Cloud-like appearance**
- **Sunburst periosteal reaction**
- **Codman's triangle**



Definition:
• A malignant bone tumor that produces osteoid (type I collagen), bone, or both

Population:
• Primary:
- Bimodal age distribution
- 75% of cases between ages 10 and 30 years
- 25% of cases occur in older adults

•Secondary:
- Paget disease
- Bone infarcts
- Radiation exposure

• Familial associations
  - Retinoblastoma (Rb)
  - Li-Fraumeni (p53)
  - Rothmund-Thompson Syndrome (RECQL4)
  - Werner syndrome (WRN)
  - Bloom syndrome (BLM)

Primary Osteosarcoma

Usual Variants

Surface
- Parosteal
- Periosteal
- High grade surface

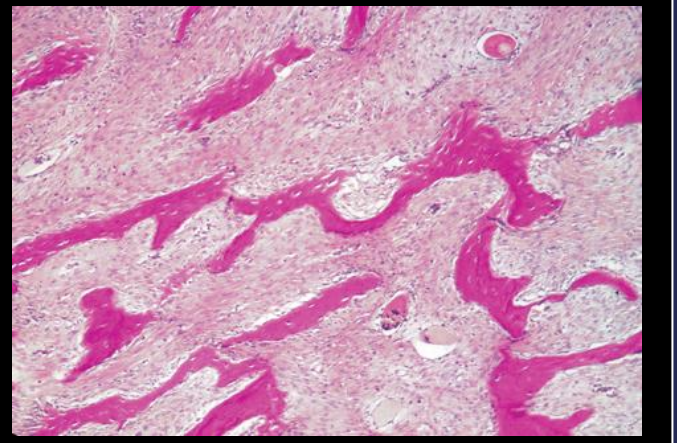
Intracortical

Medulla
- Low grade central
- Telangiectatic
- Conventional (osteoblastic, chondroblastic, fibroblastic)
- Small cell

Unusual Variants

- Osteoblastic osteosarcoma (sclerosing type)
- Osteosarcoma resembling osteoblastoma
- Chondromyxoid fibroma-like osteosarcoma
- Chondroblastoma-like osteosarcoma
- Clear cell osteosarcoma
- Malignant fibrous histiocytoma-like osteosarcoma
- Giant cell rich osteosarcoma
- Epithelioid osteosarcoma

Characteristic Features of Osteosarcoma Variants



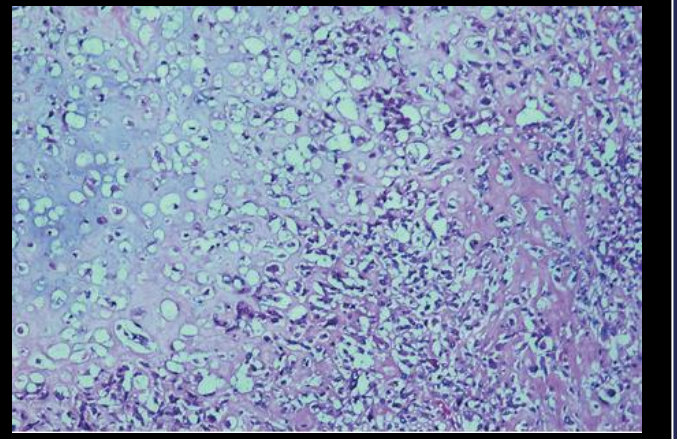
Parosteal
- Fibroblastic, metaphyseal, surface

Periosteal
- Chondroblastic, diaphyseal, surface

High grade surface
- Histology resembles conventional but is mostly confined to surface

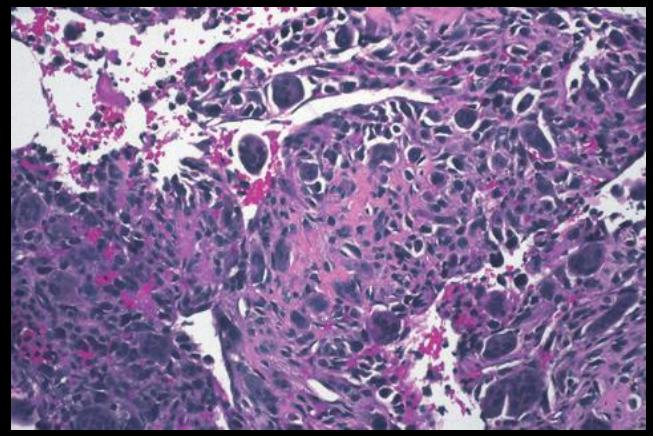
Low grade central
- Bland fibroblastic proliferation that mimics fibrous dysplasia or parosteal osteosarcoma, metaphyseal and diaphyseal

Conventional
- Malignant bone forming with variable histology, radiodense, metaphyseal
- Intramedullary component is greater than cortical or soft tissue component



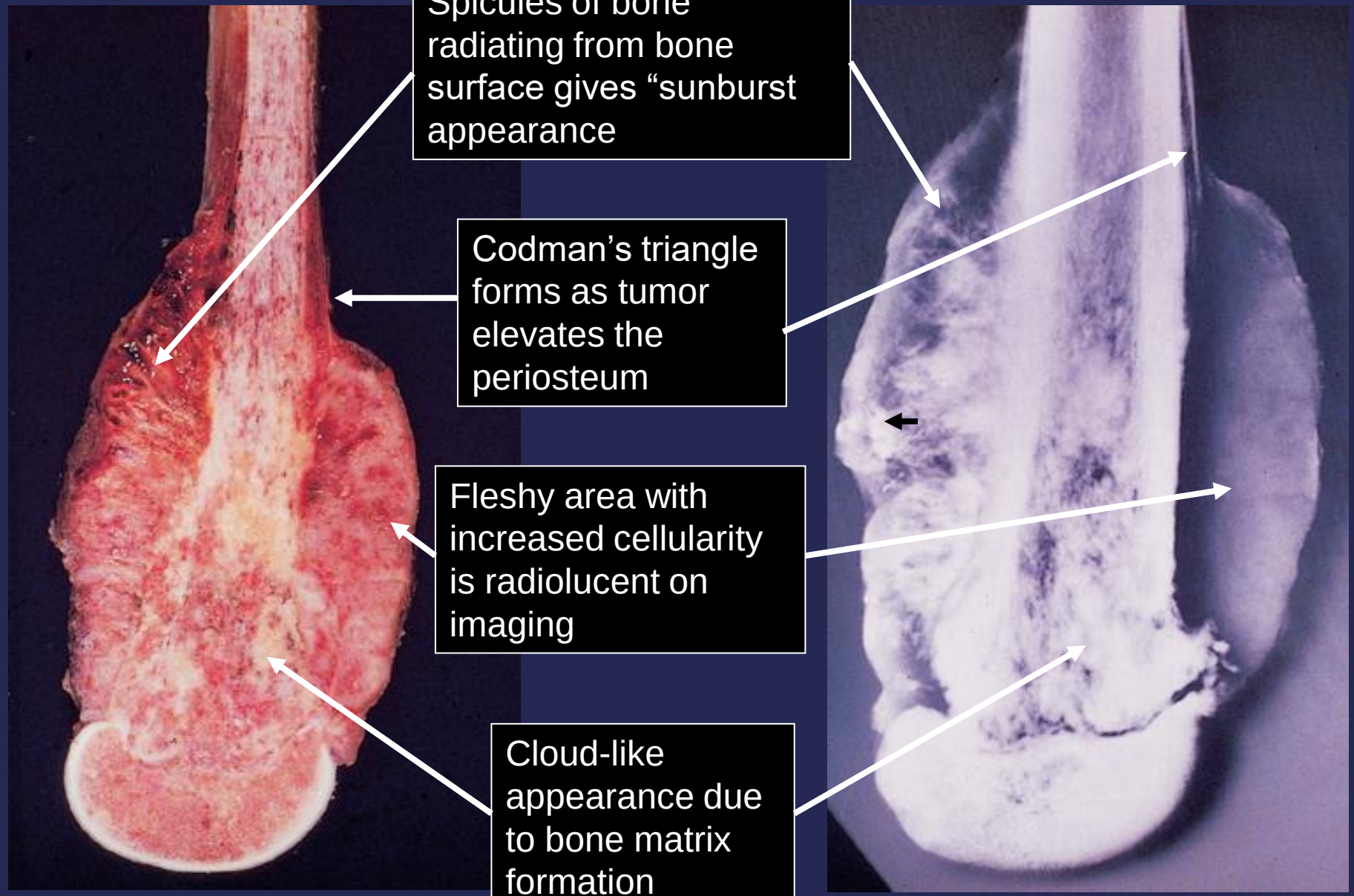
Telangiectatic
- Mimics ABC, radiolucent and cystic on imaging

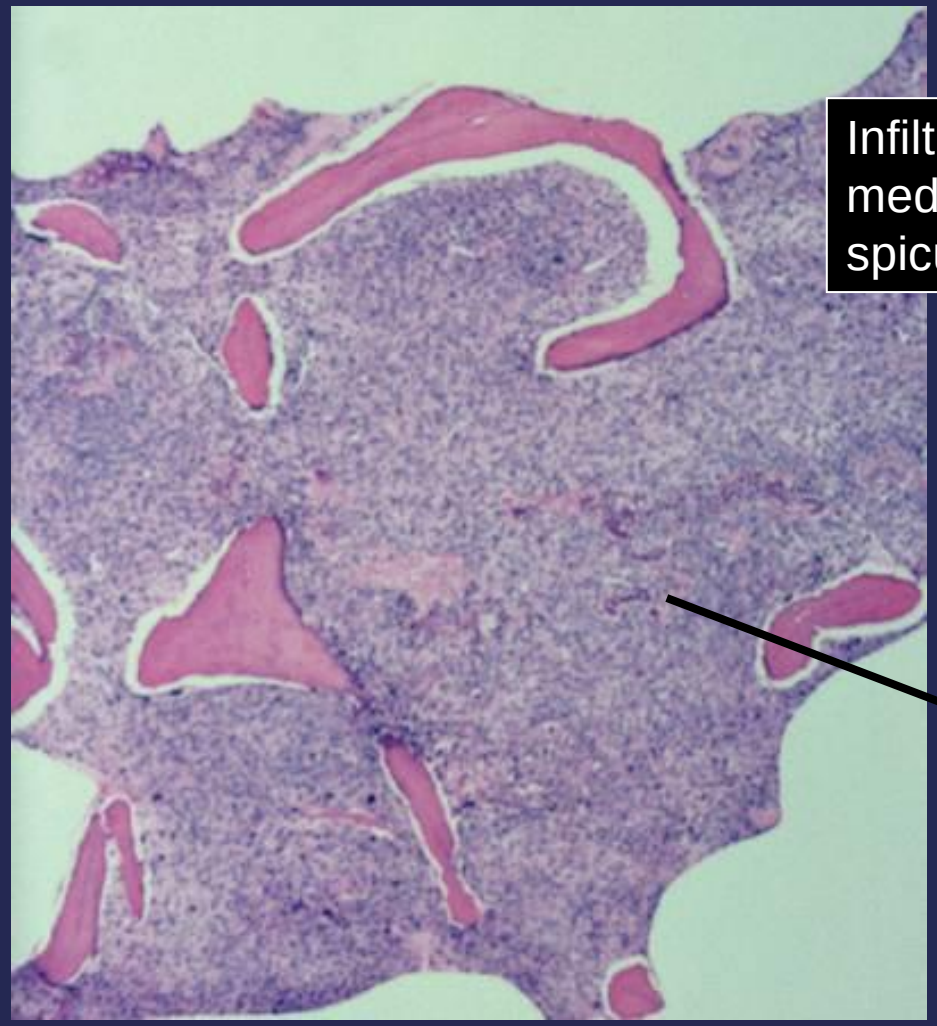
Small cell
- Focal features resemble EWS on histology



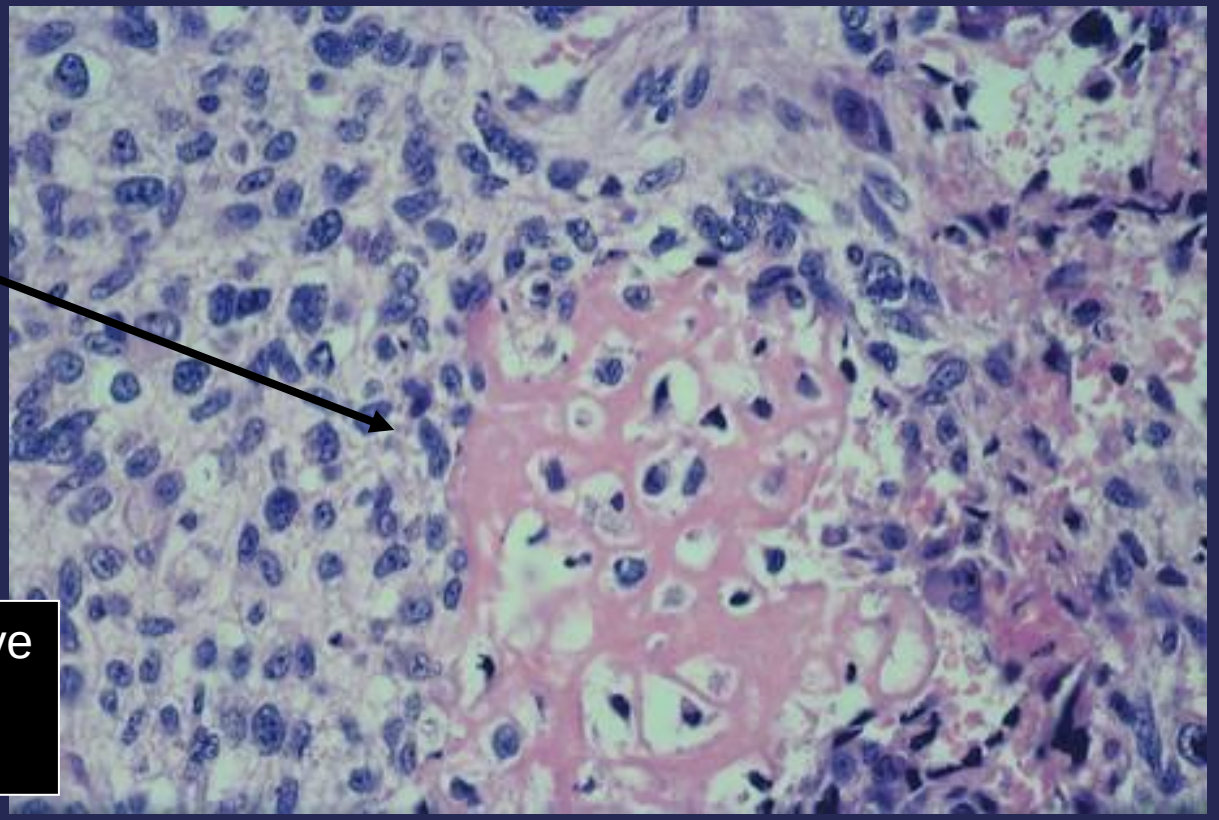
Osteoblastoma-like
- Mimics osteoblastoma

Extraosseous
- Mimics myositis ossificans

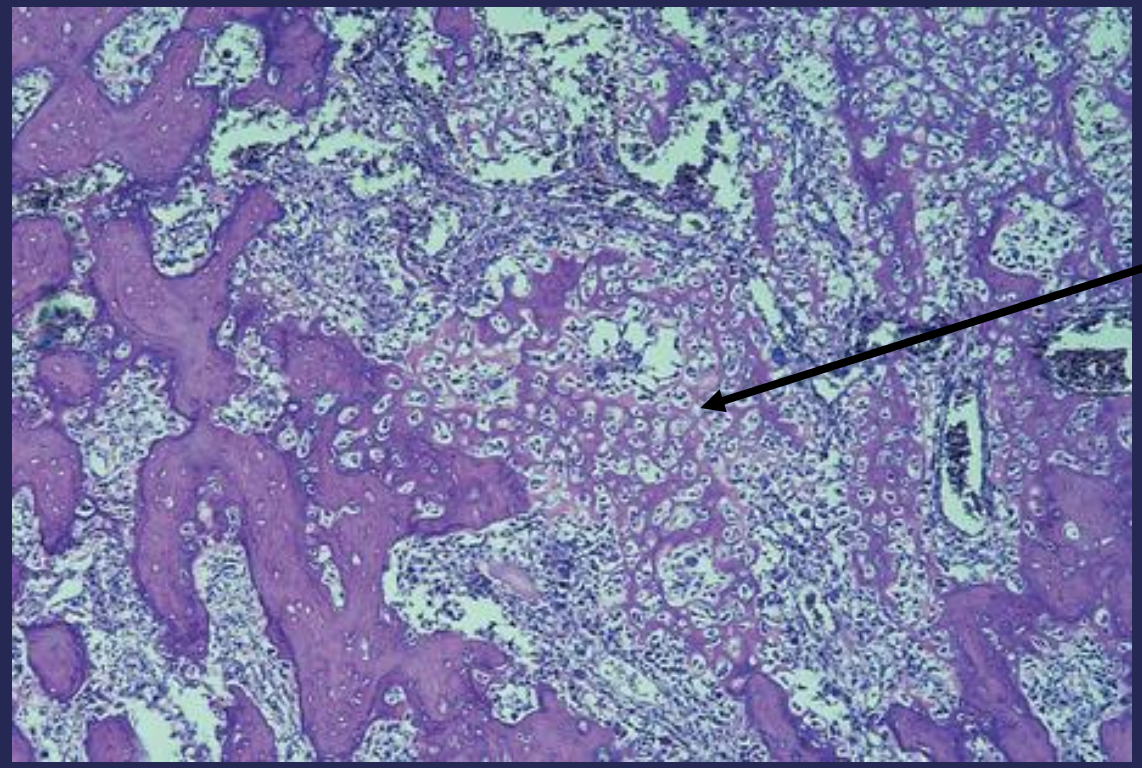

Spicules of bone radiating from bone surface gives “sunburst appearance
Codman’s triangle forms as tumor elevates the periosteum
Fleshy area with increased cellularity is radiolucent on imaging
Cloud-like appearance due to bone matrix formation



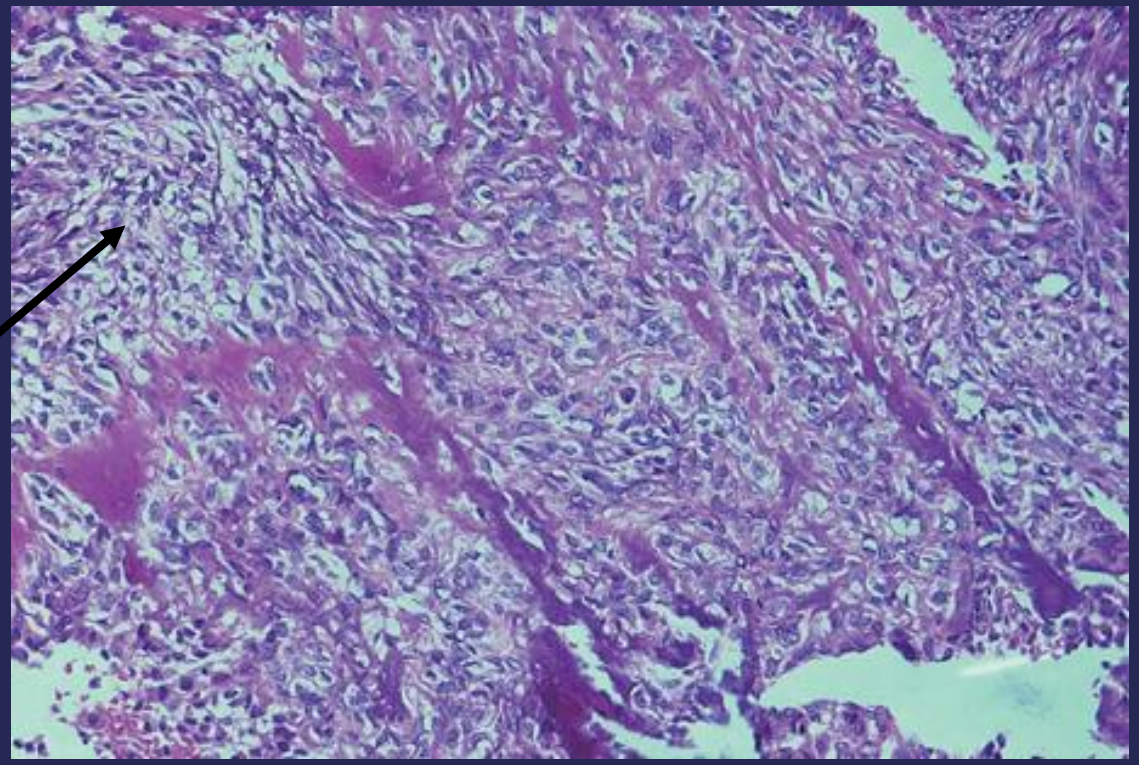
Infiltrative pattern of growth with tumor filling the medullary cavity and entrapping the pre-existing spicules of lamellar bone.



The tumor is composed of mitotically active cytologically malignant cells with areas of osteoid formation



Chondroblastic differentiation



Fibroblastic differentiation with spindled malignant cells, osteoid, and poorly formed woven bone that lacks osteoblastic rimming

Outcomes for Osteosarcoma

Patients with lung metastases at presentation

- 3 year survival
  - 1982 – 0%
  - 2009 – 50%

Patients with no metastasis at presentation

- Poor prognosis < 90% post-chemotherapy necrosis by microscopic evaluation
  - Survival rate at 8 years is < 70%
- Good prognosis > 90% post-chemotherapy necrosis by microscopic evaluation
  - Survival rate at 8 years is 70 to 87%

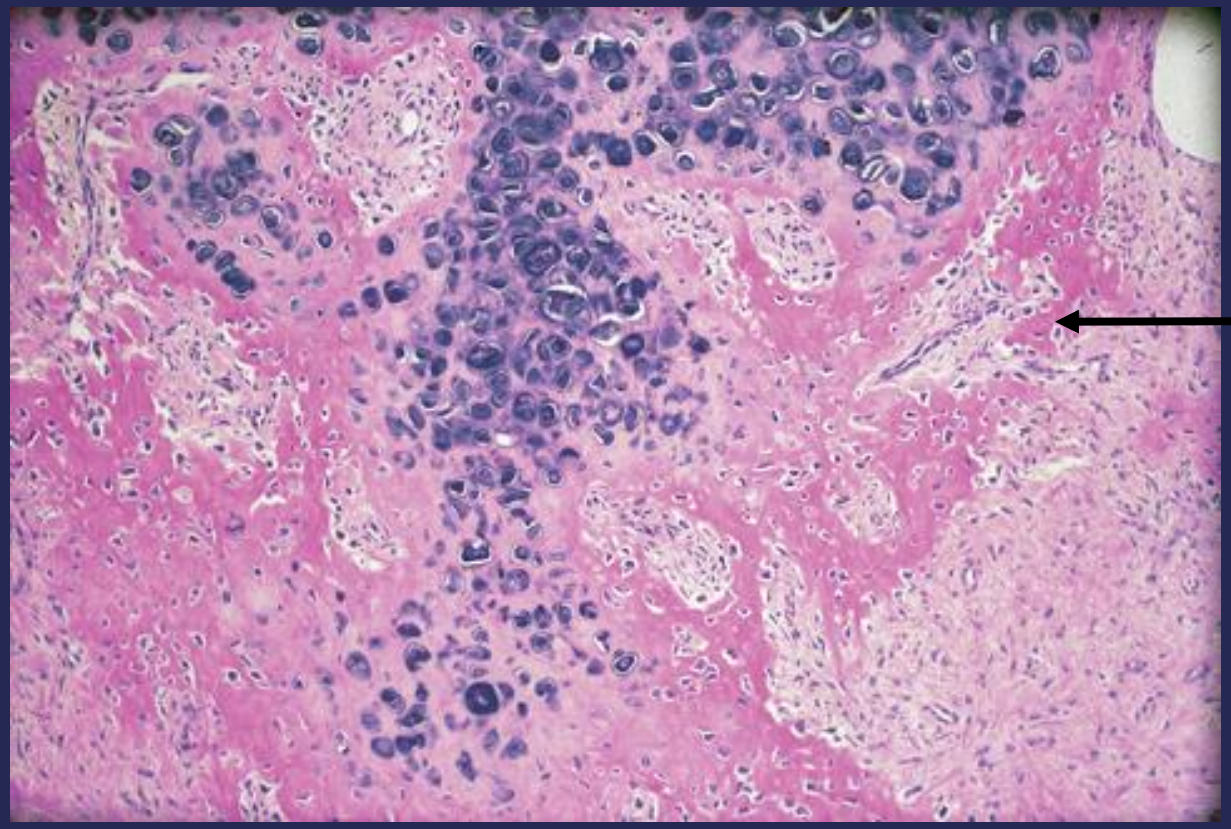
Differential Diagnosis

Fracture Callus

- Zonation with orderly transitions between fibroblastic tissue, cartilage and woven bone
- Orderly enchondral ossification
- Orderly spindle cell proliferation which lacks atypia
- Orderly osteoid with reactive osteoblasts
- Orderly woven bone formation with osteoblastic rimming
- Orderly streams of osteoid and woven bone
- Orderly creeping substitution of osteoid along pre-existing bone

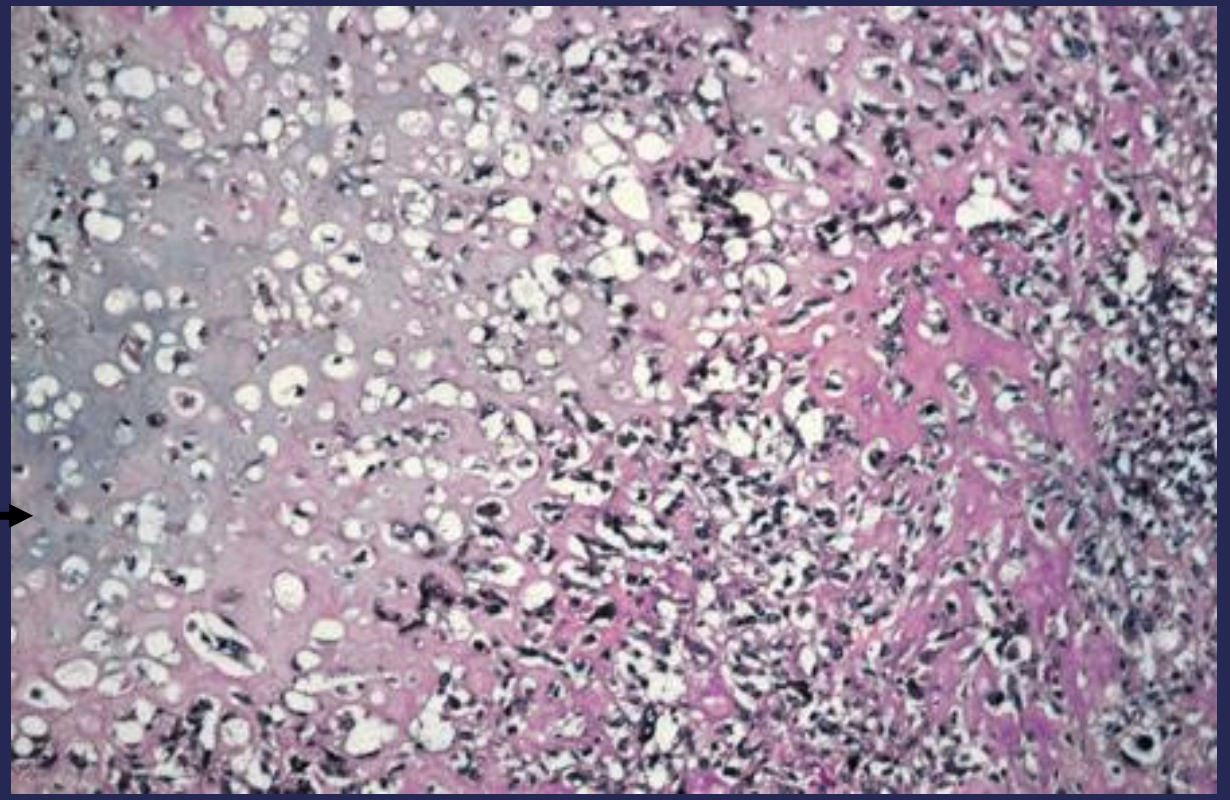
Osteosarcoma

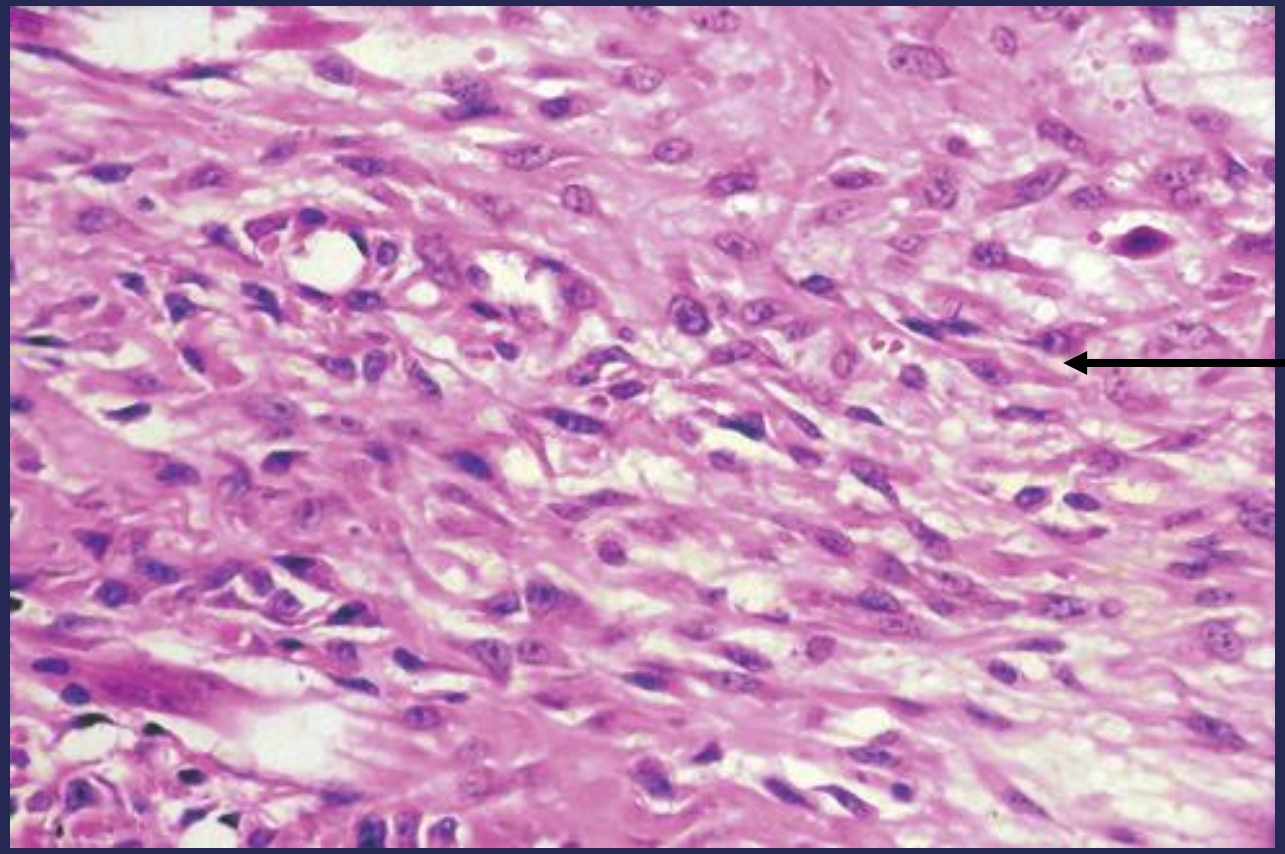
- Lack of zonation with disordered cartilage, osteoid and woven bone
- Disordered transition between cartilage and osteoid
- Disorderly and pleomorphic spindle cell population
- Disorderly osteoid (filligree and lacelike)
- Disordered woven bone or matrix mineralization with entrapping of malignant cells and lack of osteoblastic rimming
- Bizarre mineralization and architecture of woven bone
- Destructive cutting cones and bizzare enveloping of pre-existing bone



Fracture Callus:
Zonation with orderly transition between fibroblastic tissue, cartilage, and woven bone

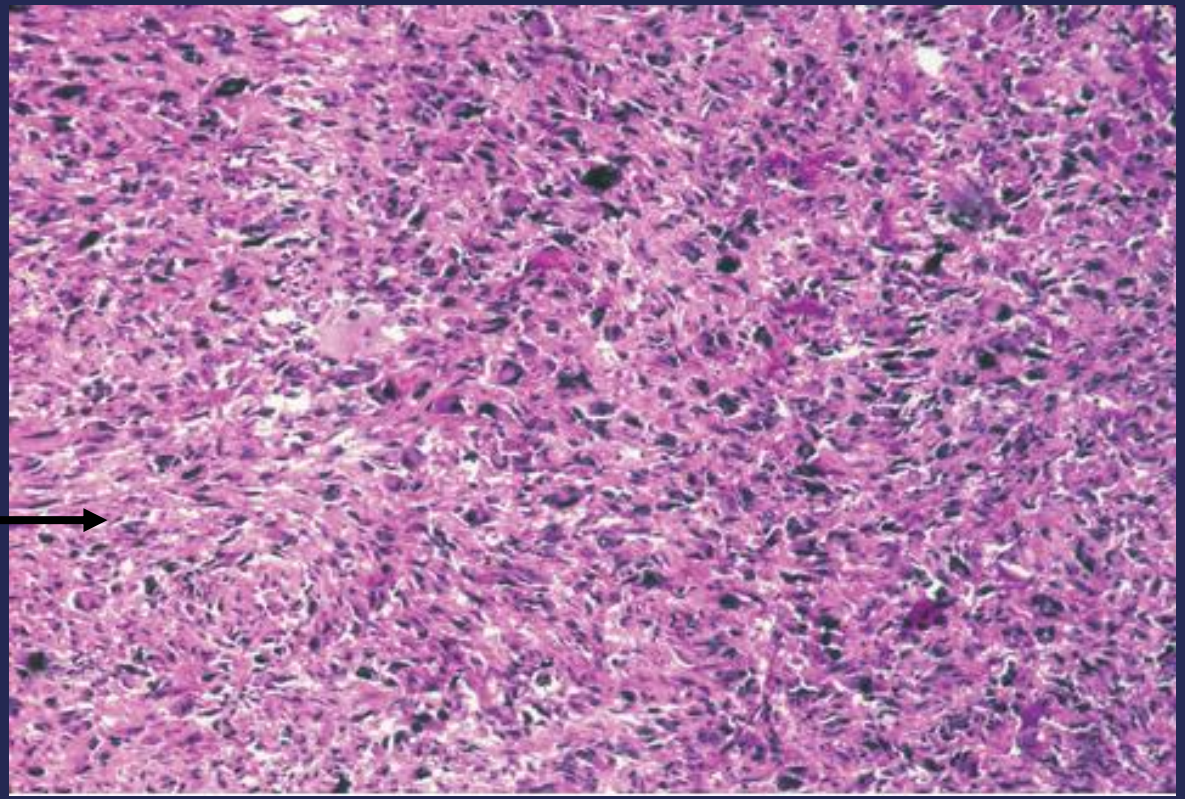
Osteosarcoma:
No zonation with disordered cartilage, osteoid, and bone formation

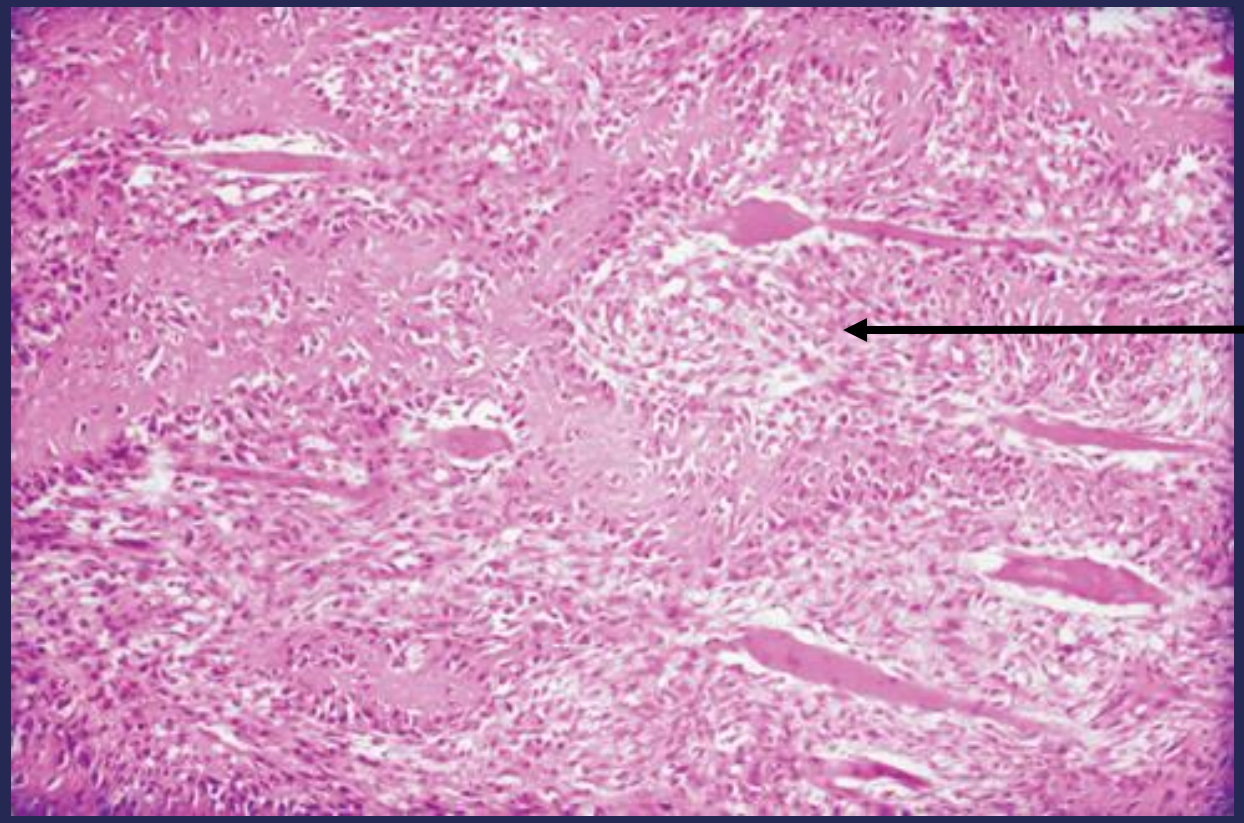




Fracture Callus:
Orderly spindle cell proliferation in the reactive fibroblastic tissue (uniform atypia)

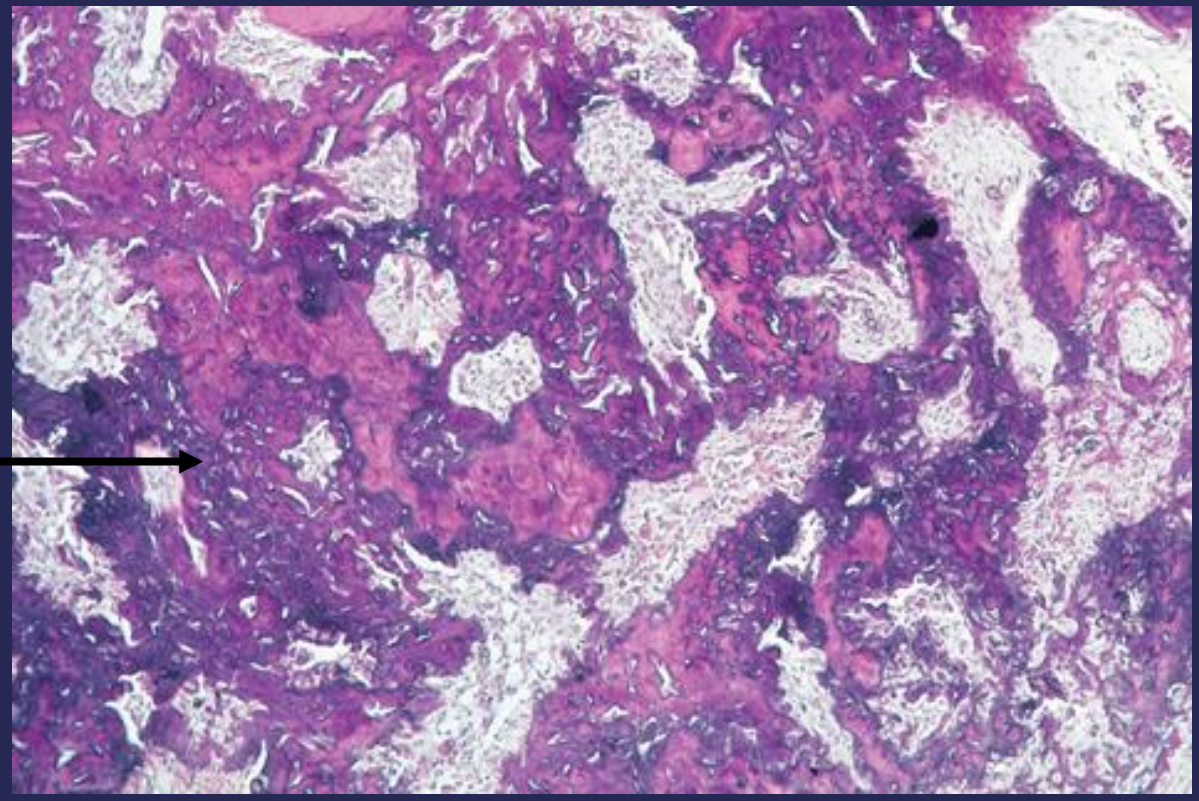
Osteosarcoma:
Disorderly spindle cell proliferation with pleomorphic spindle cells (non-uniform atypia)

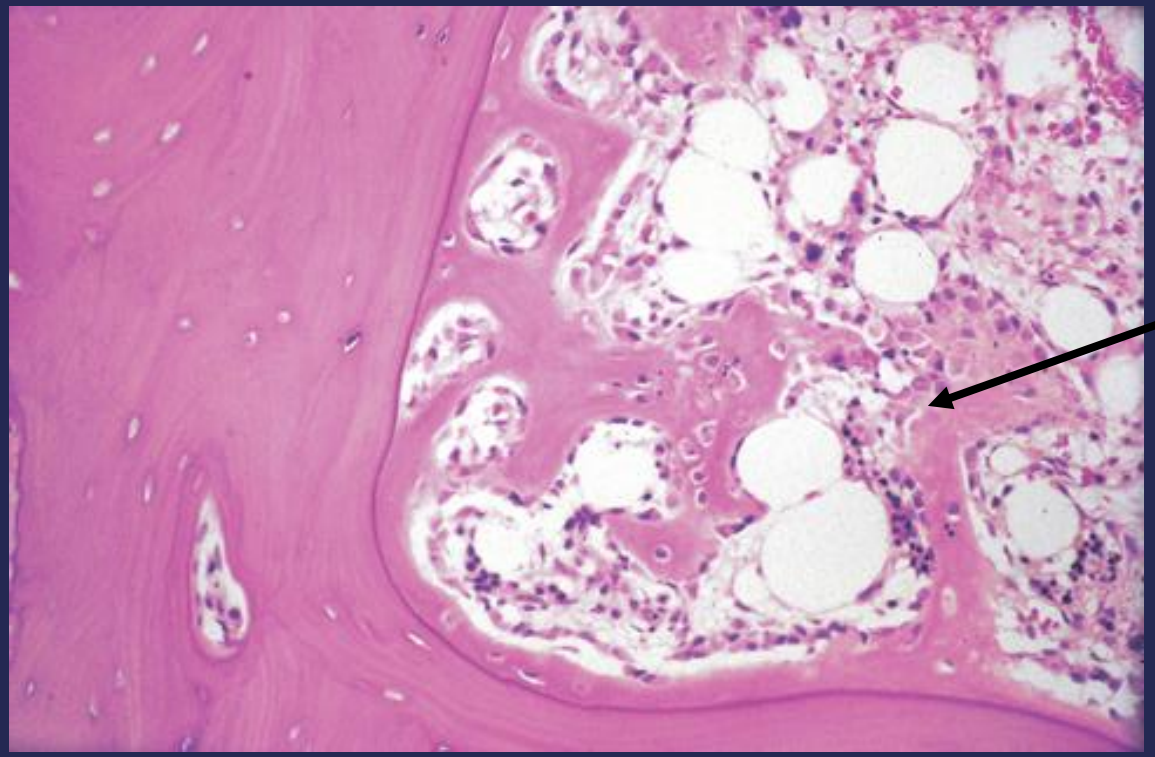




Fracture Callus:
Organized streams of osteoid and woven bone with prominent osteoblastic rimming

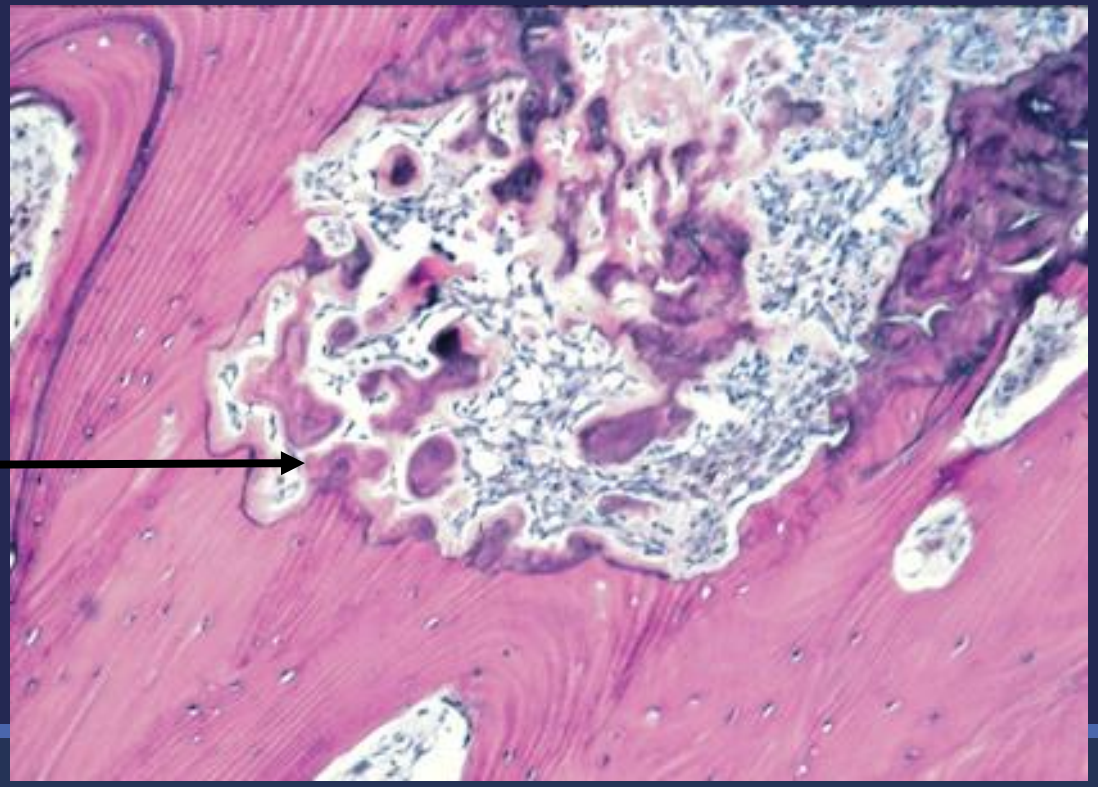
Osteosarcoma:
Bizarre mineralization and architecture of bone which lacks osteoblastic rimming





Fracture Callus:
Orderly creeping substitution

Osteosarcoma:
Disorderly and bizarre creeping substitution



Osteochondroma

Definition:

A benign growth on surface of a bone characterized by:

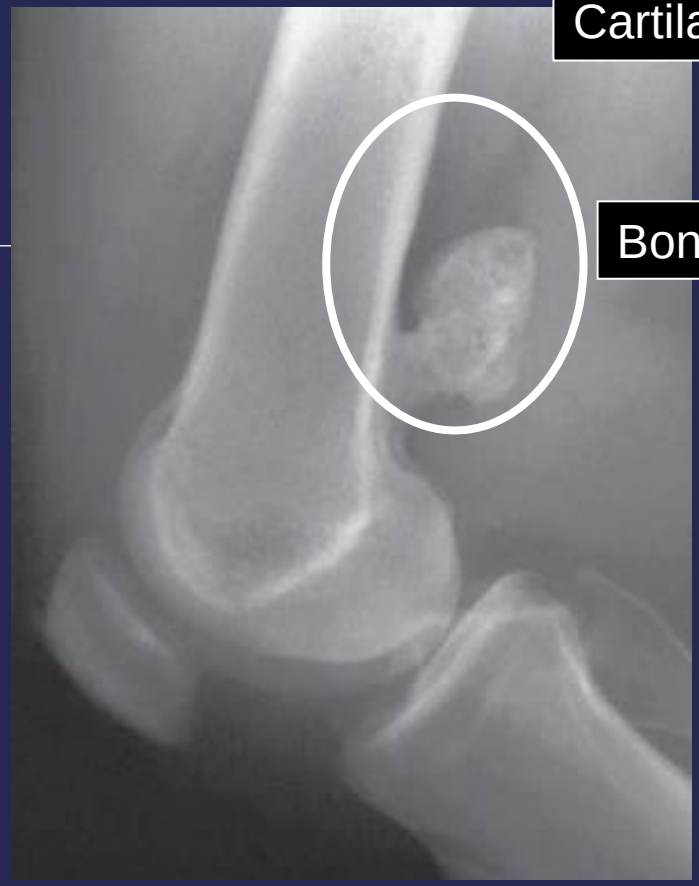
1. Cartilaginous cap
2. Zone of bone formation (ossification)
3. Continuity with underlying bone

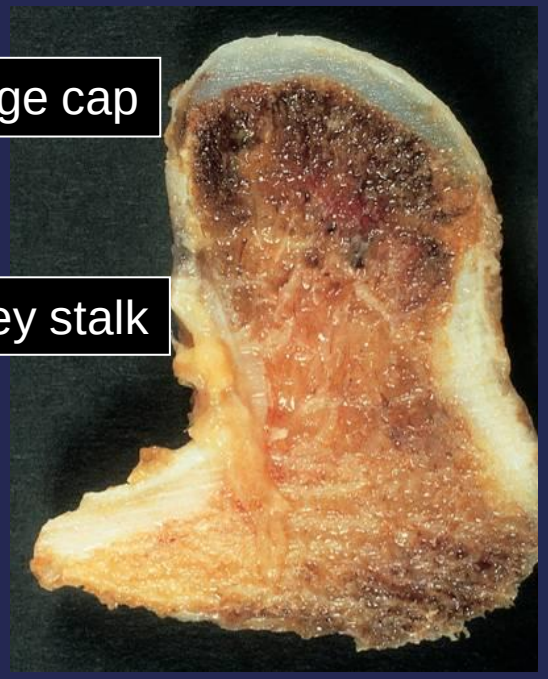
Clinical:

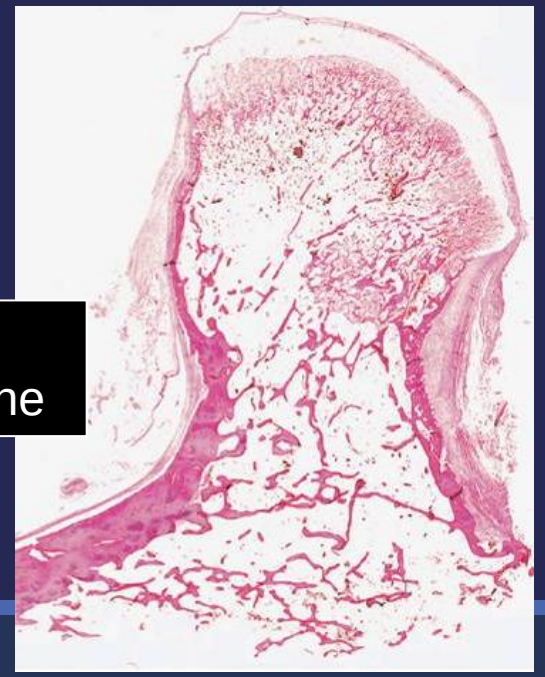
- 66% diagnosed before age 20 years
- Involves metaphysis of long bones
- 1% undergo malignant transformation to chondrosarcoma

Therapy is indicated for:

1. Pain resulting from fracture of the lesion
2. Impairment of articular function and motion
3. Excessive size
4. Unsightly deformity
5. Pressure on neurovascular structures (impingement syndromes)
6. Malignant transformation







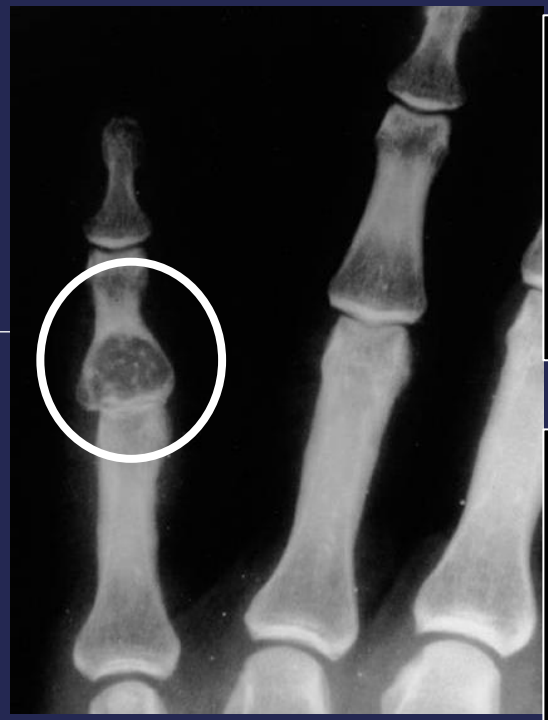
Continuity with marrow cavity of underlying bone

Enchondroma

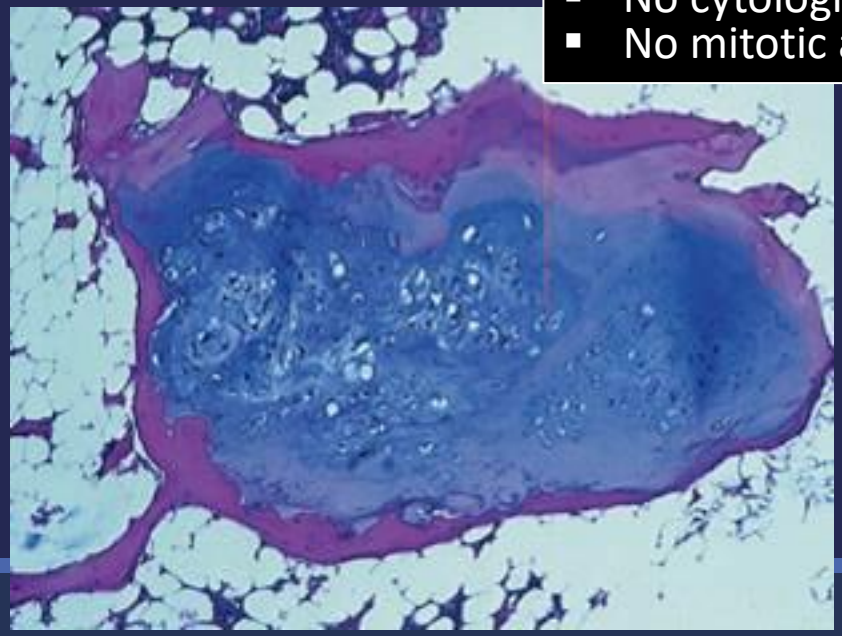
Definition:
- A benign cartilaginous located within medullary cavity of bone

Clinical:
- Commonly involves tubular bones of hands and feet
- May involve virtually any long bone
- Ages 20 and 40 years
- Usually asymptomatic and found incidentally unless causes pathological fracture
- Spontaneous pain more characteristic of chondrosarcoma

Therapy:
- Benign lesion treated with curettage



Imaging:
- Well defined lobulated lesion
- Thin sclerotic border
- Located in metaphysis
- Punctate calcifications
- Hot on bone scan due to mineralization



Micro:
- Lobulated islands of benign hyaline cartilage with thin rim of bone
- No infiltration of pre-existing bone
- No cytological atypia
- No mitotic activity

Chondroblastoma

Definition:

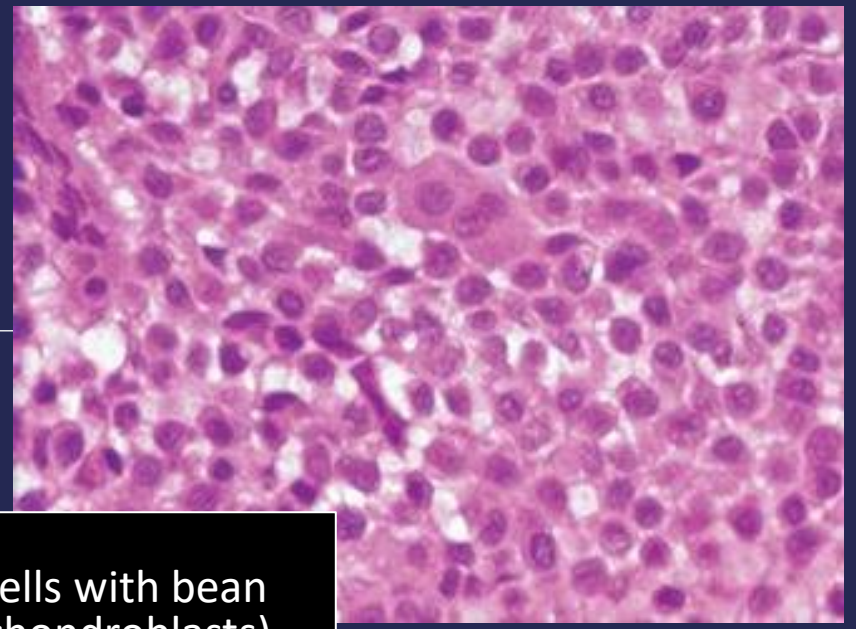
- A primitive cartilaginous tumor that arises in the epiphysis of skeletally immature individual

Clinical:

- Age 10 to 20 years (mean age 18 years)
- 58% lower extremity; 20% humerus
- Pain and tenderness around the joint adjacent to the lesion
- Impaired joint junction and joint effusion
- Intermediate lesion with 15% recurrence risk

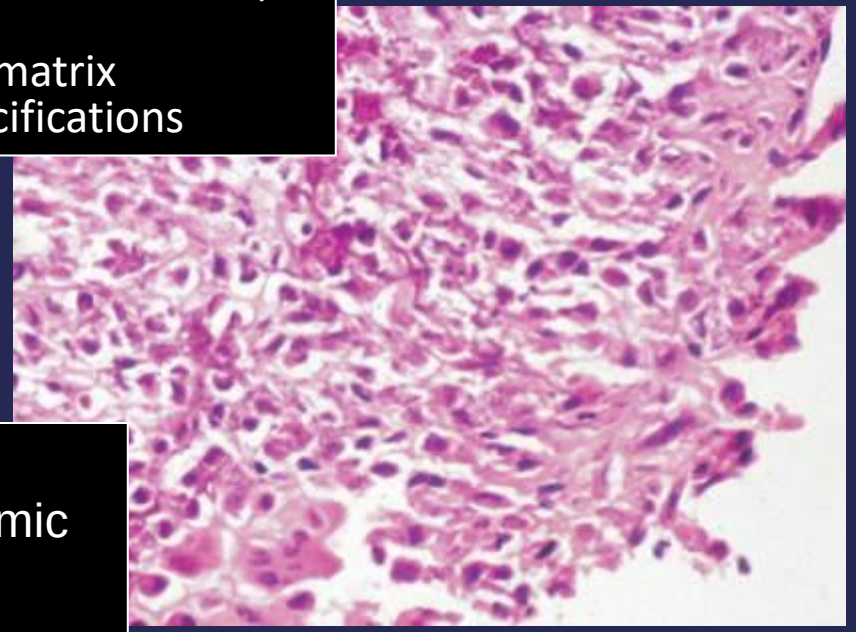
Therapy:

- Curettage with bone graft



Micro:

- Monomorphic cells with bean shaped nuclei (chondroblasts)
- Giant cells
- Pink chondroid matrix
- Chickenwire calcifications



Warning:

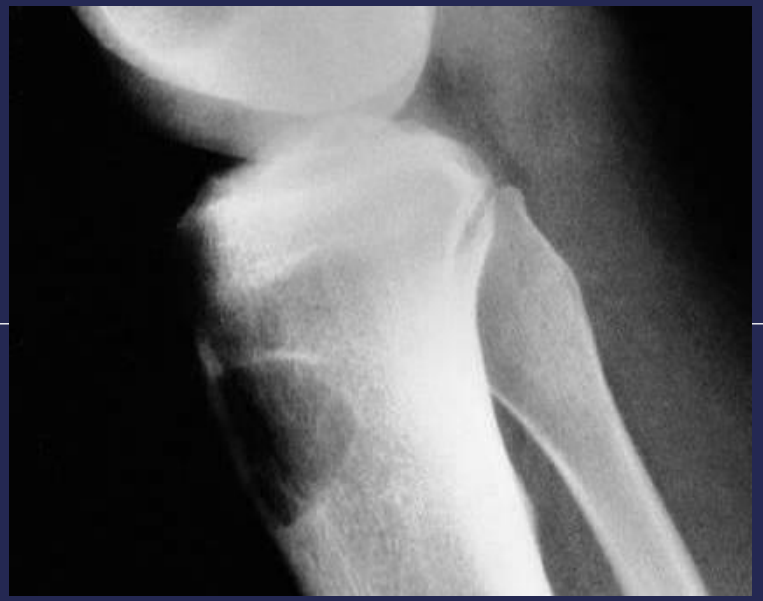
- Imaging and perilesional biopsy can mimic infection or inflammatory condition
- May be misdiagnosed as osteomyelitis

Chondromyxoid Fibroma

Definition:
- A lesion of bone that is composed of myxoid, fibrous, and chondroid-like tissue

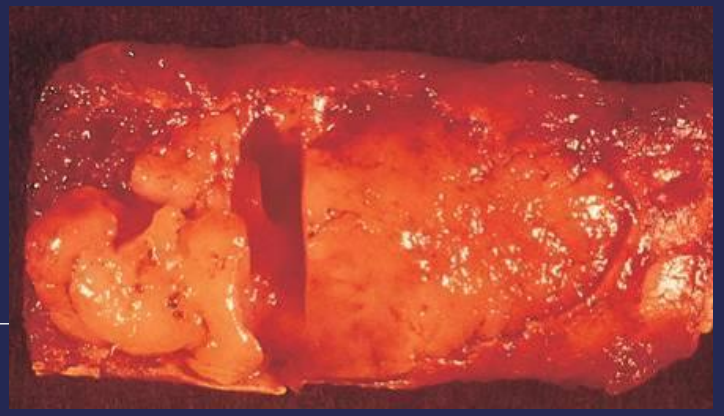
Clinical:
- 80% before age 40 years
- Lower extremity (especially bones around the knee)
- Pelvis
- Dull localized pain or swelling due to expansile growth
- Benign with high recurrence rate

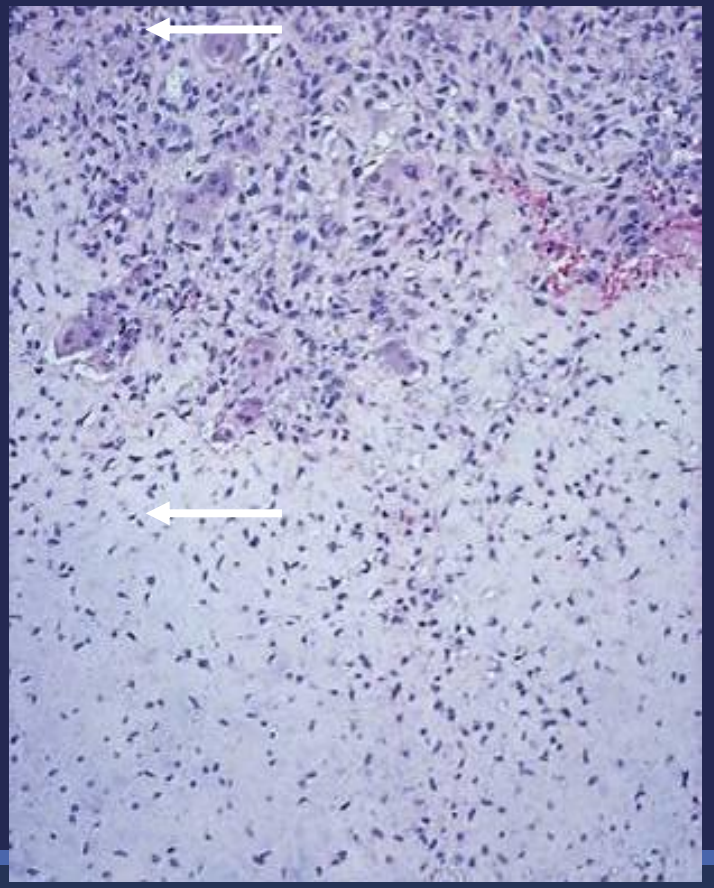
Therapy:
- Curettage ~ 80% recurrence rate
- Curettage and additional therapy ~ 20% recurrence rate
- Best outcome with en bloc resection



Imaging:
- Well circumscribed lytic lesion with faint sclerotic rim and cortical erosion

Micro:
- Hypocellular fibrous or chondroid appearing lobules surrounded by cellular zones with giant cells and spindled to stellate cells



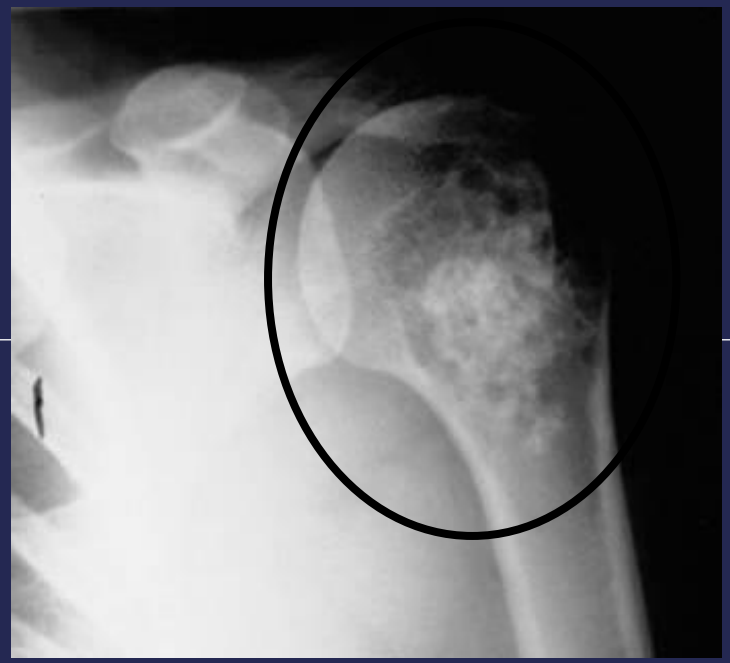


Chondrosarcoma

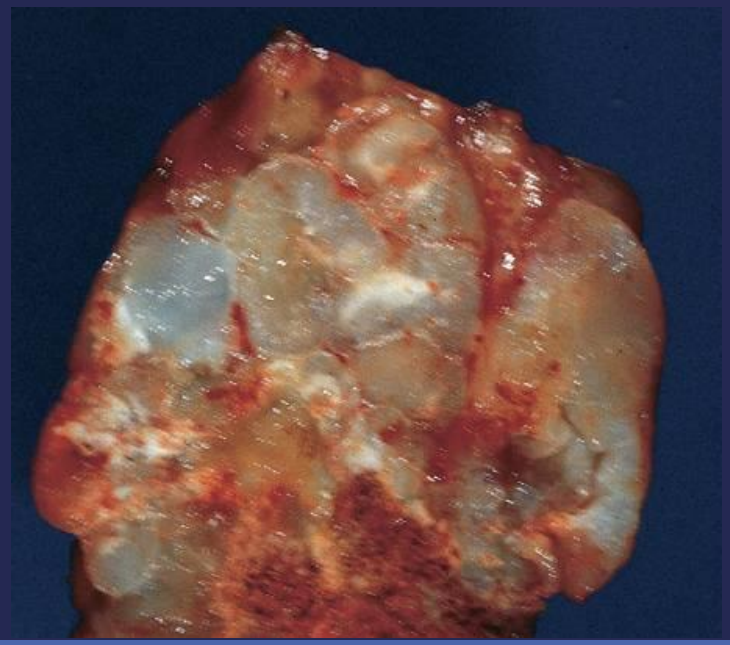
Definition:
- Malignant tumor characterized by production of cartilaginous matrix by the neoplastic cells

Clinical:
- Proximal long bones (proximal femur, proximal humerus)
- Axial skeleton (pelvis, ribs)
- Pain (constant not intermittent)
- Local swelling
- Pathological fracture

Therapy:
- Malignant tumor requires en bloc resection with clear margins
- Does not respond to radiotherapy or chemotherapy
- Some undergo dedifferentiation



Imaging:
- Lobulated lytic lesion
- Punctate calcifications
- Cortical erosion
- May have soft tissue extension



Gross:
- White - blue nodules of cartilage with expansile and permeative growth
- Soft gelatinous, firm cartilaginous, or slimy myxoid consistenty

Well Differentiated Cartilaginous Neoplasms

Enchondroma

- Cartilage nodularity is maintained
- Cartilage nodules are encased by host bone
- Enchondral ossification at the periphery of the lobules
- Cartilaginous matrix is homogeneous

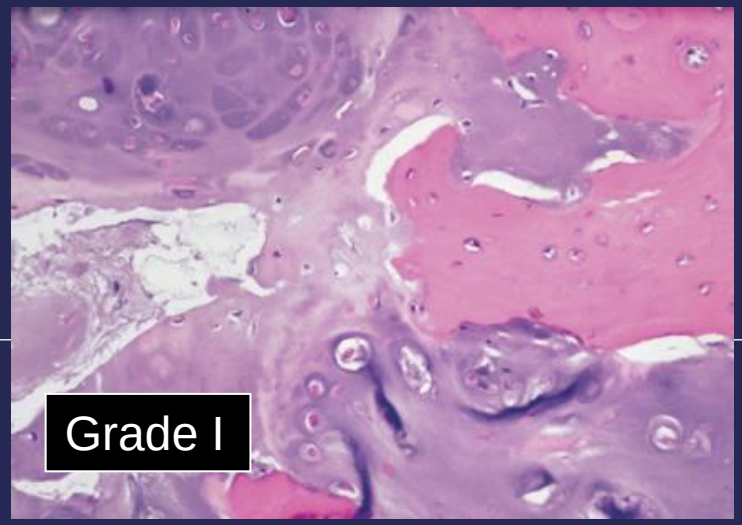
Low Grade Chondrosarcoma

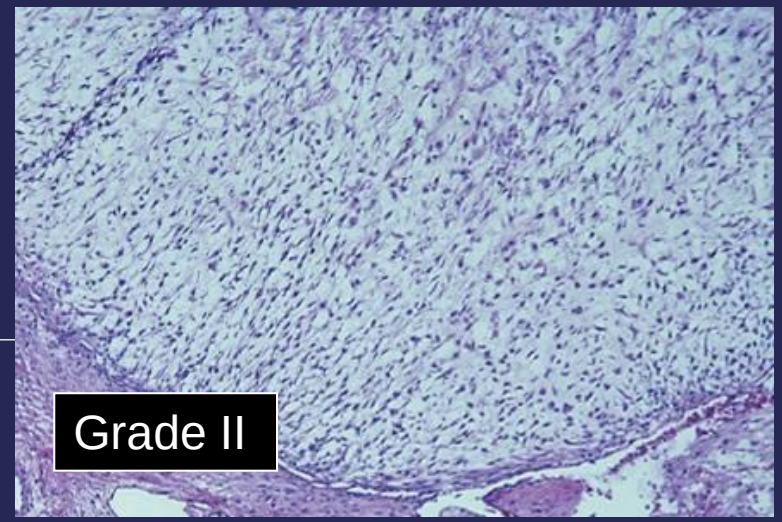
- Cartilage infiltrates and entrap host lamellar bone spicules
- Cartilage nodules penetrate cortical bone and are not encased by host bone
- Cartilage grows too fast to be encased by peripheral rim of ossification
- Cartilage matrix is nonhomogeneous with variable intensity of matrix staining and myxoid change

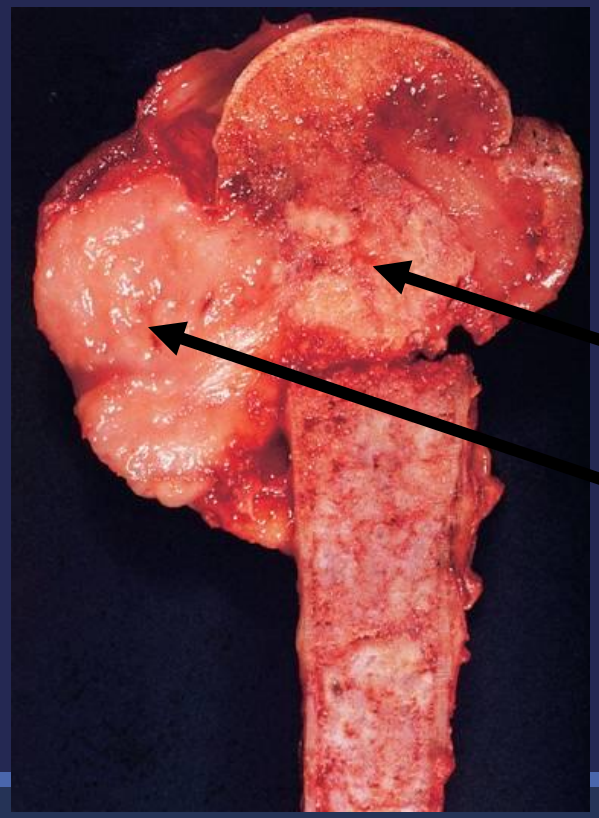
Chondrosarcoma

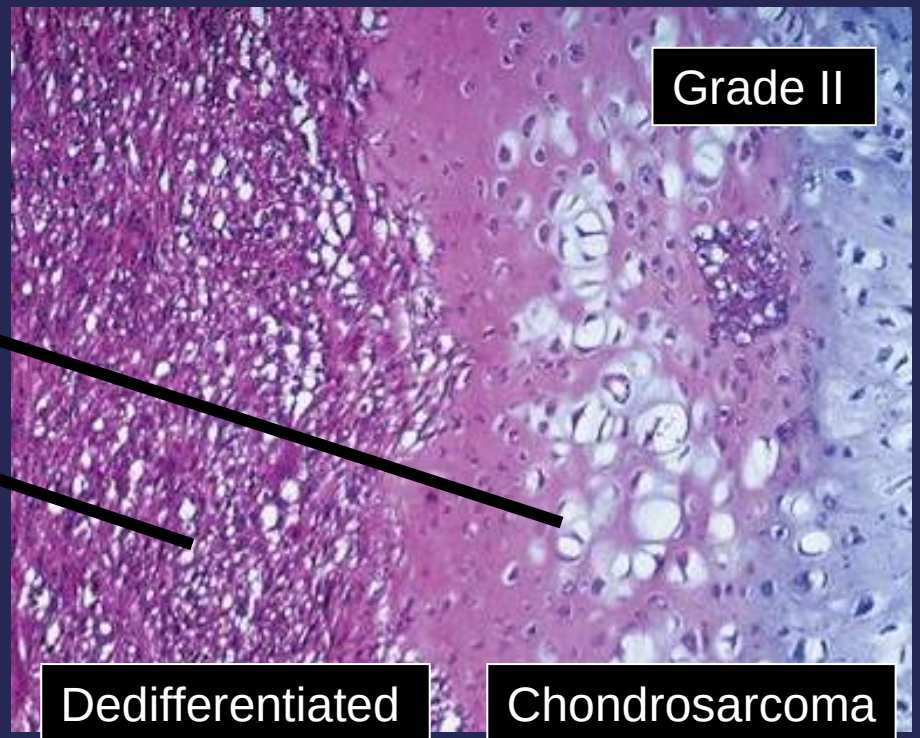
Micro:

- Low grade lesions resemble enchondroma but erode cortex and cause pain
- Main discriminating feature of low grade lesions on histological evaluation is infiltration of pre-existing lamellar bone
- High grade lesions are cellular with cytological atypia, marked myxoid alteration, and mitotic activity
- Dedifferentiation is characterized by abrupt transition to a distinct non-cartilaginous component (fibrosarcoma, osteosarcoma, rhabdomyosarcoma, pleomorphic undifferentiatedsarcoma)









Grading of Chondrosarcoma

Grade I
- Lobules of cartilage with infiltrative growth
- Rare myxoid or cystic change
- Two or more cells per lacunae (binucleation)
- Slight increased cellularity
- Slight variation in size and shape of nuclei

Grade II
- Lobules of cartilage with infiltrative growth
- Increasing myxoid or cystic change
- More frequent binucleation
- Greater cellularity (some sheet formation)
- Greater variation in size and shape of nuclei

Grade III
- Lobulated growth pattern may be absent
- Marked binucleation, nuclear variability, mitotic activity
- Marked cellularity (sheets of cells)
- Abundant myxoid change and chondroid differentiation is less obvious
- Spindle cell areas and giant cells are present

Prognosis for Chondrosarcoma

- Biological Behavior:
  - Slow growth and late metastasis
  - Venous invasion with hematogenous spread
  - Death due to metastasis or local tumor invasion
- Outcomes:
  - Overall - metastatic rate 16%, 10 year survival 50%
  - Grade I - metastatic rate 5%, mortality rate 20%
  - Grade II - metastatic rate 14%, mortality rate 60%
  - Grade III – metastatic rate 75%, mortality rate 88%
- Prognostic factors that influence survival
  - Tumor grade
  - Axial tumor location (worse prognosis)
- Independent risk factors for local recurrence and poor outcome:
  - Inadequate margins
  - Tumor size > 10cm

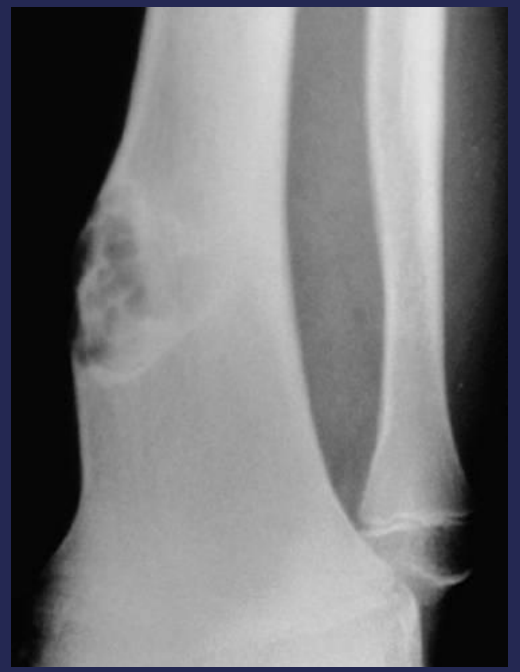
Fibrous Cortical Defect / Non-Ossifying Fibroma

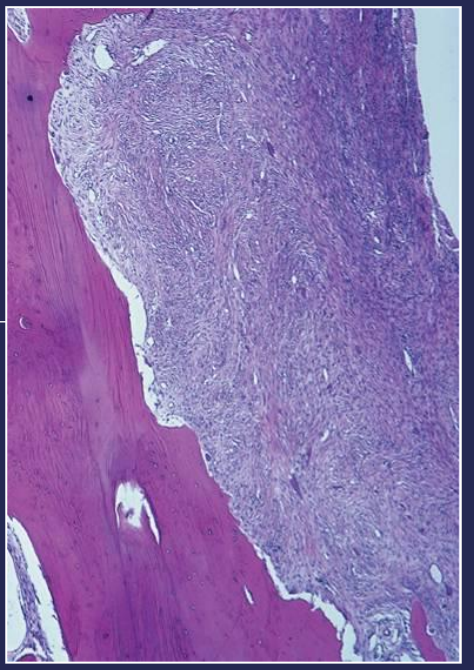
Fibrous Cortical Defect:
- A fibrous defect in the cortex of the bone that is thought to be developmental rather than a true neoplasm
- Size ~ 0.5 cm
- Incidental lesion in ~ 30% of normal children (age 4 to 8 years most common
- Regresses spontaneously or progresses to non-ossifying fibroma

Non-Ossifying Fibroma:
- A fibrous defect in the cortex detected as a larger lesion in an adolescent
- Presents with pathological fracture in adolescent
- Cortex of metaphysis
- Distal femur or proximal tibia

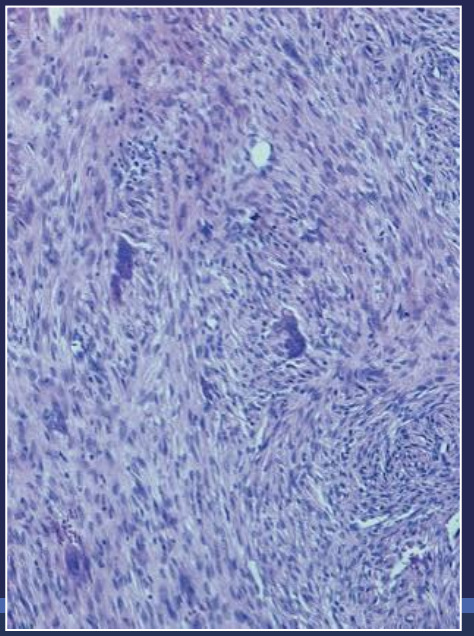
Therapy:
- Asymptomatic lesions may spontaneously regress and be replaced by normal cortical bone over time
- Progressive lesions may require biopsy and curettage to rule out other tumors and to prevent fracture.
- Good prognosis and tends not to recur following therapy

Imaging:
•Sharply defined lucency in cortex of metaphysis
•Rim of sclerosis





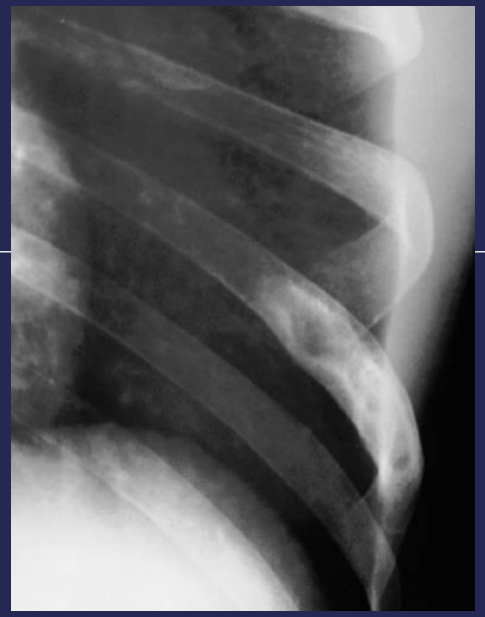
Micro:
•Bland fibroblasts
•Storiform configurations
•Foamy histiocytes
•Multinucleated giant cells



Fibrous Dysplasia

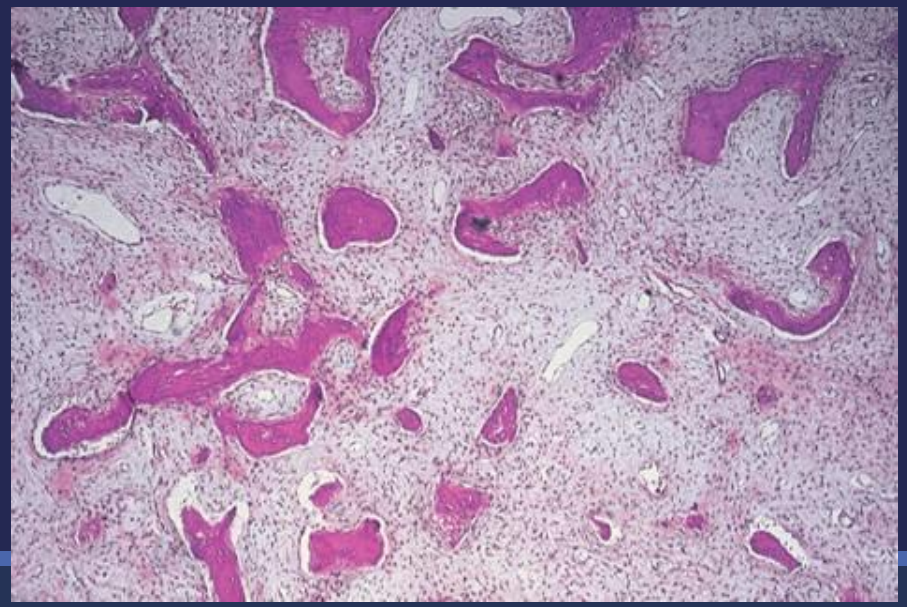
Definition:
- A developmental abnormality of the skeleton characterized by replacement of normal bone and marrow by fibrous tissue and irregular spicules of woven bone

Clinical:
- Well characterized clinical patterns:
  - Monostotic (one bone)
  - Polyostotic (multiple bones)
  - Polyostotic with café au lait spots and endocrinopathy (McCune-Albright syndrome)
- Child, adolescents, young adults
- Any type (tubular or flat) and any location of bone
- Most common in femur, tibia, rib, skull, mandible
- Surgical intervention for deformity or pathological fracture and bisphosphonates for bone pain
- May be complicated by development of sarcoma



Imaging:
- Well circumscribed solitary lesion with sclerotic rim
- Multifocal extensive lesion with bone deformity
- Ground-glass appearance
- Bone expansion and distortion

Micro:
- Curvilinear trabeculae of woven bone
- Fibrous background
- Lack of osteoblastic rimming



Undifferentiated Pleomorphic Sarcoma of Bone (MFH of Bone)

Definition:

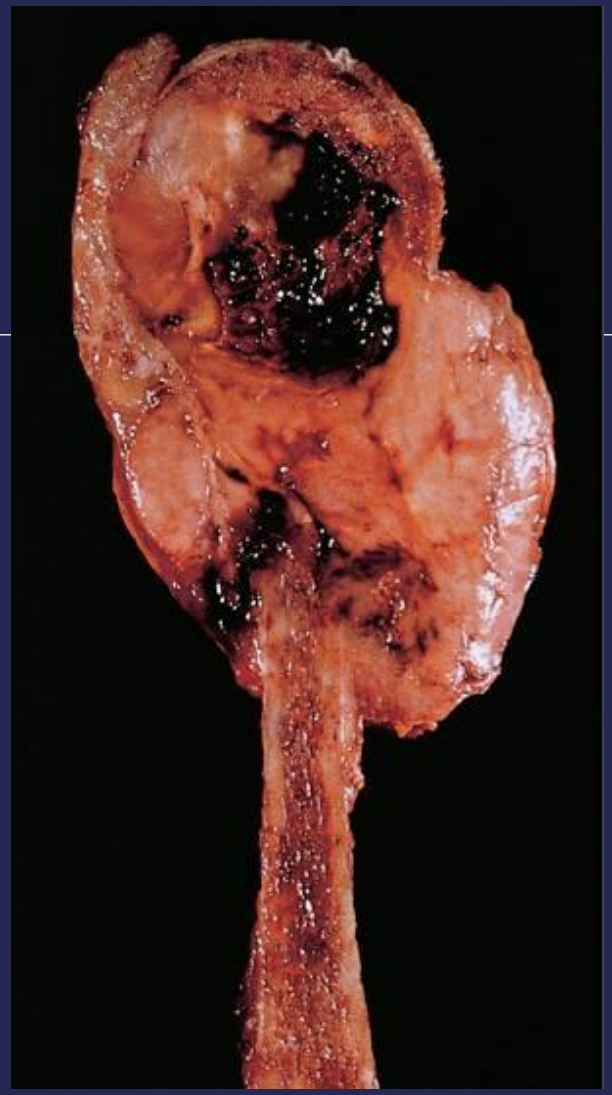
• A high grade malignant neoplasm of bone that exhibits no particular specific differentiation and is characterized by pleomorphic tumor cells and fibrous background

Clinical:

• Enlarging painful mass in metaphysis of long bone or pelvic flat bones
• Middle aged to elderly adults
• Predisposing factors
    • Bone infarct
    • Paget disease
    • Irradiation

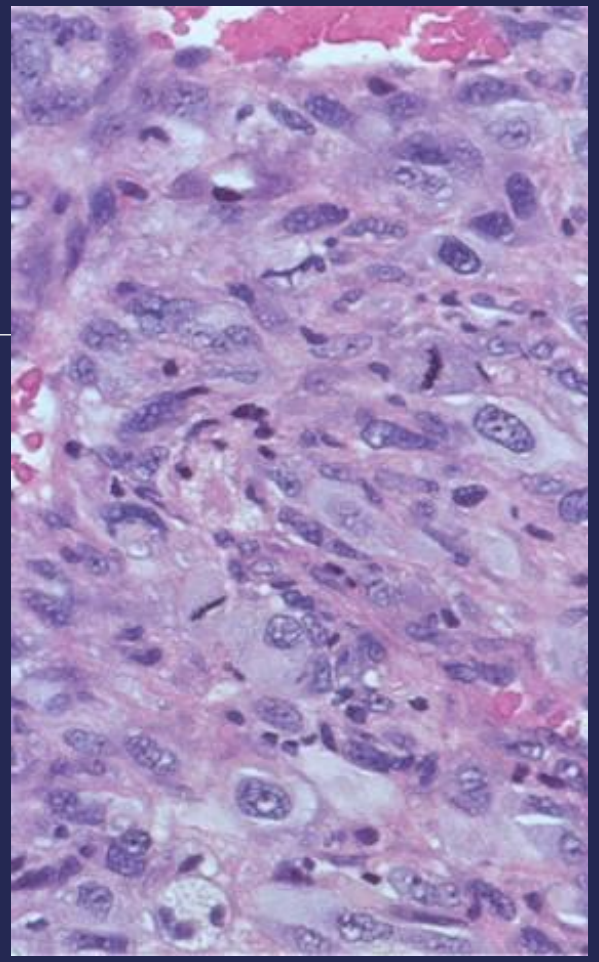
Therapy:

• Radical resection and radiation therapy
• Poor prognosis



Gross:

• Fleshy hemorrhaging and necrotic tumor in bone and extending into soft tissue



Micro:

• High grade pleomorphic malignant neoplasm with brisk mitotic rate, atypical mitoses, and fibrous background

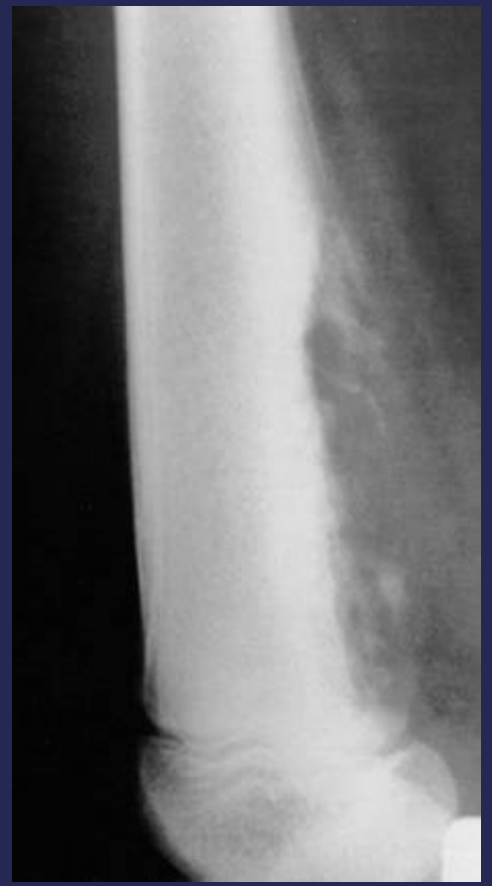
Ewing Sarcoma / PNET

Definition:
- A malignant tumor characterized by rearrangement of the EWS gene locus on chromosome 22 and small round blue cell morphology with variable neuroectodermal differentiation
- Ewing sarcoma – more primitive
- Primitive neuroectodermal tumor – more neural differentiation

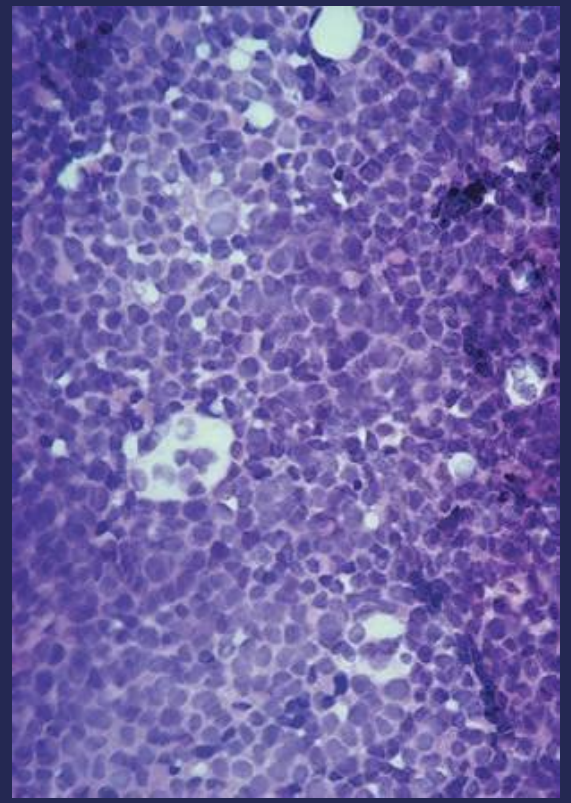
Clinical:
- Marked predilection for caucasians
- Long bones (especially femur)
- Flat bones (especially pelvis)
- Practically speaking - any bone or soft tissue
- Painful warm tender mass (mimics infection), pathological fracture
- Systemic findings: fever, ↑ESR, anemia, leukocytosis

Therapy:
- 80% less than age 20 years (but seen in all ages)
- Surgery = five year survival 5-15%
- Chemotherapy + Surgery = five year survival 75%

Imaging:
- **Destructive lytic lesion in medullary cavity**
- **Diaphysis and metaphysis**
- **Soft tissue extension**
- **Onion skin periosteal reaction**
- **Sunburst periosteal reaction**

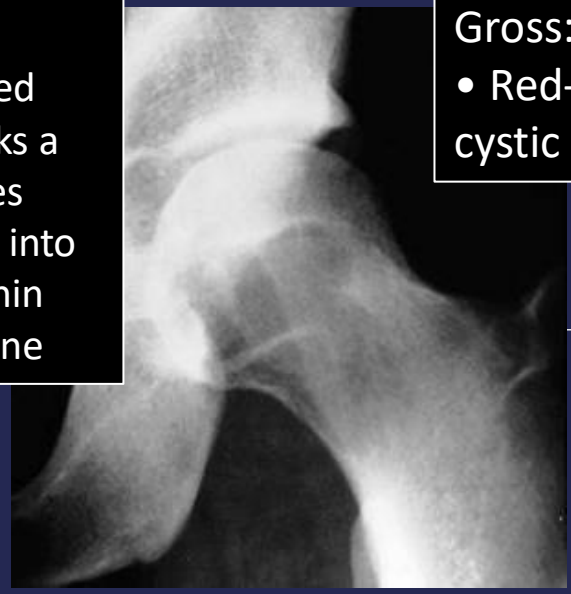


Micro:
- **Sheets of uniform round blue cells with little supportive stroma**
- **Occasional fibrous septa**
- **Homer-Wright rosettes (tumor cells arranged in circle around pink fibrillary material)**

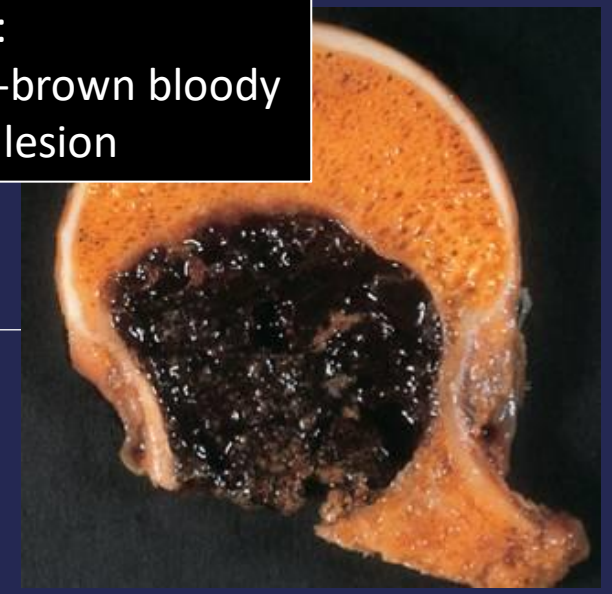


Giant Cell Tumor of Bone

Imaging:
• Well circumscribed lytic lesion that lacks a sclerotic rim, erodes bone, and expands into soft tissue with a thin shell of reactive bone



Gross:
• Red-brown bloody cystic lesion



Definition:
• A locally aggressive tumor composed of osteoclast-like giant cells and mononuclear cells derived from hematopoietic elements and an inconspicuous bone-derived spindle cell component.

Clinical:
• Young adults (age 20 to 40 years)
• Epiphysis and metaphysis of long bones
• Virtually any bone (most common around the knee)
• Enlarging mass with joint related symptoms
• Pathological fracture

Therapy:
• 40-60 % recurrence rate with curettage
• 4 % risk of lung metastasis

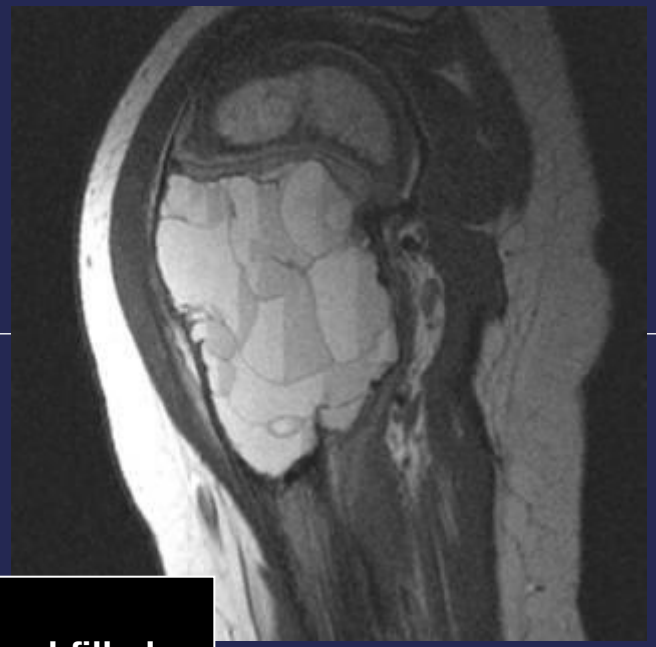
Micro:
• Uniform sheets of mononuclear cells with even distribution of osteoclast-like giant cells

Aneurysmal Bone Cyst

Definition:
- A bone tumor characterized by multiple blood-filled cystic spaces, 17p13 translocation, aggressive imaging features, and benign clinical behavior

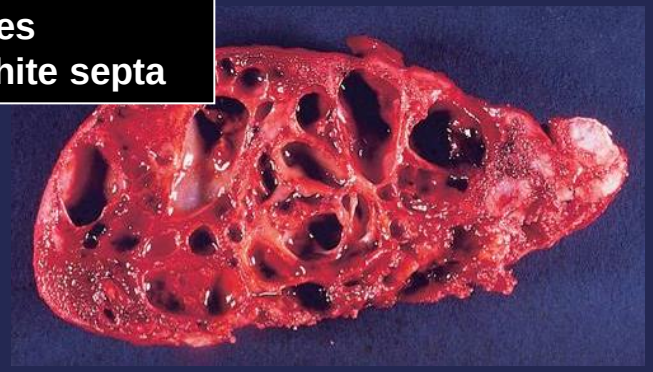
Clinical:
- Children, adolescents, young adults
- Metaphysis of long bones
- Posterior elements of vertebral column
- Pain, swelling, pathological fracture

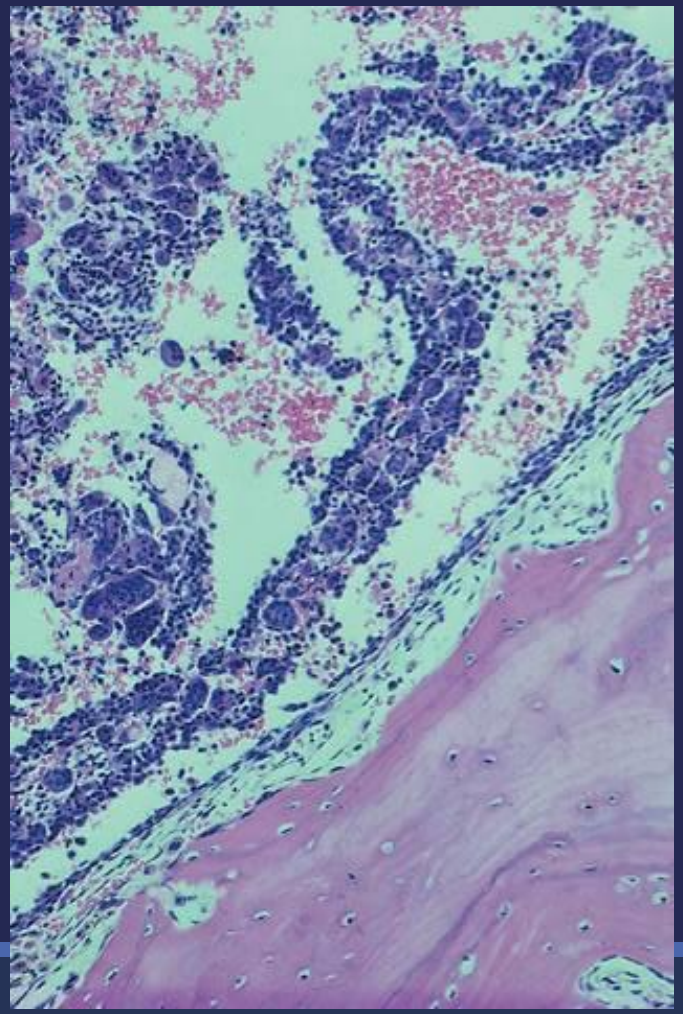
Therapy:
- Surgical curettage
- En bloc resection
- Low rate of recurrence



Imaging:
- **Eccentric**
- **Well demarcated lytic lesion**
- **Expansion of bone contour**
- **Peripheral shell of reactive bone**
- **Fluid levels**

Gross:
- **Multiple blood filled cystic spaces**
- **Thin tan-white septa**





Micro:
- **Blood filled cystic spaces**
- **Septa composed of plump uniform spindle cells, multinucleated osteoclast-like giant cells, and spicules of reactive woven bone**

I hope that this lecture is helpful to you in preparation for your examination!