

Bone Tumors

Normal Bone

Two main types of bone organization:
(highlighted by polarization)

Woven bone (Immature): collagen fibers are haphazardly arranged feltwork. Formed during ossification and rapid bone growth/repair (e.g, fracture callus). Relatively hypercellular with large cells.

Lamellar bone (Mature): collagen fibers are organized in parallel arrays. Formed through gradual remodeling of woven bone. In adults, almost all bone is lamellar. Hypocellular with small cells.

Two main types of mature lamellar bone architecture:

Cortical (Compact) Bone: Dense lamellar bone with Haversian canals surrounded by concentric lamellar units.

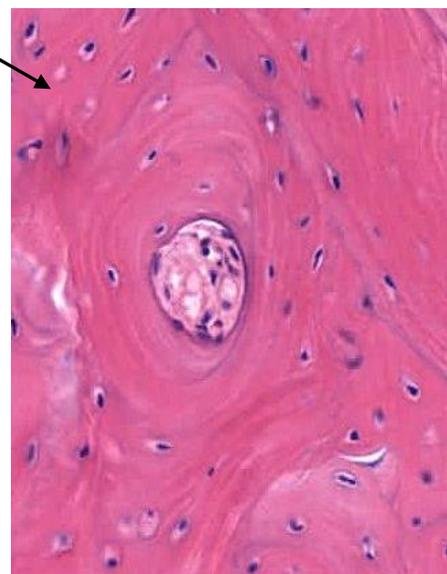
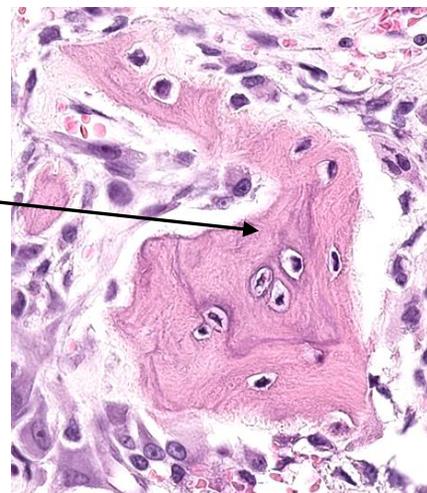
Trabecular (Cancellous) Bone: Connecting plates of lamellar bone

Tumor Bone: Typically, Woven bone. Mineralized or unmineralized.

Is that bone? It can sometimes be challenging to differentiate osteoid (unmineralized bone) from other collagen and extracellular material.

Some helpful hints:

- "**Cement lines**" (reversal lines) → thin, dark, linear lines are seen in osteoid, but not other substances (specific, but not sensitive)
- **SATB2** → Expression supports osteoblastic differentiation



Epidemiology

Overall primary clinically significant bone tumors are **rare**.

Benign, incidental benign tumors (like non-ossifying fibroma) are relatively common, but are often clinically insignificant.

Primary Bone **Sarcomas** have a **Bimodal distribution**:

First peak in second decade (teens with actively growing skeleton): 1) Osteosarcoma, 2) Ewing Sarcoma

Second peak after age 60: 1) Chondrosarcoma, 2) Osteosarcoma

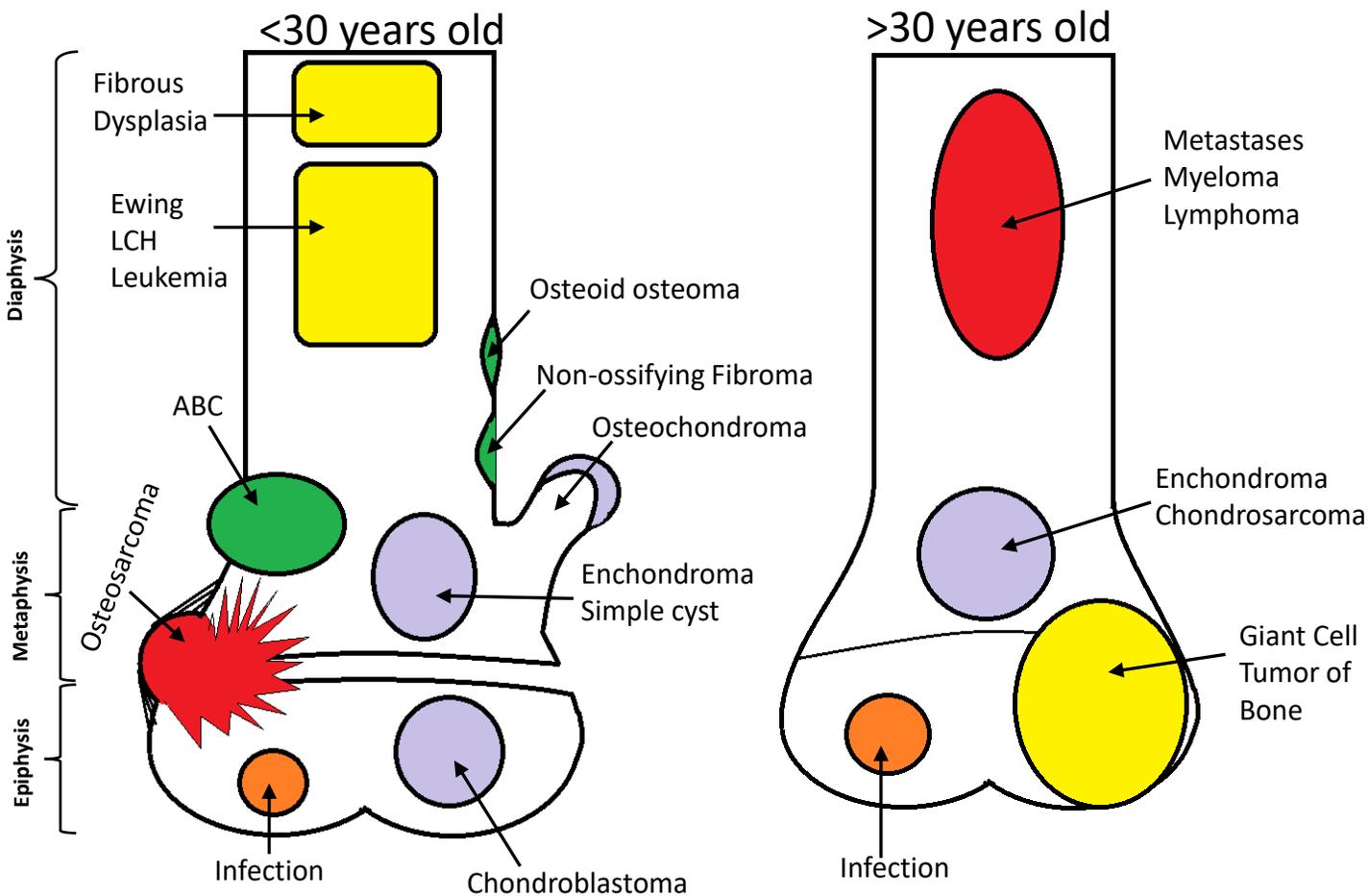
Although varies by tumor, for most, the most common location is **near the knee**, which is the site of the fastest growing growth plate.

Although most often *de novo*, conditions that predispose to osteosarcomas include: Radiation, Paget's Disease, Chronic Osteomyelitis, Bone infarcts, and prosthetic joints.

Presenting symptoms: Often pain, which is classically worse at night, and a mass
Can have pathologic fractures, swelling, tenderness,

Anatomic Sites

Radiology is Essential for bone tumors!



Skeleton	< 30 years	> 30 years
Axial (skull, vertebrae, pelvis)	Osteoblastoma Langerhans cell histiocytosis ABC Hemangioma	Metastases Plasmacytoma Hemangioma Chordoma
Appendicular (arms and legs)	Most tumors. Osteosarcoma, Ewing sarcoma	Most tumors, Chondrosarcoma, Osteosarcoma
Acral (hands and feet)	Enchondroma	Enchondroma

Classic Specific Locations:

- Anterior Cortex of Tibia → Adamantinoma and Osteofibrous dysplasia
- Posterior Cortex of Distal Femur → Parosteal Osteosarcoma
- Clivus, Vertebral bodies, Sacrum → Chordoma
- Posterior Elements of Spine → Osteoblastoma

Osteogenic Tumors generating neoplastic bone.

Wondering if something you're seeing is true bone? **SATB2** stains osteoblasts and can be helpful

Osteoid Osteoma

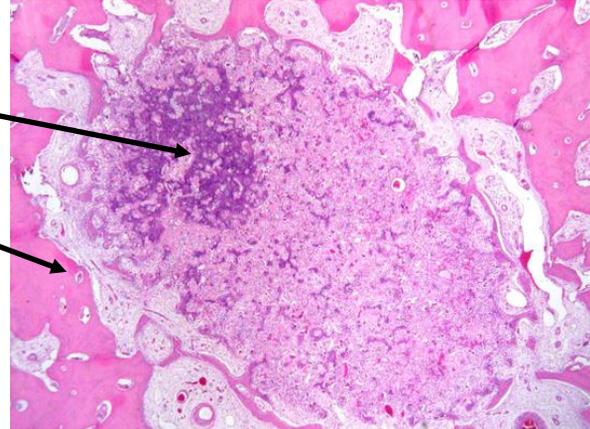
Benign. Often in the cortex of long bones.

<2 cm central **nidus** composed of microtrabecular woven bone rimmed by plump, bland osteoblasts in vascularized stroma. Often **surrounded by sclerosis** with circumscribed, abrupt transition to normal bone at edge of nidus.

NO nuclear pleomorphism or cartilage

FOS gene rearrangements.

Often recognized radiographically and ablated.
Classically present with night pain relieved by NSAIDs.



Osteoblastoma

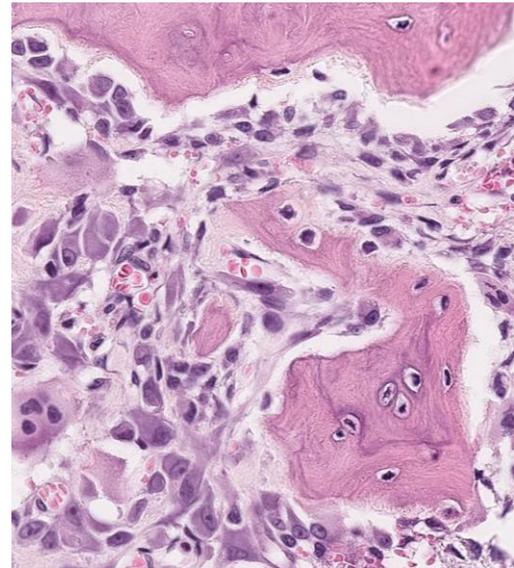
Benign. Often in the spine, particularly the neural arch.
Morphologically similar to osteoid osteoma (interconnecting delicate woven bone rimmed by a layer of plump osteoblasts)

But have growth potential and generally >2 cm.

Well-circumscribed without destructive invasion of bone (if see infiltration, consider osteoblastoma-like osteosarcoma)

FOS gene rearrangements.

Often recognized radiographically and ablated also.
Often present with pain/nerve compression symptoms, but not relieved by NSAIDs



Osteoma

Benign. Usually on face or jaw bones (sites of membranous ossification)

Often on the surface.

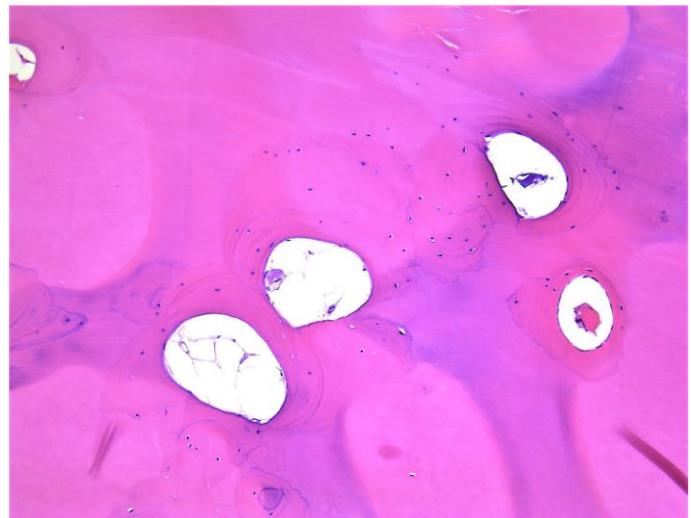
Composed of **lamellar/cortical-type bone**

Osteoblasts are inconspicuous

When develops in medullary cavity → use the term "Bone Island"

Multiple osteomas → seen in Gardner's syndrome (subset of FAP)

Generally require no treatment unless symptomatic



Conventional Osteosarcoma

High-grade sarcoma in which the tumor cells **produce bone**. Most common primary bone sarcoma. Most commonly metaphysis of long bones near the knee (site of most proliferative growth plates).

Imaging shows permeative bone destruction with fluffy immature mineralization and tumor ossification. Cortical disruption → Periosteal response → sunburst-like production of new bone → "Codman's Triangle"

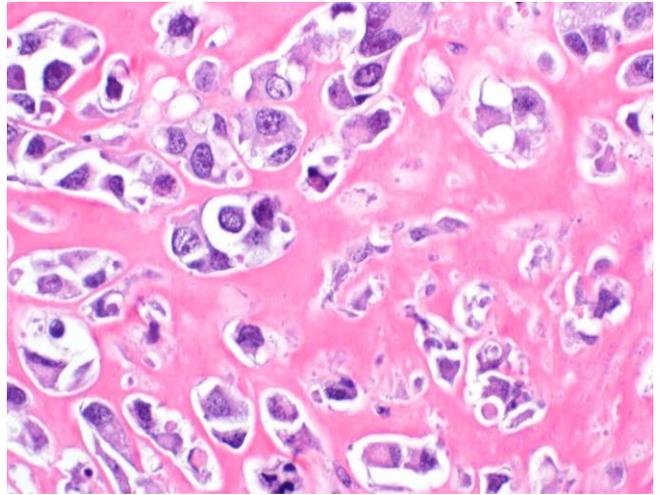
Histologic spectrum, but **requires neoplastic bone formation** (any amount is sufficient for Dx)

Bone is often intimately associated with the tumor cells and is woven with disorganized trabeculae. Bone matrix is eosinophilic (on H&E), often with purple mineralized "cement lines"

Infiltrative growth → replacing marrow space and eroding pre-existing bone

Often **high-grade cytologic atypia**, but tumor cells "normalize" (become less pleomorphic) when they are surrounded by bone matrix

Brisk mitotic activity. **Atypical mitoses** often present.



May have varying components including cartilaginous ("Chondroblastic osteosarcoma"), spindled cells ("Fibroblastic osteosarcoma"), Giant cells-rich, etc... → may only see this component on a small biopsy!

IHC: SATB2 can help identify osteoblasts. Frequently express EMA, cytokeratins, CD99, S100, and actins.

Molecular: Chromosomal instability (highly complex aneuploidy) due to chromothripsis and chromoplexy

Frequent TP53 and RB1 mutations → Increased risk in Li-Fraumeni and Hereditary retinoblastoma. Sometimes MDM2 amplifications → indicates likely arose from prior low-grade central osteosarcoma.

Aggressive tumors with local growth and rapid hematogenous dissemination, most frequently to the lungs. Often treated with pre-operative chemo → Resection → post-operative chemo

Histologic response to neoadjuvant chemotherapy is one of the most important prognosticators of survival (good response is >90% necrosis) → requires careful/extensive grossing and sampling

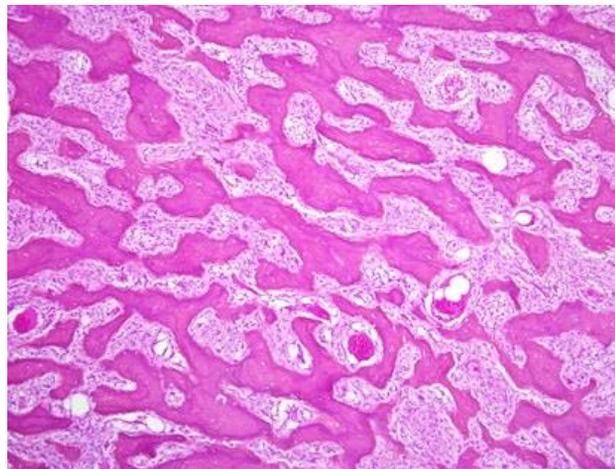
Low-grade Central Osteosarcoma

Low-grade malignant. Arises in the **intramedullary cavity**, most often in the metaphysis of long bones at the knee.

Moderately cellular **fascicles of spindled** cells with only mild nuclear atypia with admixed (usually woven) **neoplastic bone, which is composed of long and thick bony trabeculae**, often in parallel arrangement. Permeates host bone.

MDM2 amplifications.

Good prognosis if widely resected, but can dedifferentiate into conventional osteosarcoma.



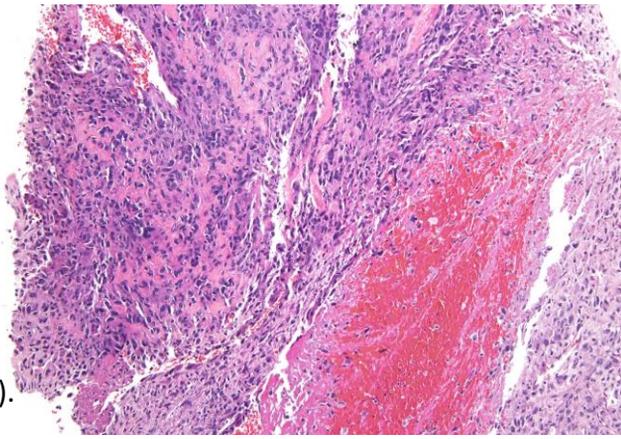
Telangiectatic Osteosarcoma

Closely resembles **aneurysmal bone cyst (ABC)**

Similar distribution to conventional osteosarcoma.

Blood-filled or empty cystic spaces separated by **fibrous septae of variable thickness with pleomorphic cells with significant nuclear atypia** and hyperchromasia and osteoclast-like giant cells

Frequent atypical mitoses. Often infiltrative.
Osteoid production is often focal (may be absent on biopsy).



Parosteal osteosarcoma

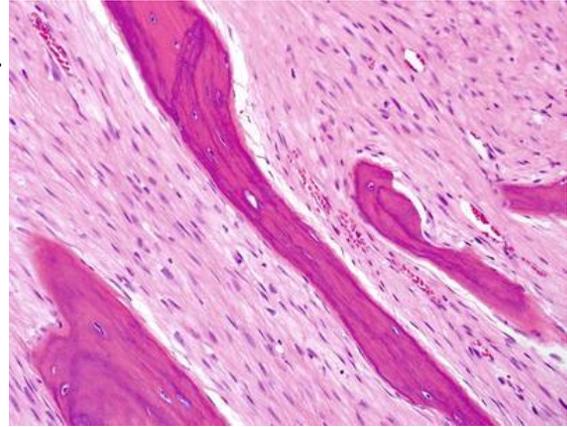
Parosteal location. Often posterior metaphysis of distal femur.
Exophytic, **lobular mass** on **bone surface**.

Low-grade spindle cell tumor with woven bone formation

Often hypocellular with minimal atypia and mitoses
Bone is often arranged in parallel, \pm osteoblastic rimming
 \sim 1/2 contain cartilage (either nodules or cap)

Molecular: **MDM2 amplifications** (from supernumerary ring chromosomes) (just like low-grade central osteosarcoma!)

Excellent prognosis. Can dedifferentiate.



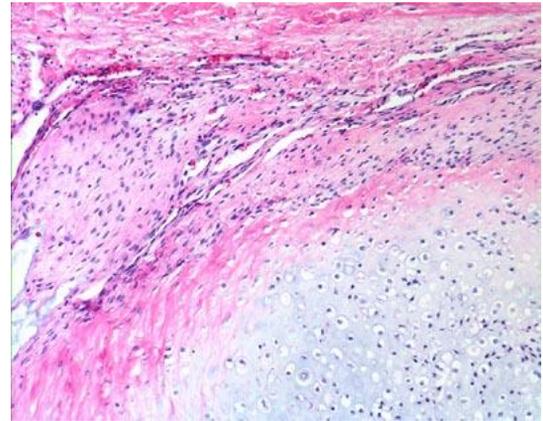
Periosteal osteosarcoma

Malignant, **predominantly chondroblastic**, intermediate-grade bone-forming sarcoma **arising from the bone surface**, usually under periosteum.

Often diaphysis of long bones, especially femur and tibia.

Most of the tumor is composed of irregular lobules of cartilage with cytologic atypia. Intervening bands of primitive sarcoma show bone formation.

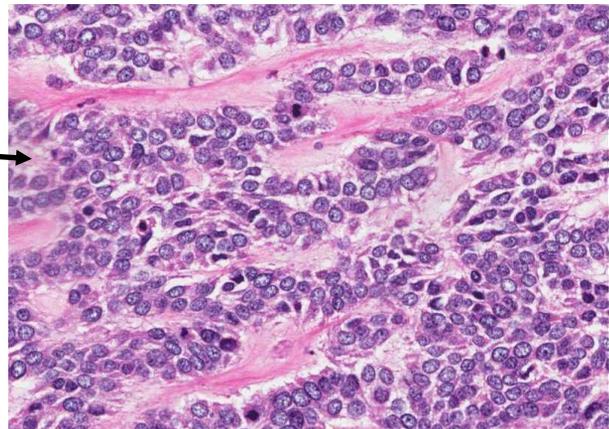
Better prognosis than conventional osteosarcoma.



Other Osteosarcoma Variants

Small Cell osteosarcoma— a subtype of conventional osteosarcoma with small round blue cell morphology with focal neoplastic bone formation. Tumor cells have scant cytoplasm and fine to course chromatin. Similar distribution to conventional osteosarcoma.

High-grade surface osteosarcoma—histologically high-grade osteosarcoma, but arising on the surface of the bone, without substantial intraosseous involvement.



Chondroblastic

Tumors with cartilage production.
Cartilage stains with S100.

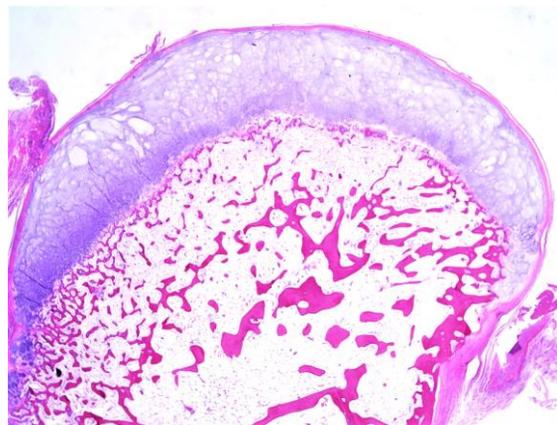
Osteochondroma

Benign. Cartilage cap with growth plate-like architecture and an underlying stalk with medullary and cortical bone.
Continuous with medullary cavity and cortex of bone.
No significant nuclear atypia or mitotic activity.

Often on the metaphysis of long bones near the knee.

Molecular: **Biallelic inactivation of EXT1 or EXT2**

Germline mutations in EXT1 are present in hereditary multiple osteochondroma syndrome



Enchondroma

Benign, relatively common. **Hyaline cartilage neoplasm** arising within the medullary cavity. Most frequently in short tubular bones of the hands, often in the metaphysis.

Abundant hyaline cartilaginous matrix. Hypocellular. Chondrocytes in sharp-edged lacunae with bland lymphocyte-like nuclei.

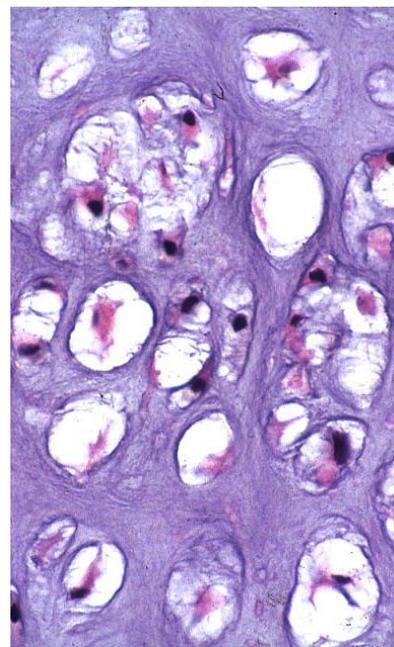
No significant cytologic atypia, mitoses, cortical invasion (destroying or entrapping cortical bone), or soft tissue extension (otherwise consider chondrosarcoma)

In small bones of hand and enchondromatosis, there is some leniency and tumors can have increased cellularity, myxoid cartilage, mild atypia (e.g., small nucleoli), and binucleation.

Molecular: **Frequent IDH1 and IDH2 mutations**

Enchondromatosis (includes Ollier disease and Maffucci syndrome) → germline IDH1 or IDH2 mutations → multiple symptomatic enchondromas

Often treated with curettage if symptomatic.



Bizarre parosteal osteochondromatous proliferation

“Nora Lesion”

Benign surface lesion composed of spindled cells, cartilage, and bone.

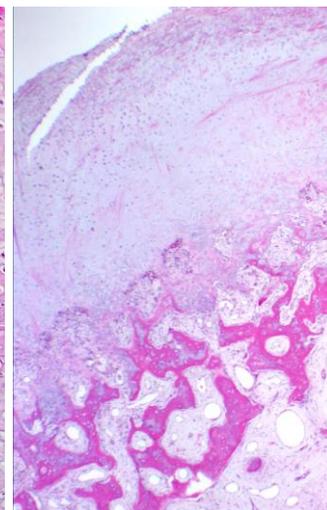
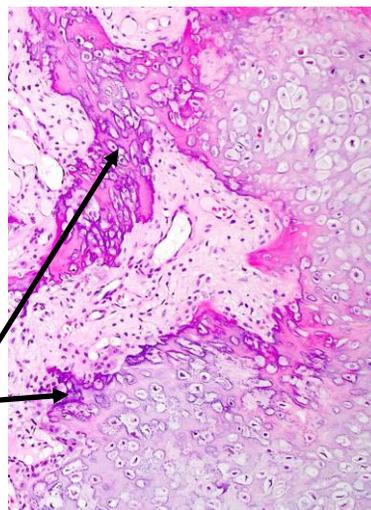
Most common in small bones of the hand and feet, often phalanges. Not contiguous with medullary cavity

Surrounded by cartilaginous cap with central trabecular bone (via endochondral ossification) and hypervascular bland spindled cells.

Between the cartilage and bone is characteristic **“Blue bone”** with basophilia

The chondrocytes can show moderate atypia

Unclear if it is a reactive process or neoplasm.



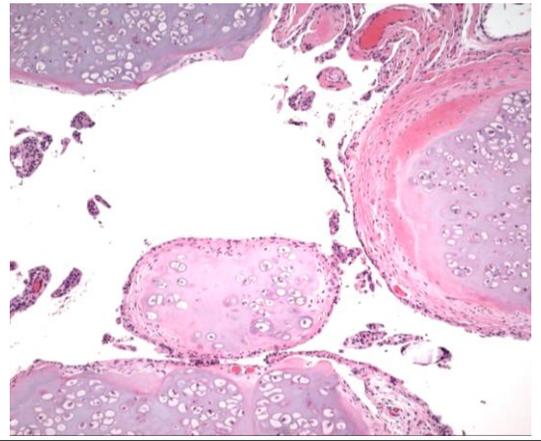
Synovial chondromatosis

Locally aggressive. Involves **large joints**, most commonly the knee.

Multiple hyaline cartilage nodules within synovium or loose in joint space. Chondrocytes cluster together in groups. Minimal atypia.

If significant atypia, loss of chondrocyte clustering, bone invasion, lots of mitoses → malignant

Molecular: **FN1-ACVR2A fusions**



Chondromyxoid fibroma

Benign. Occurs in many sites, but often long bones near the knee.

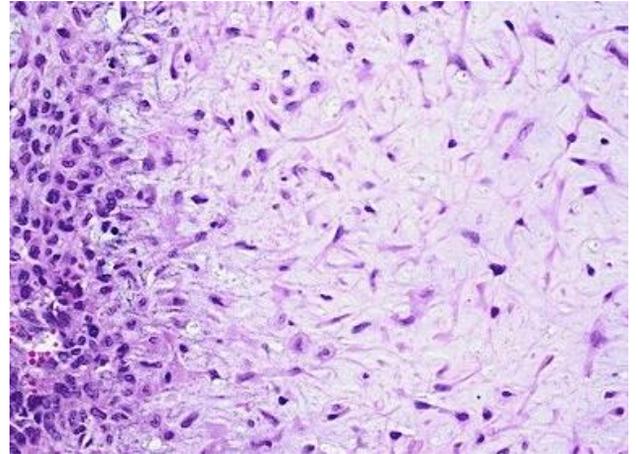
Lobulated lesion with sharp margins and zonal architecture.

Chondroid and stellate cells embedded in a chondroid to myxoid matrix in the center of each lobule.

Peripheral spindled cells and admixed giant cells.

IHC: Diffuse S100 positivity (like all cartilage)

Molecular: GRM1 fusions/upregulation



Chondroblastoma

Benign. Involve the **epiphysis of long bones**, most commonly the femur.

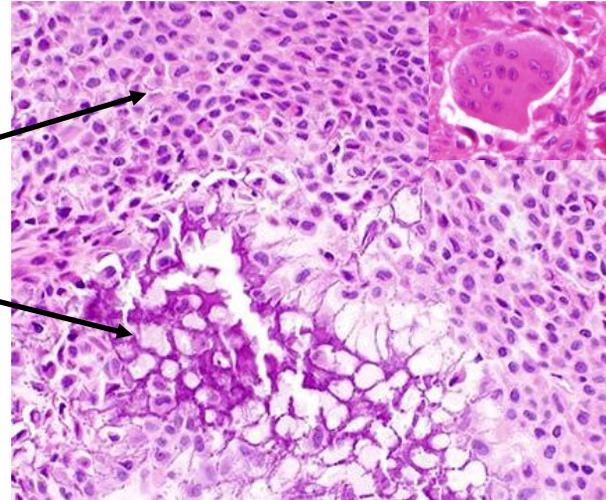
Sheets of ovoid to polygonal cells with a **single grooved nucleus** and eosinophilic cytoplasm and interspersed multinucleated giant cells.

Characteristic "lace-like" or "**chicken wire-like**" **calcification**

Islands of eosinophilic chondroid matrix.

Can have cystic degeneration, nuclear atypia, and mitoses.

Molecular: **H3.3 K36M substitution** (similar histone to giant cell tumor of bone). IHC: (+) S100, DOG1



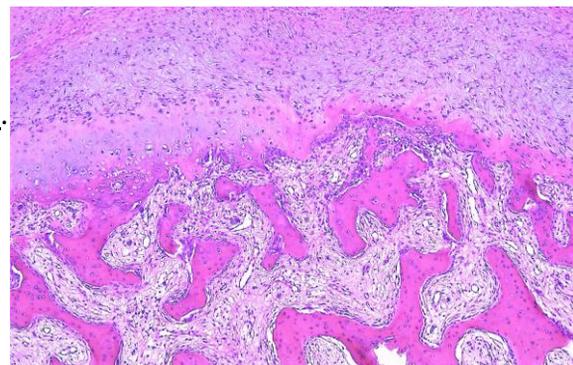
Subungual exostosis

Benign **osteocartilaginous surface** lesion in the distal pharyngeal bone **underneath the nail bed**. Most often **big toe**. Often young adults.

Sometimes cartilage is mildly atypical with mitoses.

No continuity with medullary cavity (as is seen in osteochondromas)

Recurrent cytogenetic breakpoint resulting in increased IRS4 expression.



Chondrosarcoma

Atypical Cartilaginous Tumor/Chondrosarcoma Grade 1:

Locally aggressive and can progress, but don't metastasize

Appendicular skeleton (easier to resect) → ACT

Axial skeleton (harder to resect) → Chondrosarcoma, grade 1

Abundant cartilaginous matrix (usually **hyaline**, but sometimes partially myxoid), with **lobular growth** and **entrapment** of pre-existing bone. **Increased cellularity**, but bland condensed nuclei. Binucleated cells common. **No** significant nuclear atypia or mitotic activity.

Chondrosarcoma Grade 2/3:

Malignant with metastatic potential.

Same as above, but increased cellularity, more myxoid matrix, and mitoses. Grade as below. No osteoid production by tumor cells.

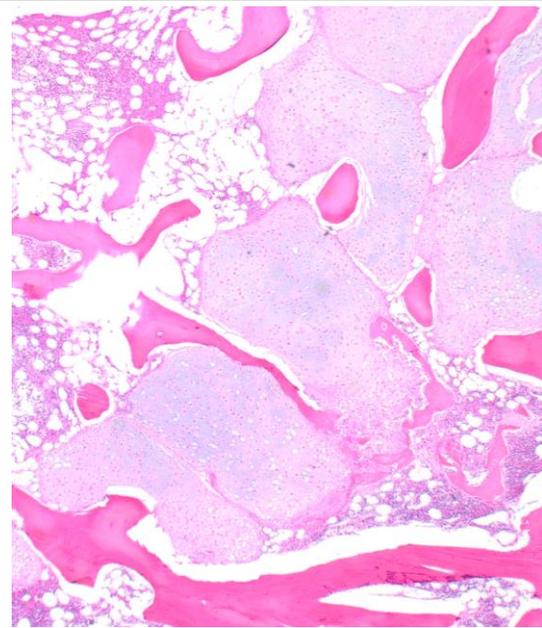
Molecular: ~1/2 have **IDH1 or 2** mutations (likely progressed from enchondroma). Higher grade tumors may also have TP53, RB1, and CDKN2A mutations.

Central: arising in the medulla of the bone

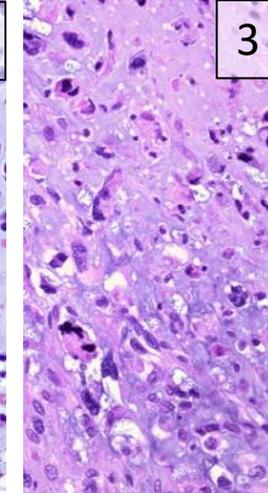
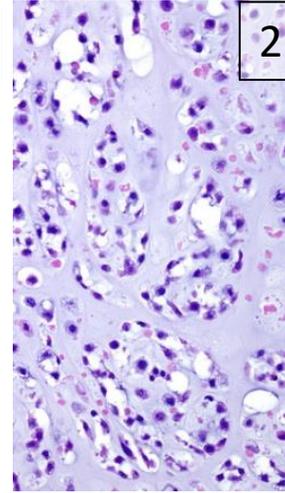
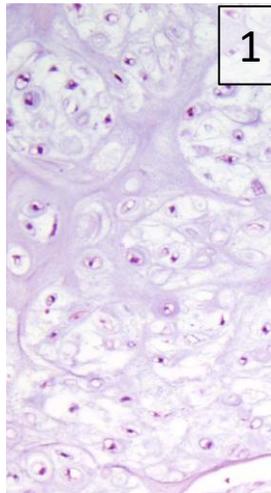
Central Primary: no pre-existing precursor

Central Secondary: arising from an enchondroma

Secondary Peripheral: arising in the pre-existing cartilaginous cap of an osteochondroma (cap > 2 cm)



Grade:



	Grade	Cellularity	Cytology
Radiographically, lobulations looks like "Popcorn" calcifications	1	Hypocellular	Nuclei are small and dark with fine chromatin (lymphocyte-like)
	2	More cellular	Nuclei are larger, irregular, and have coarse chromatin; mitoses infrequent
	3	Hypercellular	Severe pleomorphism and mitoses. Cells often more spindled.

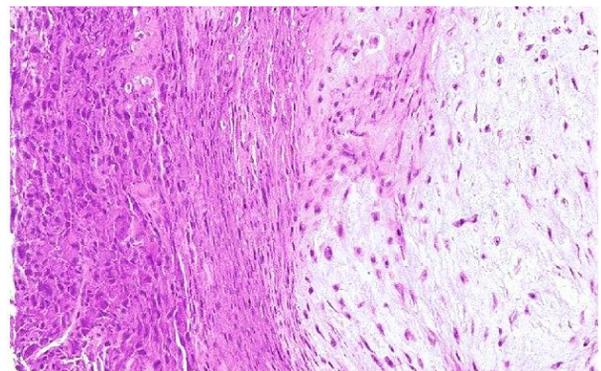
Dedifferentiated chondrosarcoma

Conventional chondrosarcoma with an abrupt transition to a high-grade non-cartilaginous sarcoma.

Most commonly located in the femur of elderly.

Molecular: Complex karyotypes with frequent IDH1/2 and TP53 mutations.

Very poor prognosis.



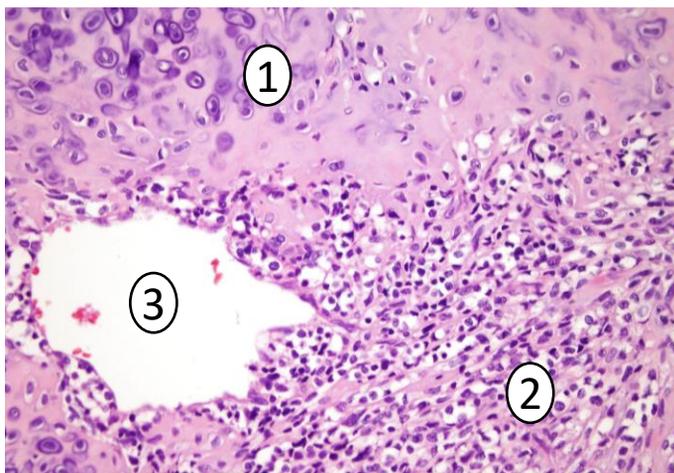
Mesenchymal Chondrosarcoma

Biphasic tumor with 1) Islands of organized **hyaline cartilage** in 2) an **undifferentiated component with high N:C ratios**. Frequent **staghorn vessels** (3).

Varied locations, but often craniofacial

Molecular: **HEY1-NCOA2 fusions**.

Aggressive behavior.



Clear cell chondrosarcoma

Clear cells with abundant cytoplasm, centrally placed nuclei, and **distinct cell membranes**.

Woven bone and osteoclast-like giant cells

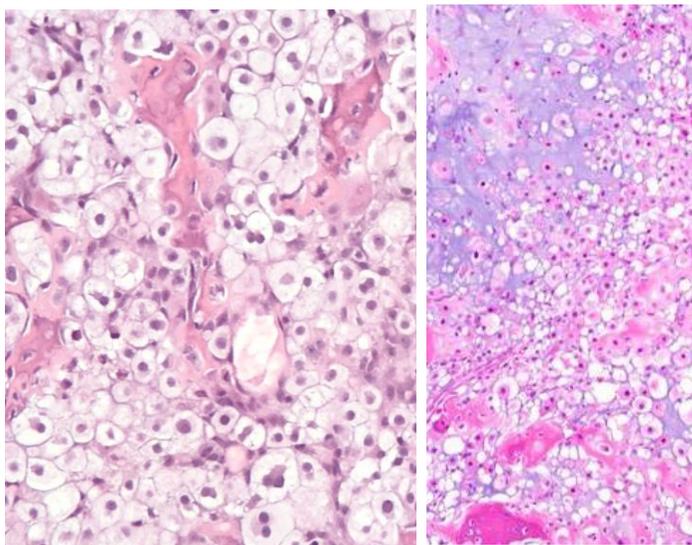
Minimal atypia and low mitotic activity

~1/2 of cases have a conventional low-grade chondrosarcoma component

Frequently in the epiphysis, particularly the femoral head.

IHC: **Strong S100** in clear cells.

Low-grade malignant.



Periosteal chondrosarcoma

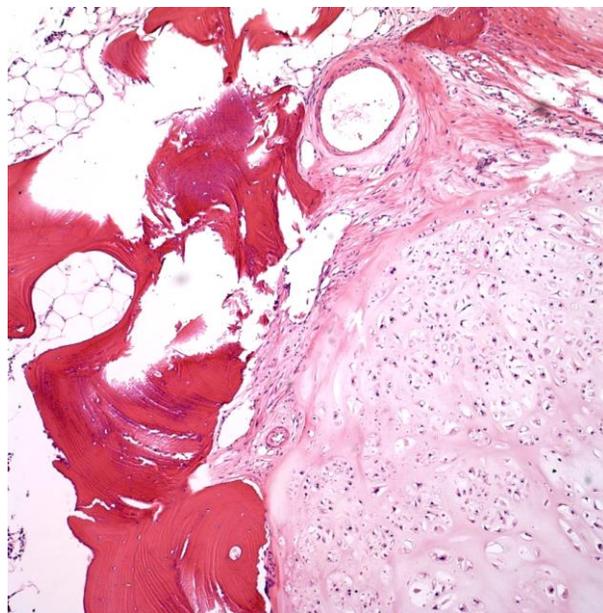
Cartilaginous tumor arising on the surface of a bone in close association with the periosteum with either:

- 1) **Invasion of the underlying bone**, or
- 2) **Size > 5.0 cm**

Located on the surface of long tubular bones, usually the distal femur.

Molecular: Comparatively low IDH1/2 mutation rate

Low metastatic rate, grading not predictive.



Vs. "Periosteal Chondroma"

Well-margined, lobulated cartilaginous tumor arising on the bone surface, with elevation of the periosteum and erosion, but no invasion of the underlying bone cortex. Low to moderate cellularity, and relatively uniform chondrocytes. Usually < 5 cm. Also frequently has IDH1 mutations. Benign and treated with curettage.

Hematopoietic Neoplasms

Plasma cell neoplasms

Sheets of neoplastic plasma cells.

Often characteristic morphology with perinuclear hof and “soccer ball” nuclei. Plasma cells may be small and mature, or large, immature, and atypical.

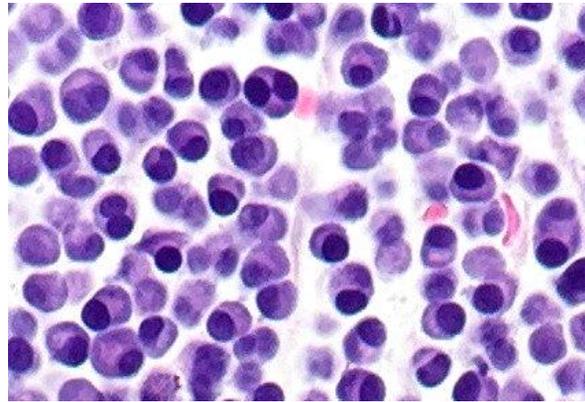
May see associated amyloid or crystal-storing histiocytosis.

IHC/Flow cytometry demonstrates **CD138+**, CD45 – or dim, with **monotypic Ig light chain expression**.

If solitary → Solitary plasmacytoma

If systemic → often “CRAB” symptoms (hyper**C**alcemia, **R**enal insufficiency, **A**nemia, **B**one involvement)

→ Plasma cell myeloma



Leukemia/Lymphoma

Always a consideration for cellular tumors with scant cytoplasm and no significant extracellular matrix.

May be primary to the bone or bone involvement by a systemic process.

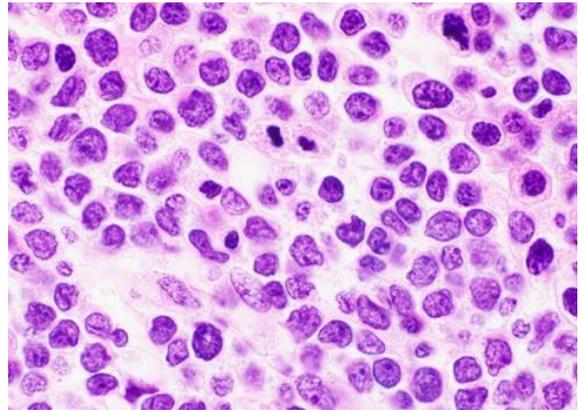
Consider sending for flow cytometry if a sample is received for frozen section or FNA adequacy and/or doing multiple heme stains.

Consider at least:

CD45 (“LCA,” a good broad marker)

TdT and/or CD34 (for lymphoblastic leukemias)

CD138 (for plasmacytoid things)



Langerhans cell histiocytosis “LCH”

Clonal neoplasm resembling Langerhans cells:

Characteristic grooved or folded nuclei

Moderate amounts of eosinophilic cytoplasm

Lots of associated **eosinophils**, histiocytes, and giant cells.

No prominent nucleoli or significant atypia

IHC: cells express **S100**, **CD1a**, **Langerin** (CD207), and CD68

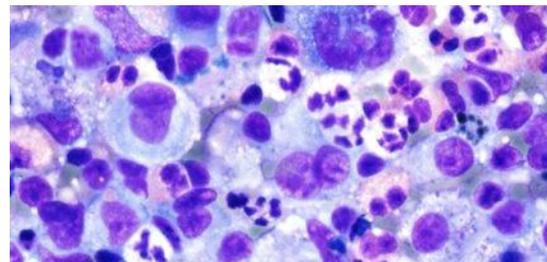
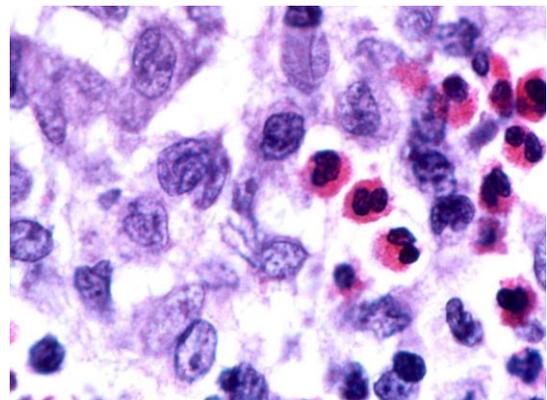
Molecular: **MAPK pathway activation** (e.g., BRAF V600E)

If “single system” → often impacts skull

If “multisystem” → can impact many bones and organs

Most common in kids.

Prognosis depends on stage, but is generally good (and excellent in single system disease)



Erdheim-Chester Disease

A clonal systemic histiocytosis with inflammation and fibrosis. Infiltration by **foamy, lipid-laden histiocytes**.

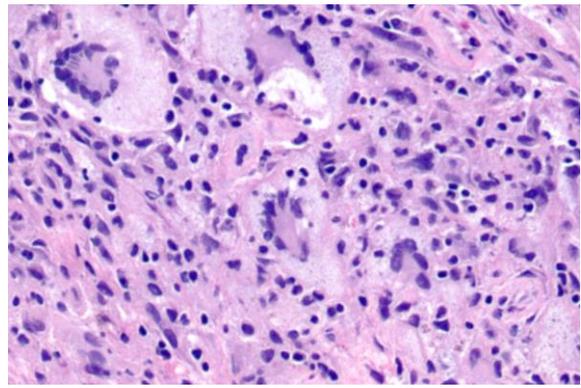
Variable amounts of **Touton giant cells**, small lymphocytes, and other inflammatory cells.

Fibrosis is usually present and can be extensive.

Usually involves long bones, but multisystem disease.

IHC: Foamy histiocytes stain with CD68, CD163, and CD14

Molecular: Activations of **MAPK pathway** (e.g., BRAF)



Rosai-Dorfman Disease

Histiocytic proliferation composed of **large, S100-positive histiocytes** with **emperipolesis**.

Cells have abundant eosinophilic to foamy cytoplasm.

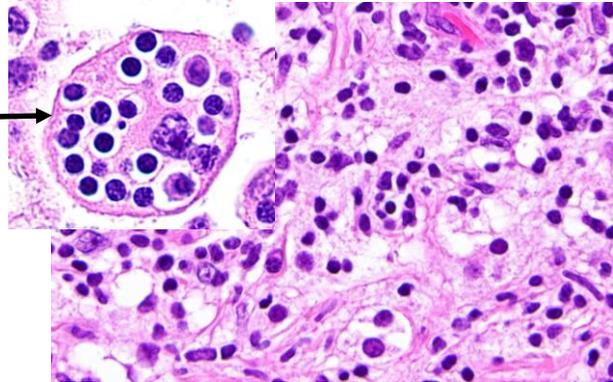
Round to reniform nuclei with vesicular chromatin.

Associated fibrosis and inflammatory cells.

IHC: **(+) S100**, (-)CD1a, Langerin

Molecular: Probably RAS/MAPK pathway activation

Good prognosis.



Osteoclastic Giant Cell Rich Tumors

Non-Ossifying Fibroma

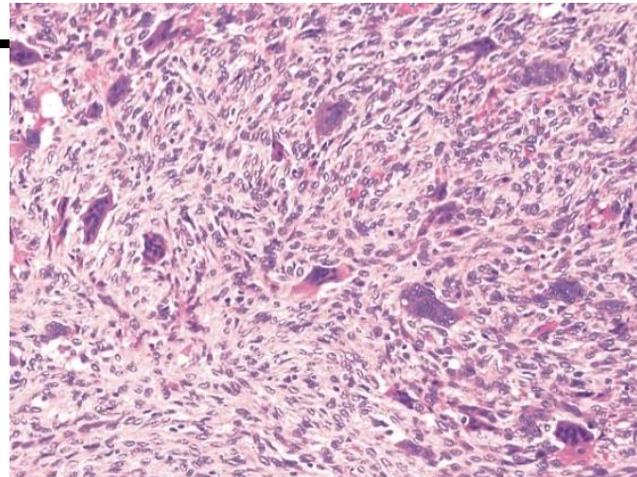
Benign, generally self-limited.

Storiform proliferation of plump spindled cells with intermingled giant cells.

Scattered hemosiderophages and foamy macrophages.

Skeletally immature patients in cortex of metaphysis in long bones, often near knee.

Molecular: KRAS or FGFR1 mutations → MAPK pathway activation



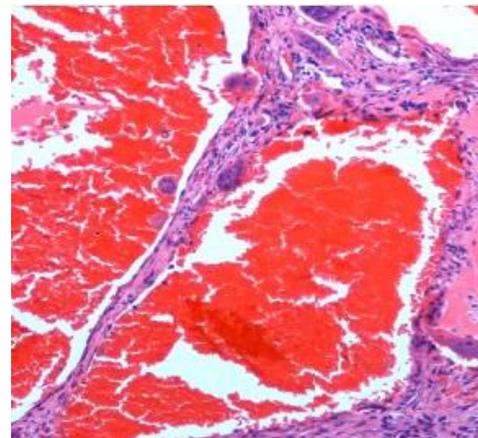
Aneurysmal Bone Cyst

Benign. **Multiloculated blood-filled cystic spaces.**

Cyst wall is composed of fibroblasts, osteoclast-like giant cells, hemosiderin pigment, and new bone formation. Well-circumscribed. Mitoses are common. Can be solid.

Most often in the metaphysis of long bones and posterior vertebrae
Most common in kids, but all ages can get.

Molecular: **USP6 gene rearrangements** (same as nodular fasciitis)



Giant Cell Tumor of Bone

Locally aggressive with rare metastases (often to lung)
Proliferation of numerous (reactive) **large osteoclasts** together with a **mononuclear neoplastic component** without atypia.

Generally **skeletally mature** individuals, involving the **epiphysis**

Mononuclear cells have oval nuclei with even chromatin and ill-defined cytoplasm. Often associated hemorrhage, hemosiderin, and macrophages.

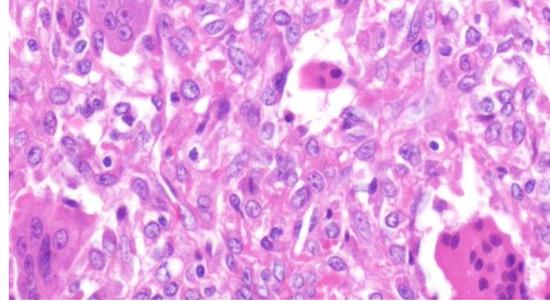
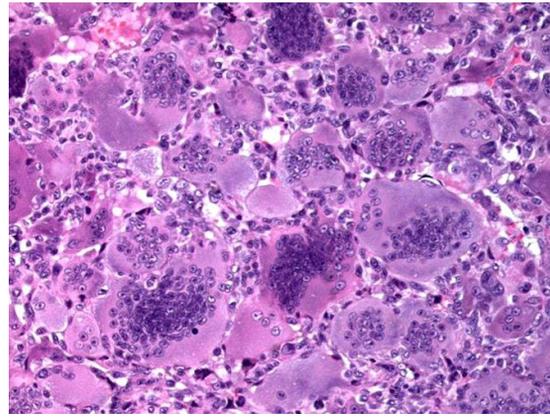
Molecular: H3.3 gene mutations, most commonly H3.3 G34W (chondroblastoma has similar mutation, but is usually in the epiphysis of *kids*)

IHC: (+)H3.3 G34W, often p63,

Can be treated with the RANK ligand inhibitor Denosumab → giant cells disappear → bland spindled cells with new bone deposition

Malignant Giant Cell Tumor of Bone:

Uncommon. Sarcomatous transformation of pre-existing Giant cell tumor. Can resemble any high-grade sarcoma. Often retained H3.3 mutation.



Also

Chondroblastoma

Some osteosarcomas

Paget's disease

Fibrogenic Tumors

Desmoplastic Fibroma

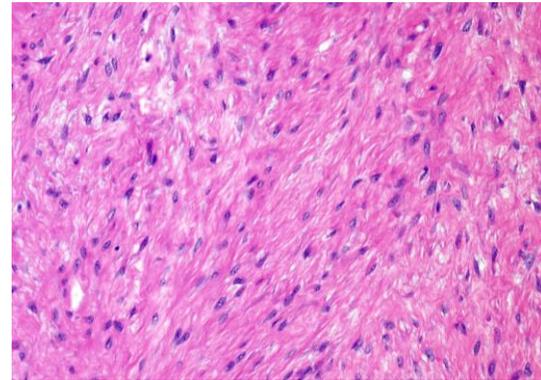
Locally aggressive proliferation of spindled cells resembling **desmoid-type fibromatosis**.

Infiltrative growth. Low cellularity proliferation of bland spindled cells set in collagenous stroma.

IHC: Variable SMA; nuclear β -catenin in a subset.

Most common in mandible of children.

Must exclude low-grade central osteosarcoma and fibrous dysplasia.



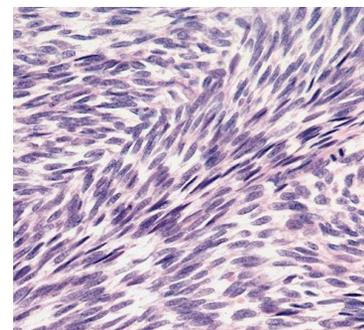
Fibrosarcoma

Malignant. **Diagnosis of exclusion**.

Monomorphic spindle cell proliferation with fascicular architecture.

Lacks morphologic, IHC, and genetic features suggesting an alternative Dx.

Classically, "herringbone fascicles"



Vascular Lesions

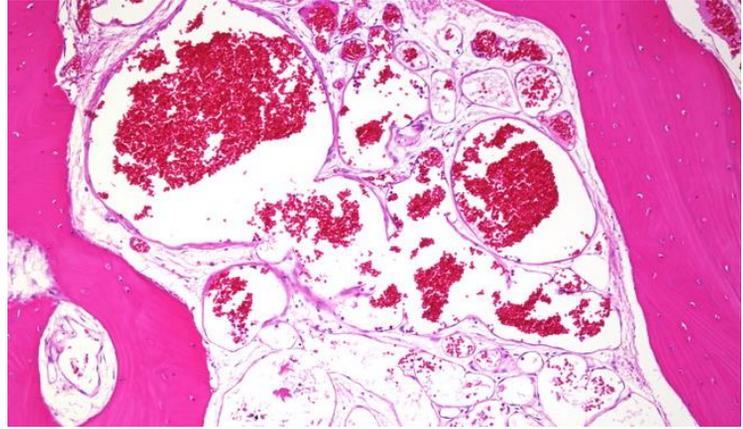
Tumors showing **vascular/endothelial differentiation**.
Endothelial markers include: ERG, CD31, CD34, FLI-1, and Factor VIII

Hemangioma

Benign tumor composed of small or large caliber **thin-walled blood vessels**.
Single layer of non-atypical endothelial cells.

Most common in **vertebral bodies**.
Often asymptomatic.

Unknown if neoplasm or developmental abnormality

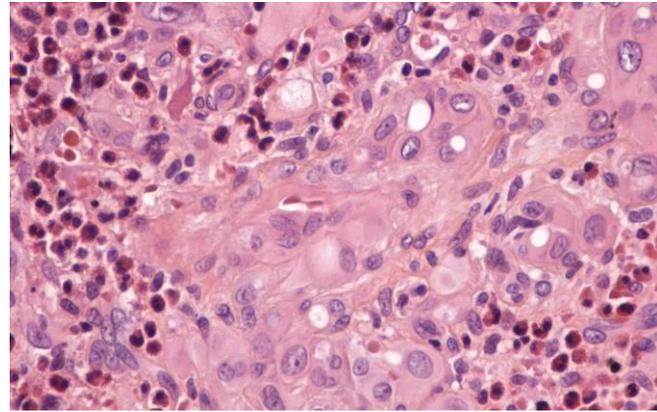


Epithelioid Hemangioma

Locally aggressive vascular neoplasm.
Large, epithelioid endothelial cells with densely eosinophilic cytoplasm. Distinct **vasoformation**.
Lobular architecture. Can have solid areas.
Mitoses are infrequent and not atypical.
Often rich inflammatory infiltrate with **eosinophils**.

Most common in long bones. Can be multifocal.

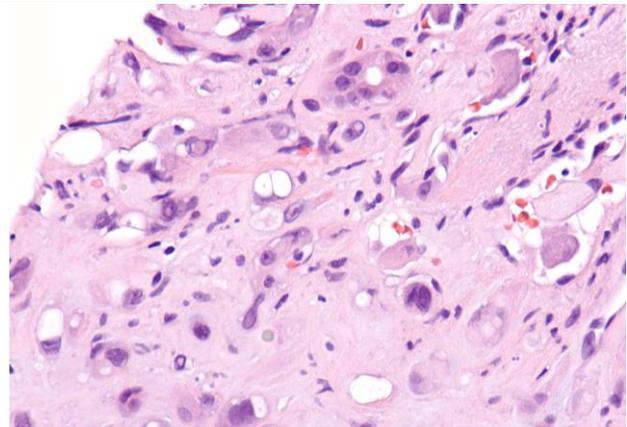
IHC: Vascular markers, **Keratins**, EMA, \pm FOS/B
Molecular: Rearrangements of **FOS** or FOSB



Epithelioid Hemangioendothelioma

Low to intermediate-grade malignancy.
Cords and nests of epithelioid endothelial cells within **myxohyaline stroma**. NO lobular architecture.
Large cells with abundant eosinophilic cytoplasm, some of which have **intracytoplasmic lumina with RBCs**.

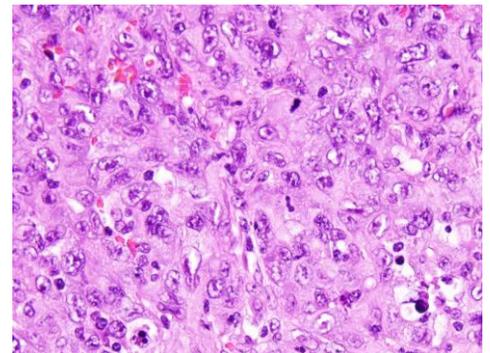
IHCs: Vascular markers, Keratins, EMA, CAMTA1
Molecular: **WWTR1-CAMTA1 fusion** (majority of cases),
or YAP1-TFE3 fusion (minority of cases)



Angiosarcoma

High-grade malignant neoplasm with **endothelial differentiation**.
Vasoformative architecture and/or expression of endothelial markers.
Often epithelioid in bone with frequent solid growth.
Numerous extravasated RBCs and variable inflammation
Prominent nuclear atypia and readily observed mitoses.

IHC: Vascular markers, frequent keratins (if epithelioid)



Notochordal Tumors

Tumors derived from/showing **notochordal differentiation**

Both stain with **Brachyury**, Cytokeratin, EMA and (variable) S100

Benign Notochordal Tumor

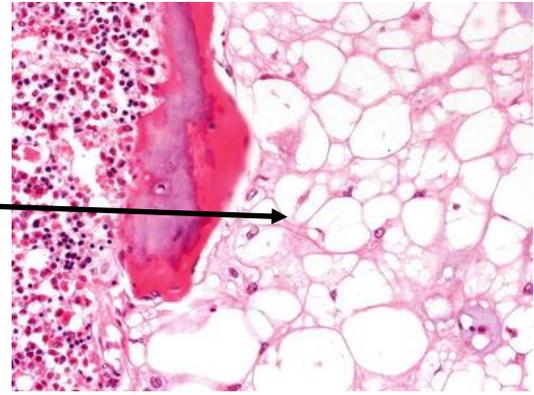
Benign. Often incidentally found.

Axial skeleton: Usually skull base, vertebral bodies, or sacrum.

Solid sheets of adipocyte-like vacuolated cells and eosinophilic less vacuolated cells.

Bland nuclei. No mitoses. Sometimes cystic areas.

Unlike Chordoma, there should be NO: extracellular myxoid matrix, tumor vasculature, fibrous septae, or lobular architecture



Chordoma

Malignant. Usually in the **axial skeleton**, equally distributed between skull base (esp. clivus), vertebrae, and sacrum.

Large epithelioid cells with eosinophilic to clear cytoplasm separated into **lobules** by fibrous septae.

Some cells have bubbly "**physaliphorous**" cytoplasm

Arranged in cords and nests embedded in abundant **myxoid matrix** or more cellular packets.

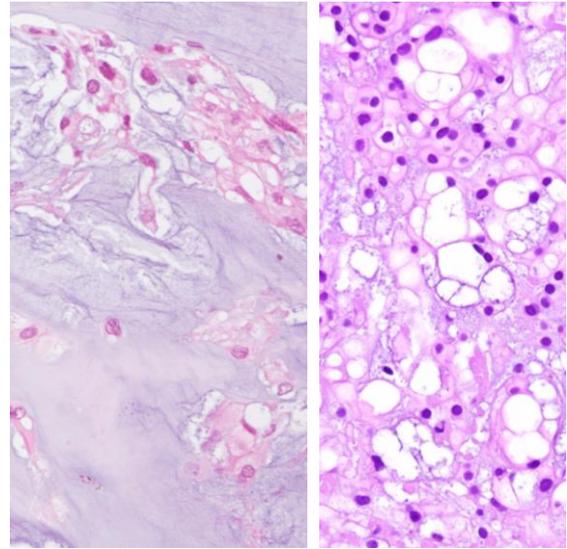
Variable pleomorphism and mitotic activity.

IHC: Expresses **Brachyury** and cytokeratin

Molecular: A subset of cases have Brachyury (TBXT) copy number variations

Intermediate aggressiveness, but can dedifferentiate.

"Poorly differentiated chordoma:" Cohesive nests of epithelioid cells with abundant eosinophilic cytoplasm. Scattered signet ring-like cells. Often rhabdoid areas. Loss of SMARCB1 (INI1) expression. Poor prognosis.



Miscellaneous Tumors

Simple Bone Cyst

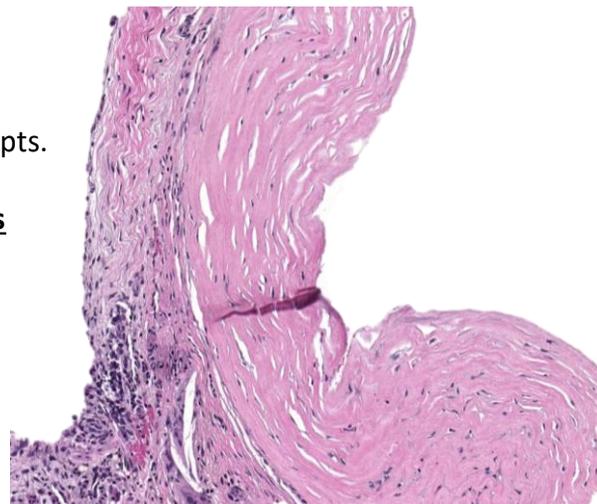
Benign. **Intramedullary**, usually **unilocular**.

Often in the proximal humerus or femur. Usually in younger pts.

Simple cyst, lacking a true lining, with a thin wall of fibrous tissue.

Often with fibrin deposition within cyst, which can calcify.

May have foci of chronic inflammation, histiocytes, multinucleated giant cells, hemosiderin, cholesterol, and reactive bone.



Fibrous Dysplasia

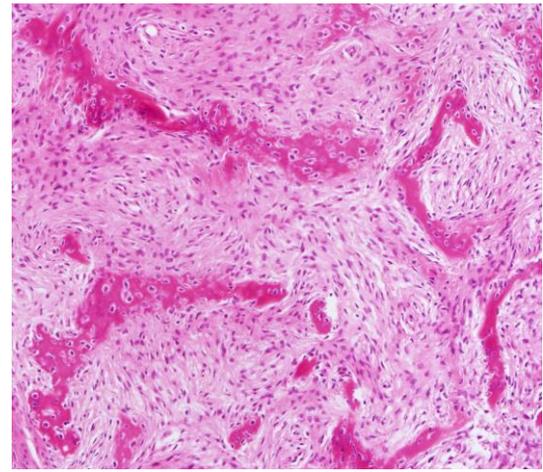
骨病理很棒

Benign. Often **medullary** in the craniofacial bones or femur. Can be monostotic (one bone, more common) or polyostotic (multiple bones, often presenting younger)

Fibro-osseous lesion with: 1) **irregular, curvilinear woven bone** (“Chinese letters”) without conspicuous osteoblastic rimming, and 2) **fibrous tissue** composed of bland fibroblastic cells.

Molecular: **GNAS** activating missense mutations

Both **Mazabraud syndrome** (FD + Intramuscular myxomas) and **McCune-Albright syndrome** (FD + Café-au-lait macules + endocrinopathies) have GNAS mutations



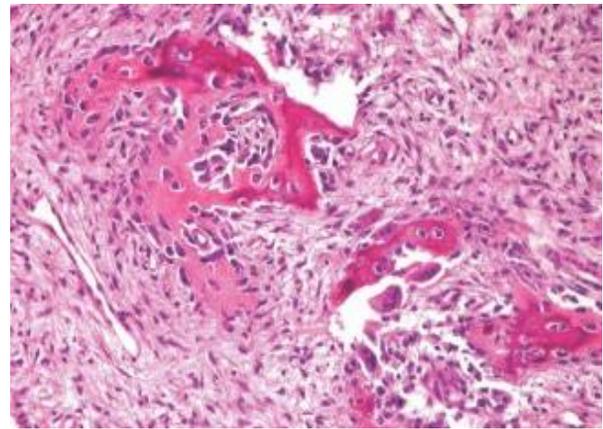
Osteofibrous Dysplasia

Benign. Almost exclusively in **Tibia** or Fibula anterior **cortex** during childhood.

Woven bone with prominent osteoblastic rimming with intervening bland fibrous tissue.

IHC: Cytokeratin highlights scattered SINGLE cells.

If CK highlights **clusters** of cells, consider: Osteofibrous dysplasia-like adamantinoma

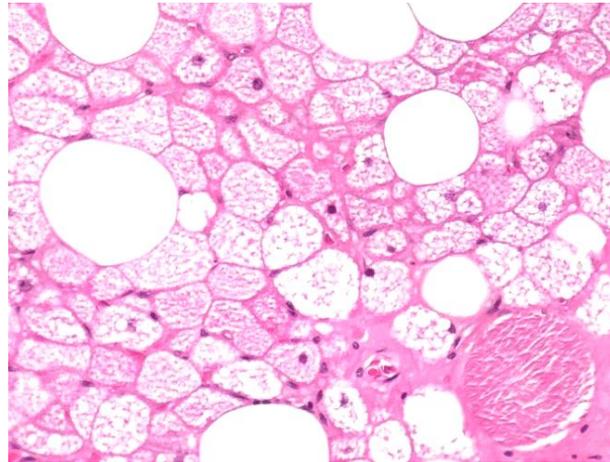


Lipoma/Hibernoma

Benign. Often calcaneus or metaphysis of long bones.

Lipoma: Lobules of **mature-appearing adipocytes** with a single large vacuole that displaces the nucleus. There may be woven bone present.

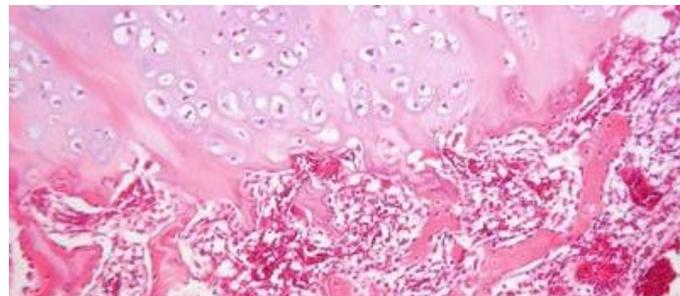
Hibernoma: Composed of **brown fat**, with large cells with eosinophilic cytoplasm with numerous small clear vacuoles and a central nucleus.



Chondromesenchymal Hamartoma of Chest Wall

Benign. Well-circumscribed mass arising from the **rib**, **present at birth**.

Composed of: nodules of **hyaline cartilage**, admixed with **blood-filled cystic spaces**, reactive **bone**, bland **spindled cells**, and osteoclast-like giant cells.



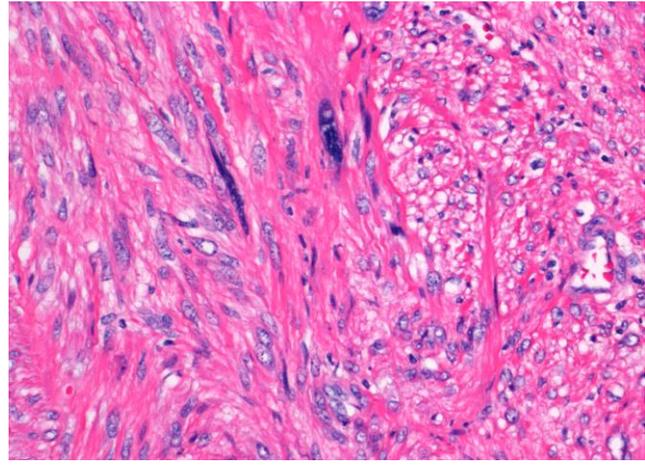
Leiomyosarcoma

Malignant. Often lower extremity near knee.

Intersecting fascicles of uniform cells with eosinophilic fibrillar cytoplasm and elongated cigar-like nuclei and variable pleomorphism demonstrating **smooth muscle differentiation**.

IHC: SMA, Desmin, and/or H-caldesmon

Must exclude a metastasis!!



Ewing Sarcoma

Malignant. Most common in the **diaphysis of long bones** (but can be in any bone and soft tissue).

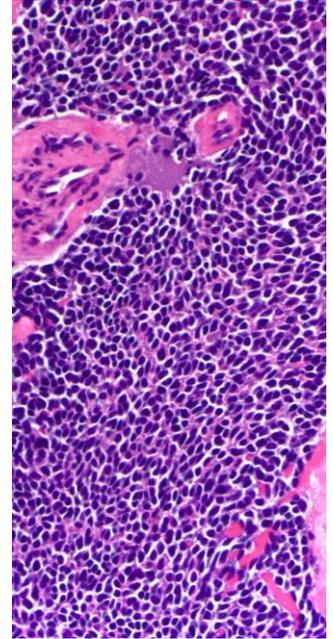
On imaging causes a multilaminated periosteal reaction → **“onion skinning”**

Most common in **children** and young adults.

Small round blue cell morphology. Uniform. Stippled chromatin and scant clear to eosinophilic cytoplasm. Can form rosettes.

IHC: **CD99 diffuse strong membranous** staining (not specific though) NKX2-2 (much more specific). FLI1 and ERG in cases with corresponding fusions. Occasional keratin expression.

Molecular: **EWSR1 fusions**, most commonly with FL1, sometimes with ERG, or rarely other combinations.



Adamantinoma

Locally aggressive to Malignant. Often youngish adult.

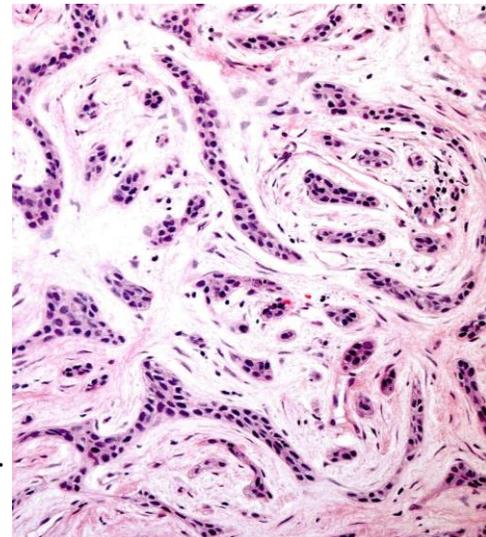
Located in **cortex** of anterior **Tibia** or Fibula

Biphasic with a variety of morphologic patterns with variable **epithelial component** within a bland **osteofibrous component**.

Classic adamantinoma: obvious epithelial element in fibro-osseous stroma. Epithelium can be squamous, basaloid, tubular, or spindled. Malignant.

Osteofibrous dysplasia-like adamantinoma: Inconspicuous epithelial cells (see clusters on CK IHC), primarily osteofibrous lesion. Locally aggressive.

Dedifferentiated adamantinoma: epithelial component progressed to high-grade sarcoma.

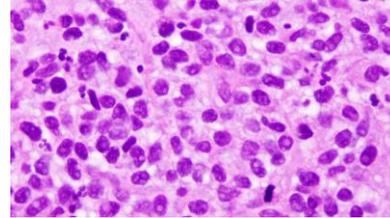
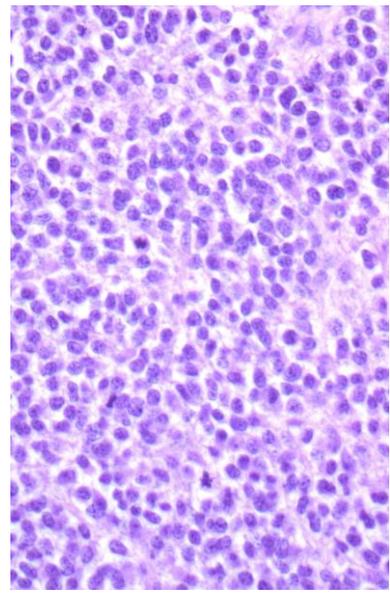


Other Small Round Blue Cell Sarcomas

CIC-rearranged sarcoma: High-grade round cell undifferentiated sarcomas with CIC gene fusions, most commonly **CIC-DUX4**. Most commonly in soft tissue, rarely bone. Common in young adults. By IHC: CD99 variable, frequent WT1, ERG, and calretinin staining. **Significantly worse prognosis** than Ewing Sarcoma.

Sarcoma with BCOR genetic alterations: Primitive round to spindled cells arranged in nests, sheets, or fascicles. Variably myxoid stroma with delicate vasculature. Can see either **BCOR gene fusions** (e.g., BCOR-CCNB3) or BCOR internal tandem duplications. By IHC: (+) BCOR, SATB2, TLE1, and CyclinD1. CD99 variable. Survival similar to Ewing sarcoma.

Round cell sarcoma with EWSR1-non-ETS fusions ("*Ewing-like Sarcoma*"): Like the name says, round cell sarcomas with a fusion of EWSR1 to a non-traditional fusion partner (i.e., not FLI, ERG, or FUS). Most often in the bone (like Ewing sarcoma). Most common fusions: EWSR1-NFATC2 and FUS-NFATC2. IHC very variable.



Undifferentiated Pleomorphic Sarcoma

Malignant. *Diagnosis of exclusion!*

Often in the long tubular bones near the knee of adults (**often older**).

A pleomorphic malignant neoplasm with **no identifiable line of differentiation**.

Diffusely composed of **spindled to epithelioid cells with marked pleomorphism in various growth patterns** (often storiform to fascicular)

Brisk mitotic activity and frequent necrosis.

Collagenous stroma, but **NO osteoid or cartilage production**.

IHC: Do at least S100, SMA, Desmin, CK AE1/AE3

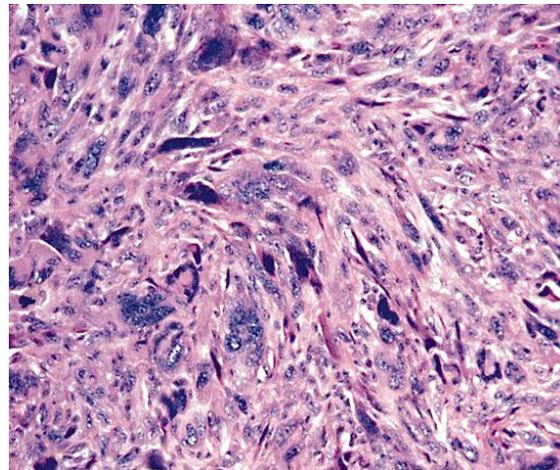
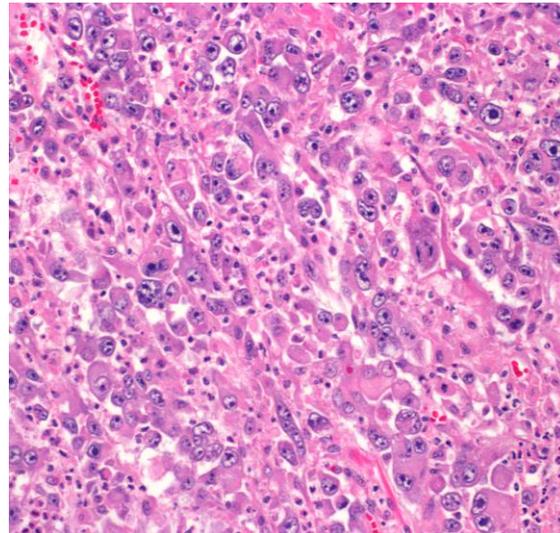
Can see focal keratin staining, but if extensive consider metastatic carcinoma.

Can see focal staining with one muscle marker (e.g., SMA), but if more markers also positive (e.g., Desmin) → consider leiomyosarcoma.

SATB2 can be positive

H3.3 p.Gly34Trp expression suggests derived from giant cell tumor of bone.

IDH1/2 mutations can suggest dedifferentiated chondrosarcoma



Genetics/Molecular

Alteration	Tumors
EWSR1	Ewing sarcoma (and MANY other tumors, including clear cell sarcoma, angiomatoid fibrous histiocytoma, desmoplastic small round cell tumor, extraskeletal myxoid chondrosarcoma, etc...)
FOS rearrangements	Osteoid Osteoma, Osteoblastoma, Epithelioid hemangioma
MDM2 amplifications	Low-grade central osteosarcoma, Parosteal osteosarcoma, Conventional osteosarcomas derived from either of these (and Well-differentiated liposarcoma and Intimal sarcoma)
EXT1 or EXT2 biallelic inactivation	Osteochondroma
IDH1 or IDH2	Enchondroma, Chondrosarcoma or Dedifferentiated chondrosarcoma derived from an enchondroma
GNAS	Fibrous dysplasia, (also intramuscular myxoma)
H3.3	K36M→Chondroblastoma, G34W→Giant cell tumor of bone
HEY1-NCOA2 fusions	Mesenchymal chondrosarcoma
USP6 rearrangements	Aneurysmal bone cyst (also nodular fasciitis)
MAPK pathway activation	Non-ossifying fibroma, Langerhans cell histiocytosis, Erdheim-Chester disease, Rosai-Dorfman disease
GRM1 fusions/upregulation	Chondromyxoid fibroma
FN1-ACVR2A fusions	Synovial chondromatosis
WWTR1-CAMTA1 fusion	Epithelioid hemangioendothelioma

Syndrome	Gene	Manifestations
Li-Fraumeni Syndrome	TP53	Early onset of a broad spectrum of cancers, most commonly breast cancer, followed by soft tissue sarcomas, brain tumors, and osteosarcomas
Enchondromatosis	IDH1/2	<u>Ollier disease</u> : Multiple enchondromas in multiple bones <u>Maffucci syndrome</u> : Multiple enchondromas + hemangiomas
McCune—Albright syndrome	GNAS	Fibrous dysplasia (monostotic or polyostotic), hyperfunctioning endocrinopathies (precocious puberty, hyperthyroid, hypercortisolism, etc.), various GI polyps, and intramuscular myxomas (FD + myxoma = <u>Mazabraud syndrome</u>)
Multiple Osteochondromas	EXT1/2	Multiple osteochondromas during early life that stop growing when growth plates close. May be asymptomatic.