Pathology of Bone Tumors

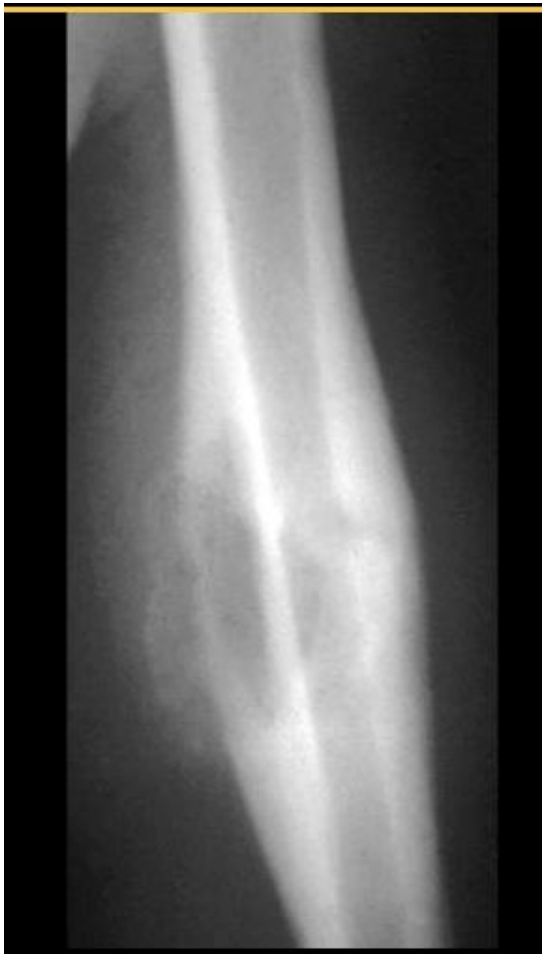
By Konstantinos Linos M.D.

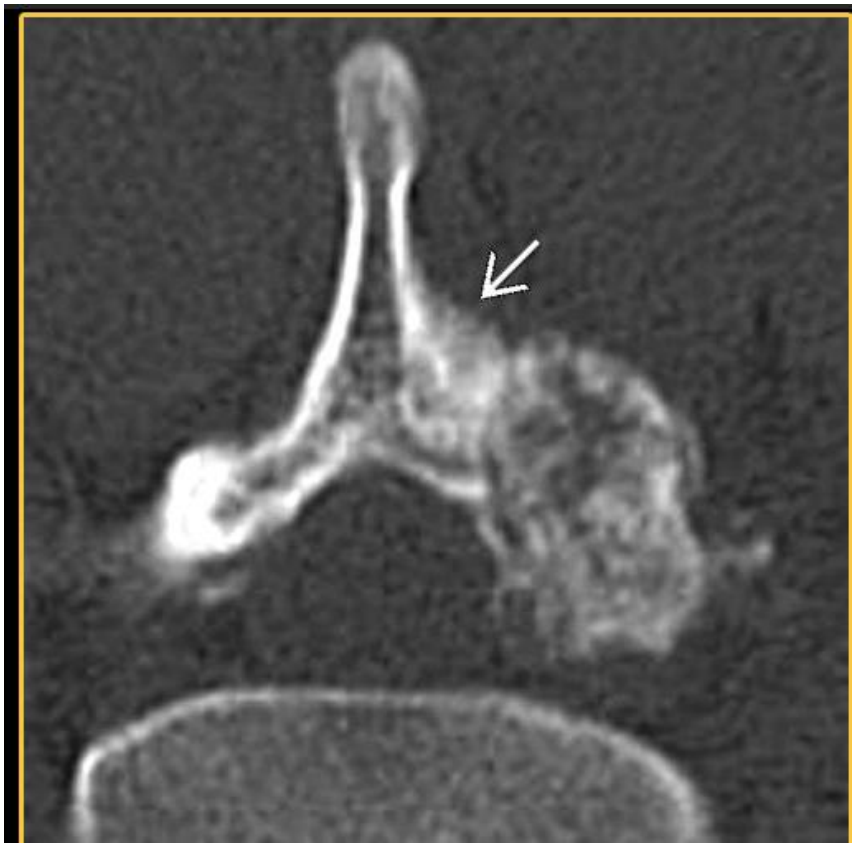
Benign-bone forming tumors

Osteoblastoma

- Benign bone-forming neoplasm >2cm in dimension
- Diagnosed in young adults with male predominance of 2:1
- Commonly arises in tubular bones and posterior elements of spinal column
- Presents with pain and swelling with neurologic symptoms in some spinal lesions
- Treated with currettage or en block excision
- Excellent prognosis with local recurrence rate of 20%

Image findings





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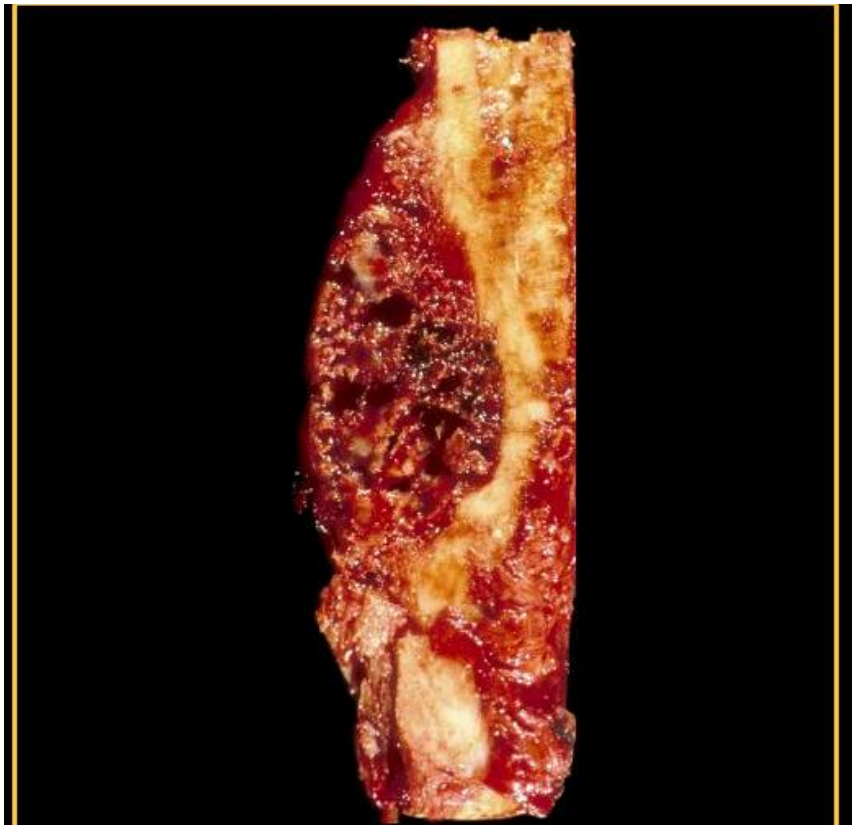

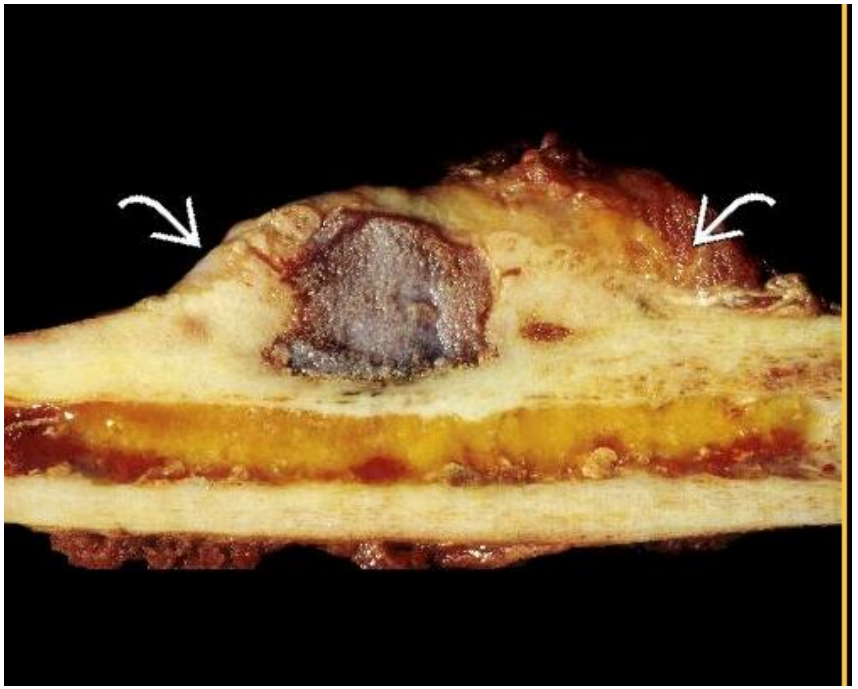

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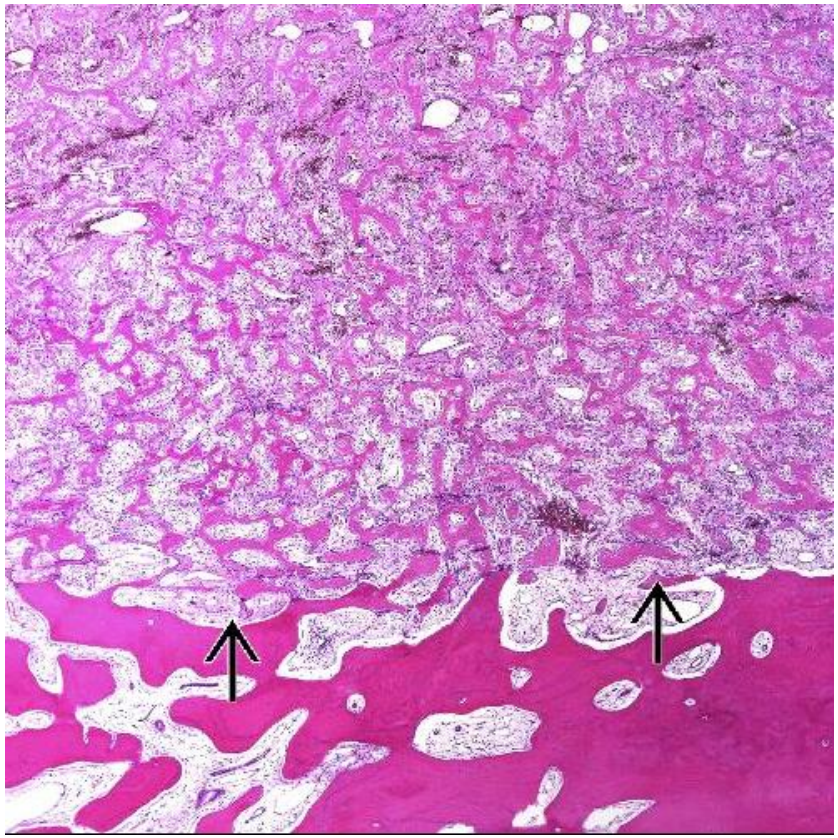
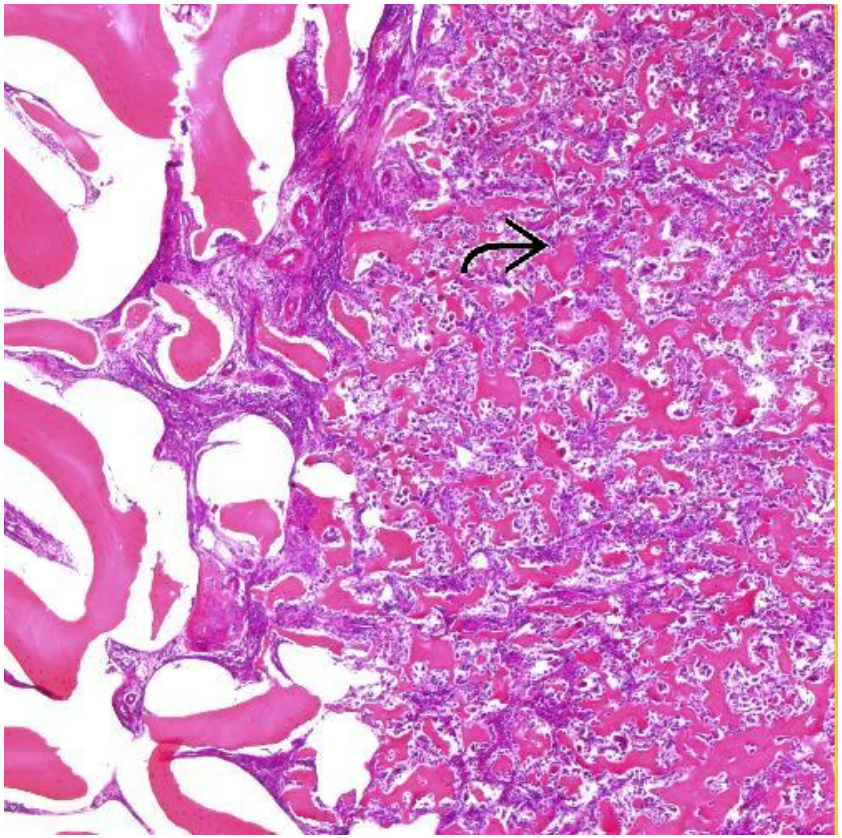
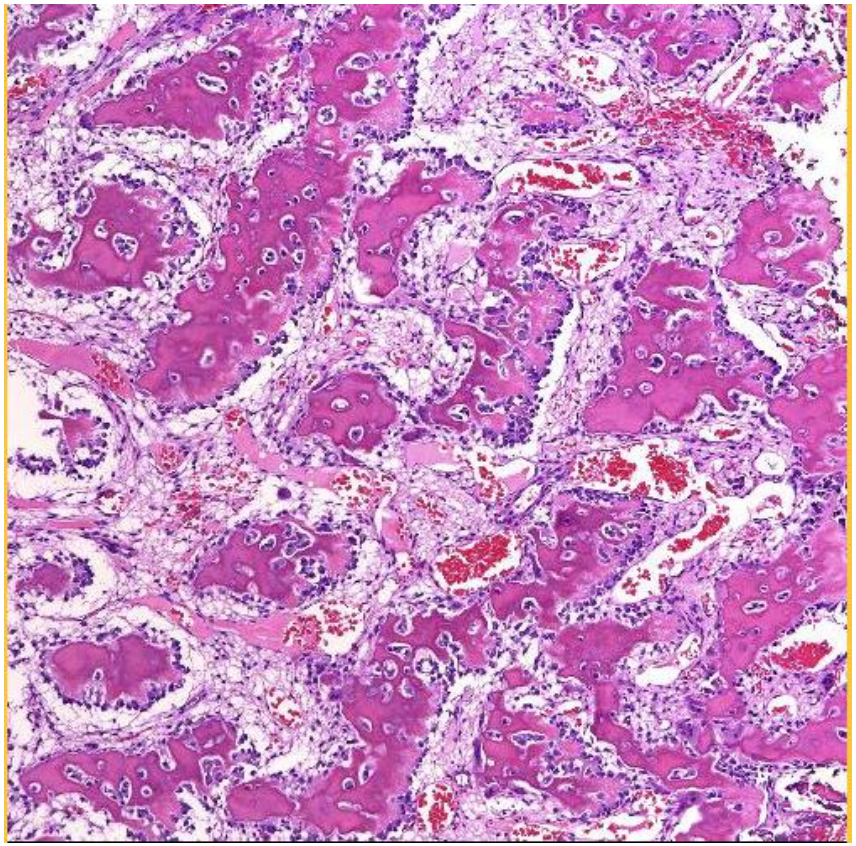
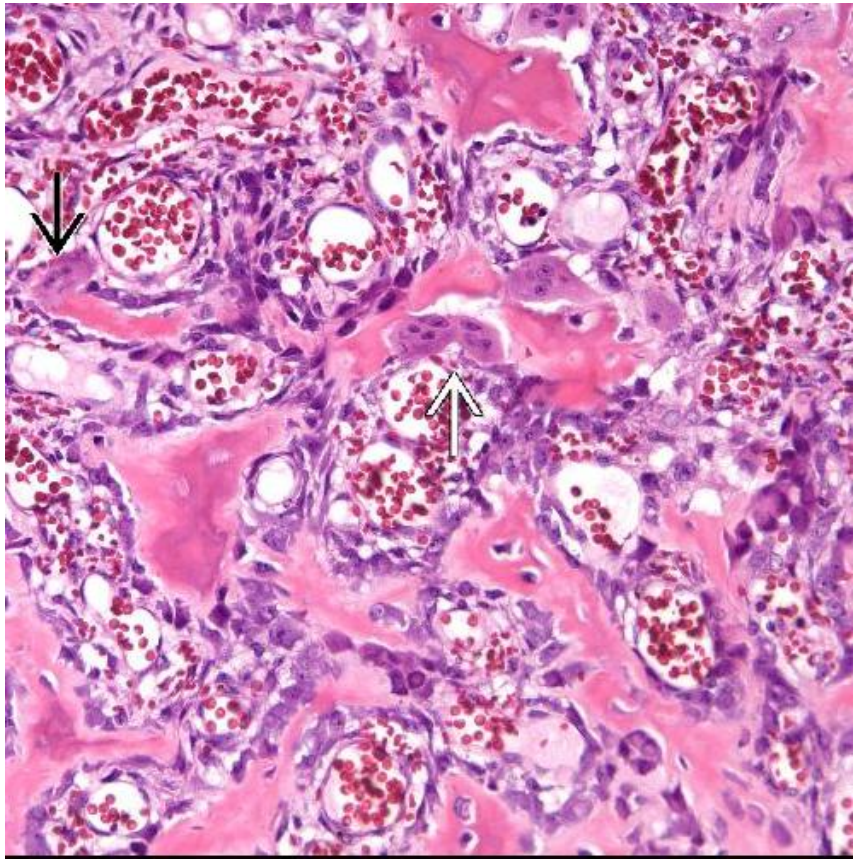








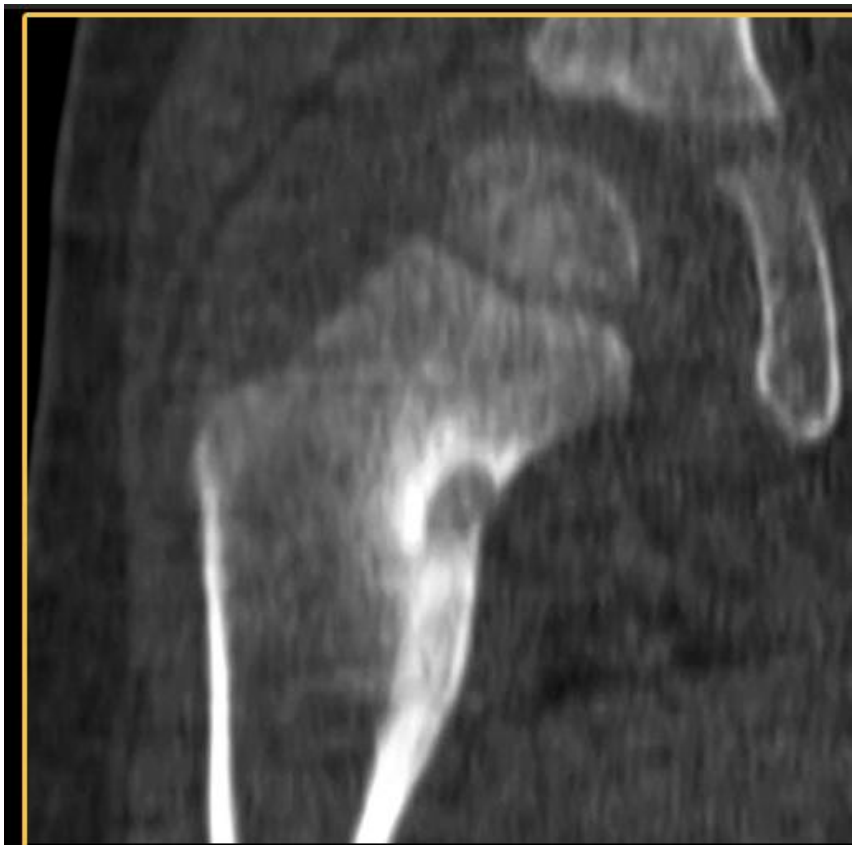
Osteoid osteoma

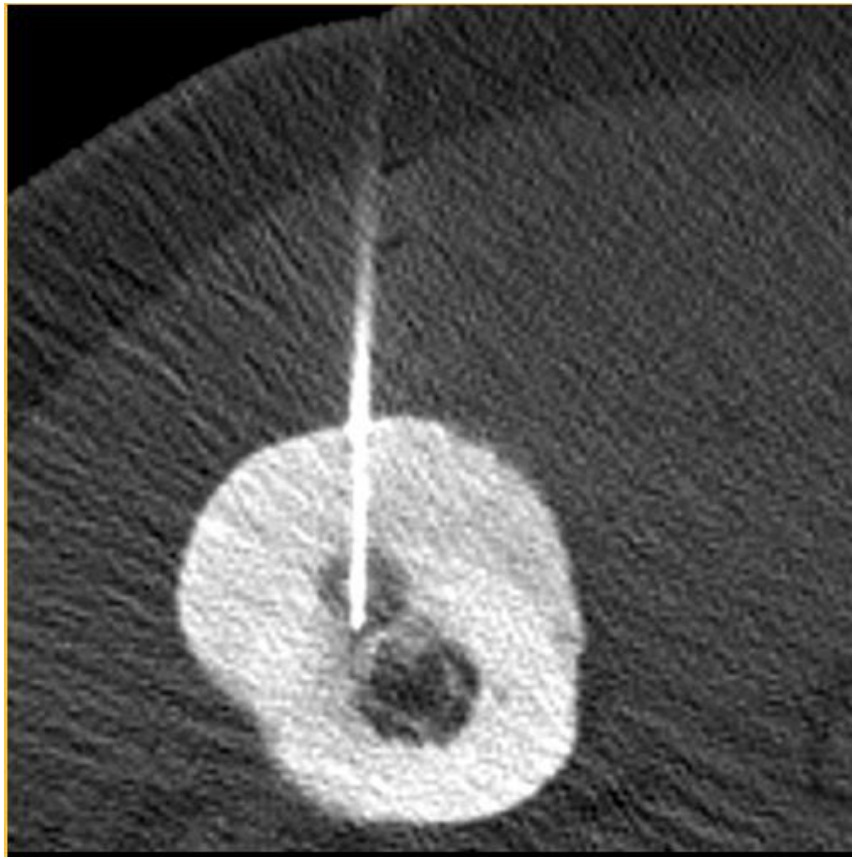
- Benign bone-forming tumor characterized by its small size, limited growth potential, classic pattern of pain and composition of woven bone trabeculae rimmed by osteoblasts

Clinical

- Accounts approximately 13% of all primary benign bone tumors and 3% of all other primary bone tumors
- Long tubular bones, especially lower extremity, followed by posterior elements of spine and tubular bones of hands and feet
- Presents as severe localized pain that is often worse at night
- Treatment of choice: Radiofrequency ablation
- Excellent prognosis

Image findings





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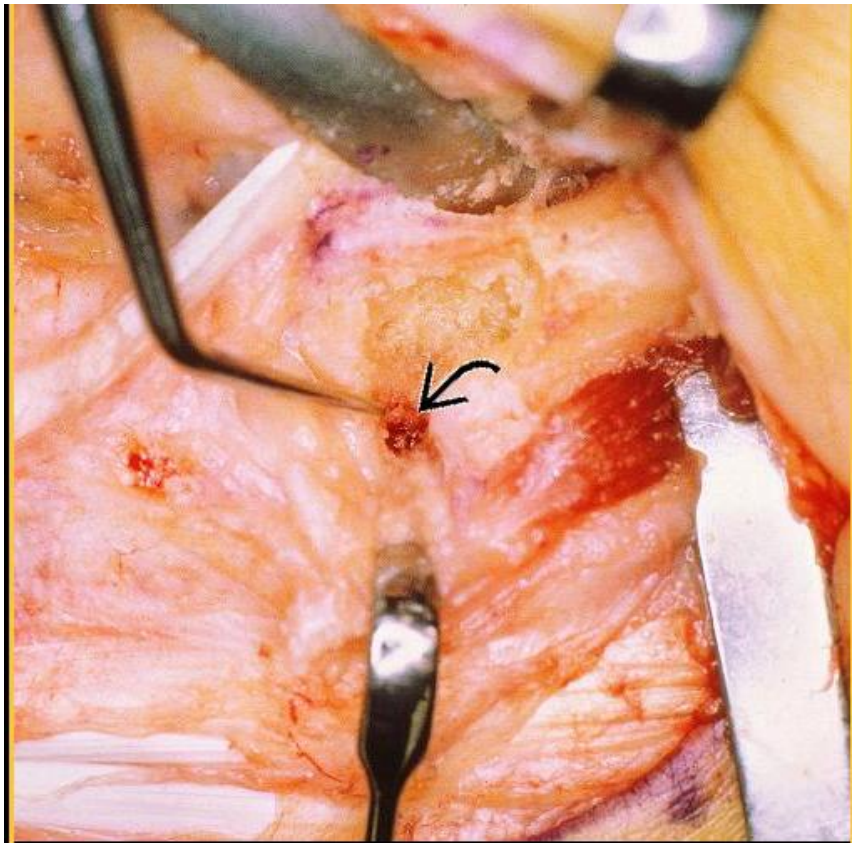

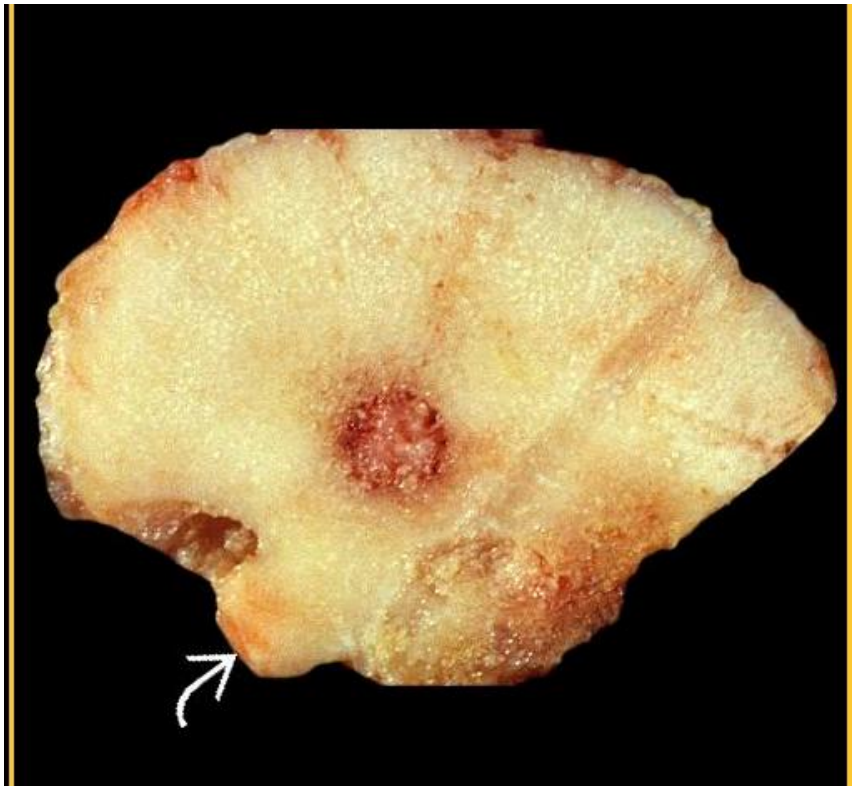

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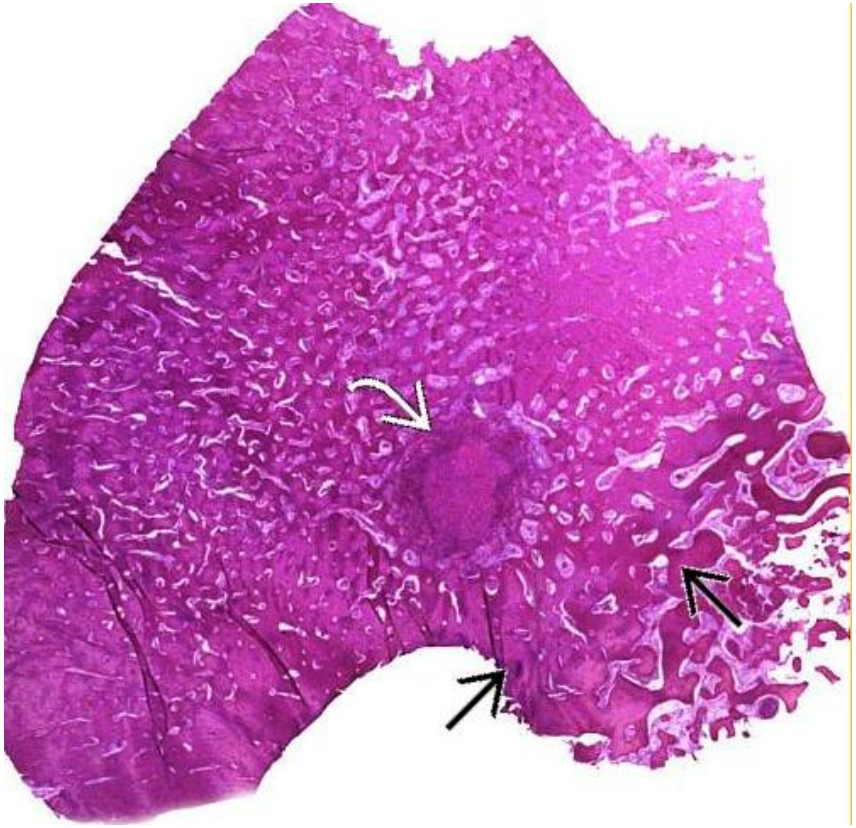

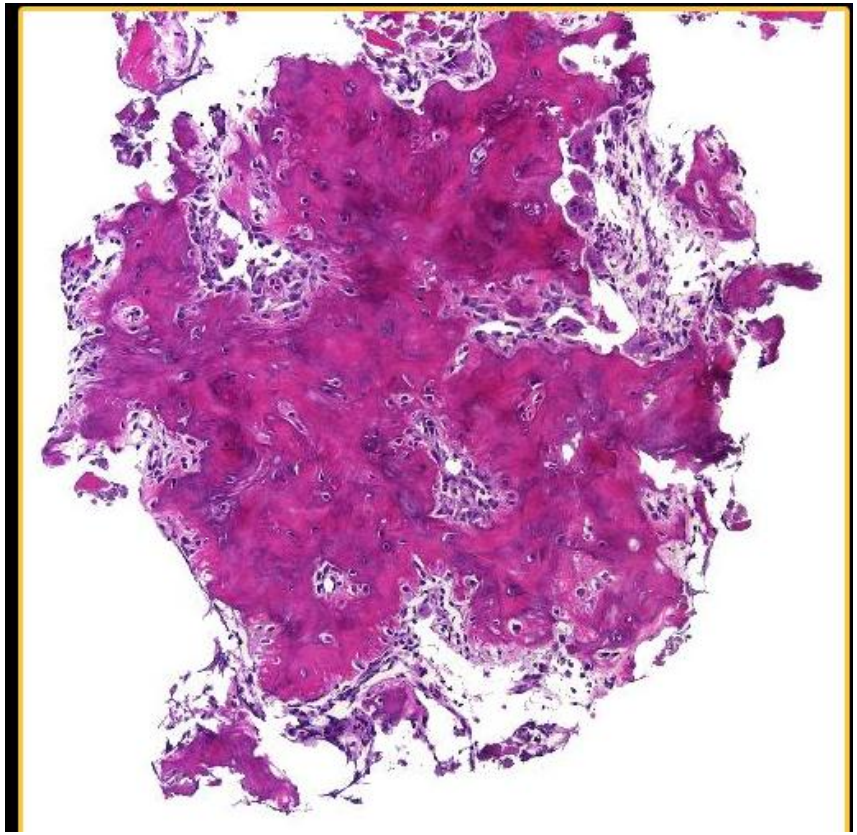

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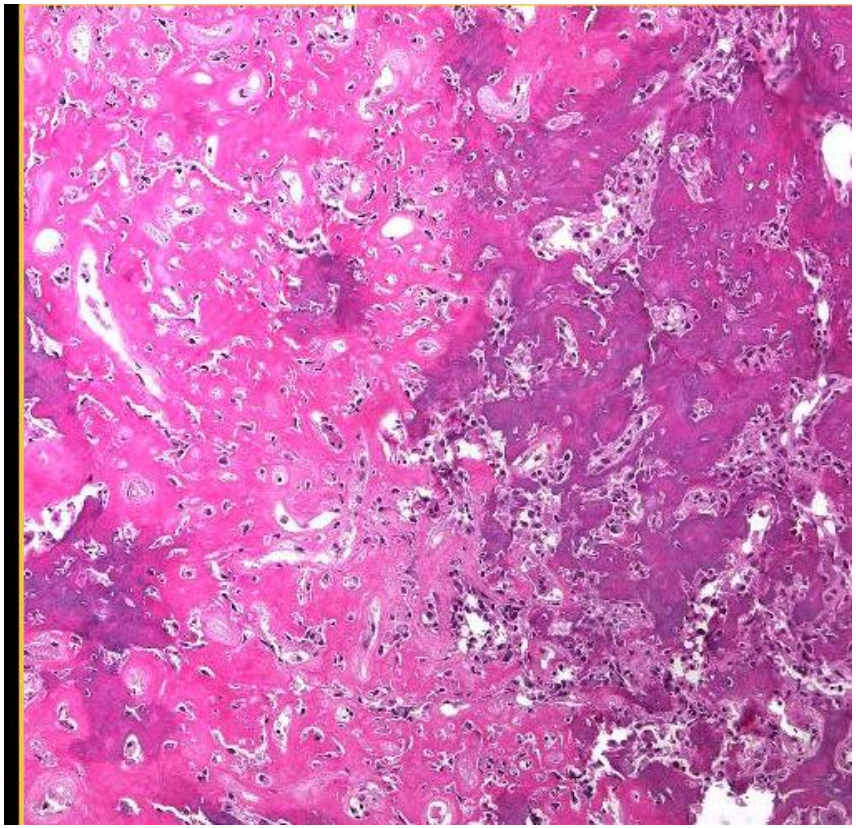
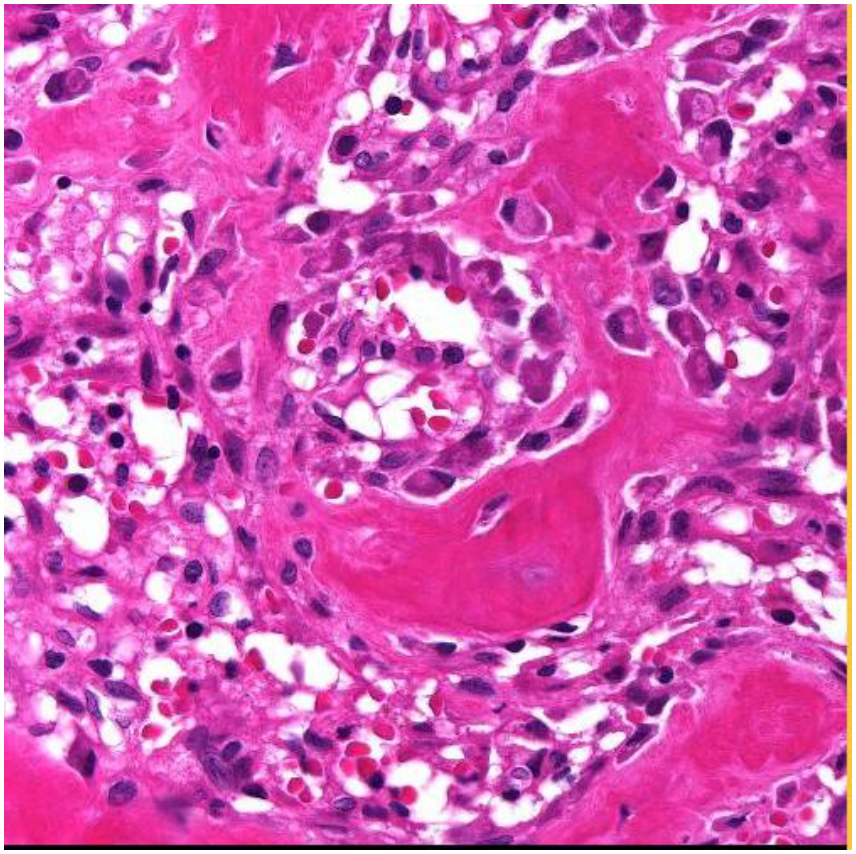




Differential Diagnosis

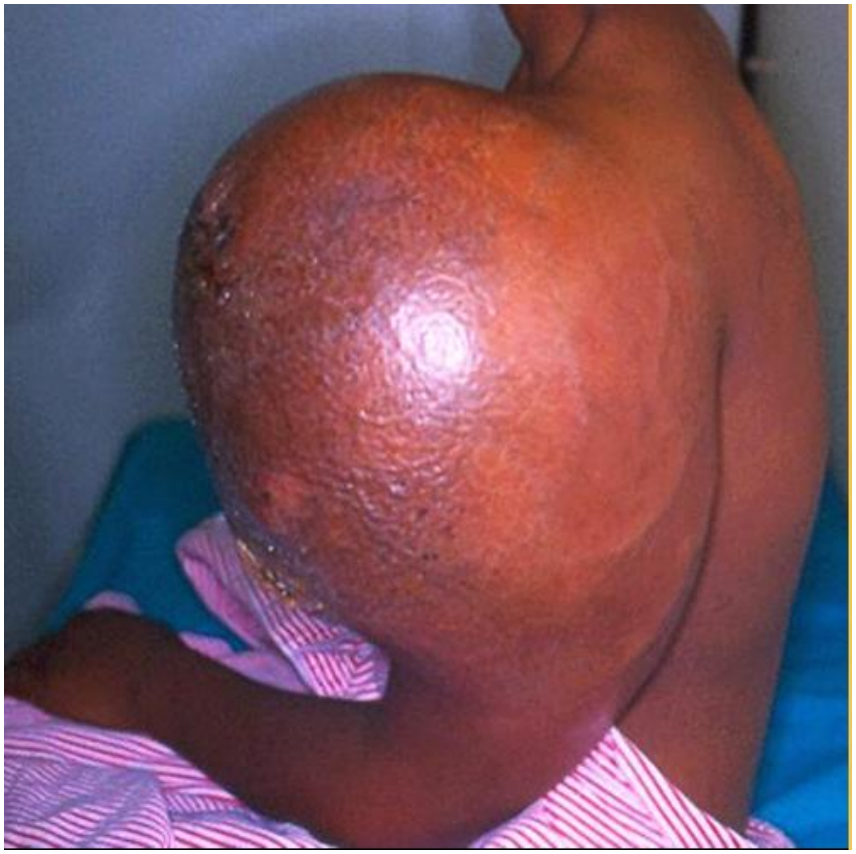
- Osteoblastoma
  - >2cm morphologic overlap
- Intraosseous abscess(Brodie abscess)
  - Rich in inflammatory cells and granulation tissue
- Stress fracture
  - Reactive woven and bone network well oriented around fractured trabeculae

Malignant bone forming tumors

Conventional Osteosarcoma

- High grade malignant tumor in which neoplastic cells produce bone
- Most common primary malignant tumor; exclusive hematopoietic malignancies
- Most patients young, 10 and 20 years of age
- Most commonly in long tubular bones
- Distal femur>proximal tibia>proximal humerus
- Limb salvage; complete excision with wide negative margins optimal
- Preoperative chemotherapy often administered

Clinical



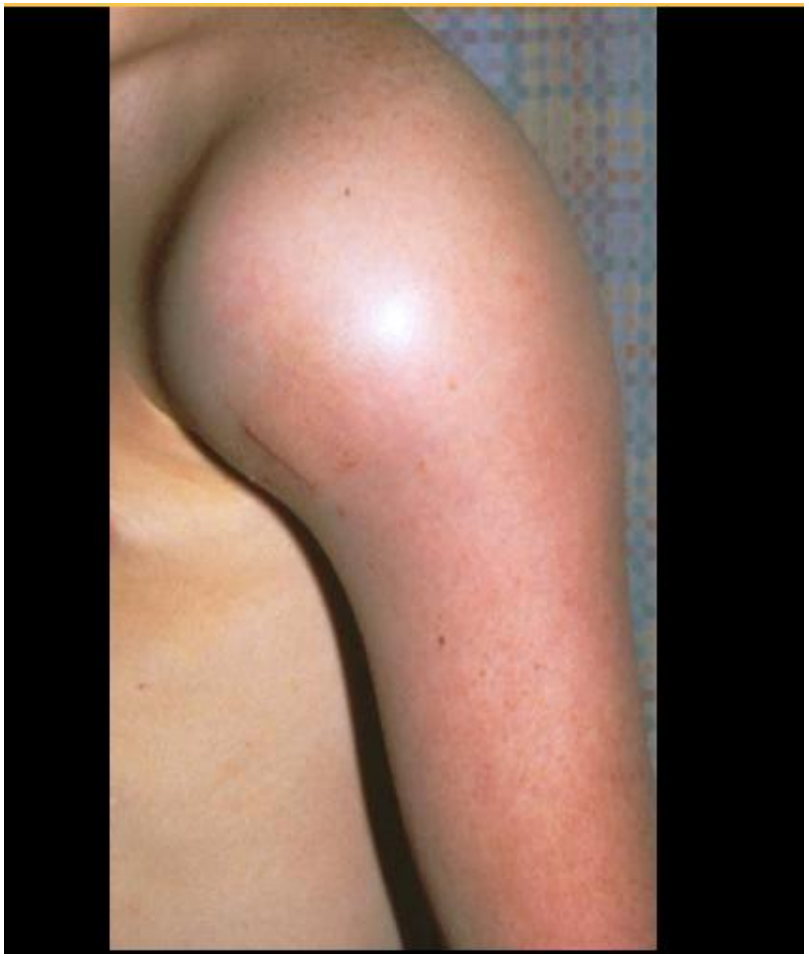
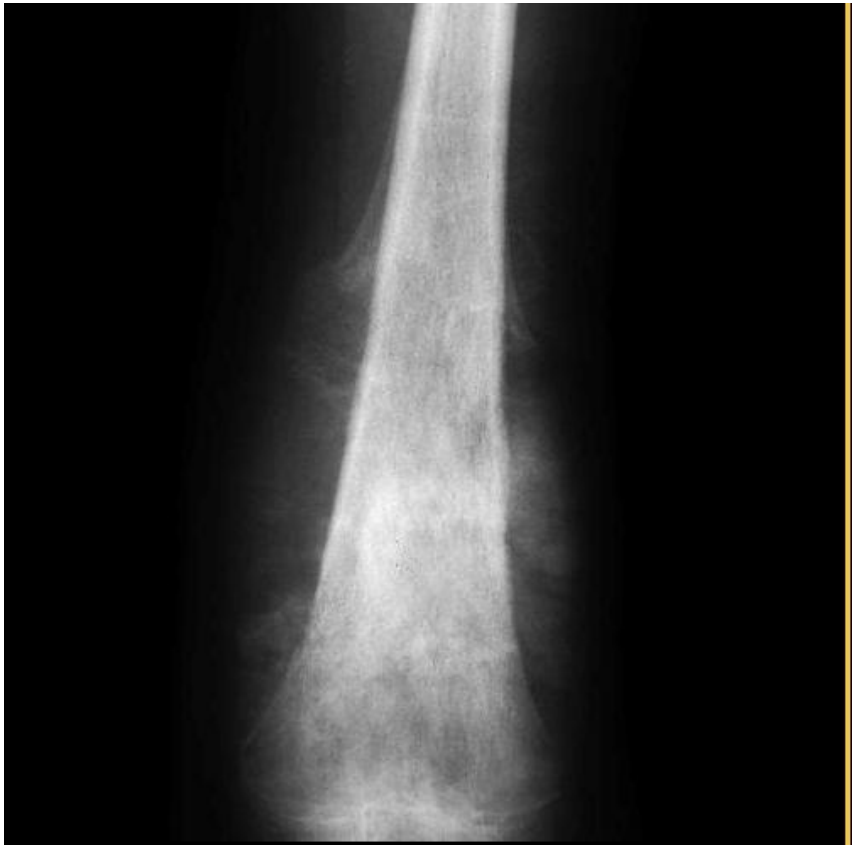
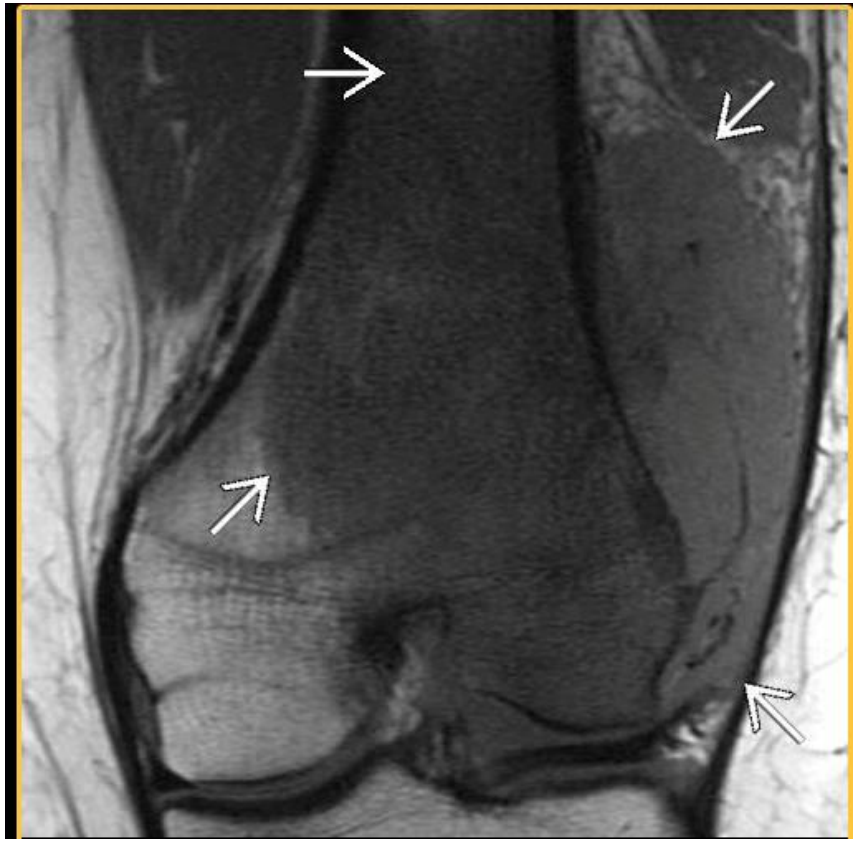


Image findings





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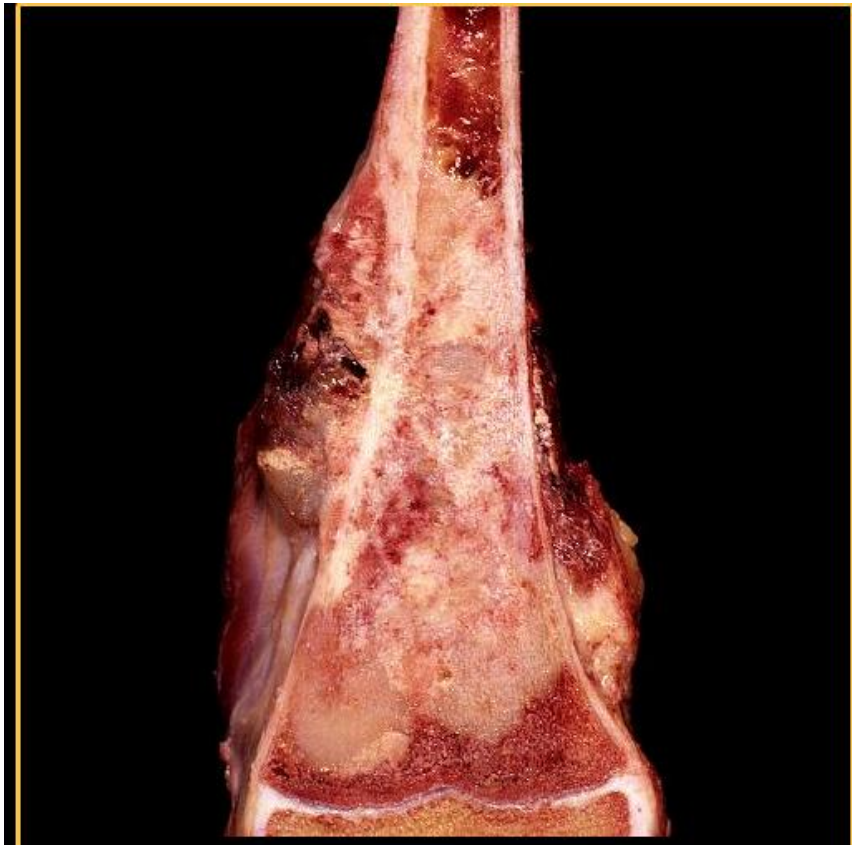

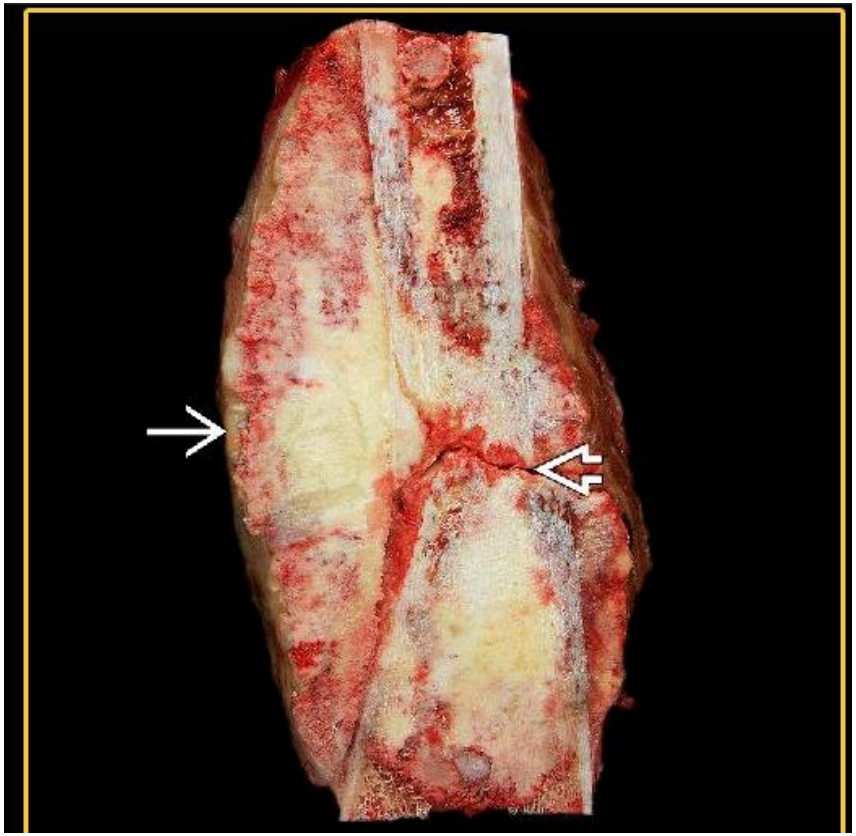

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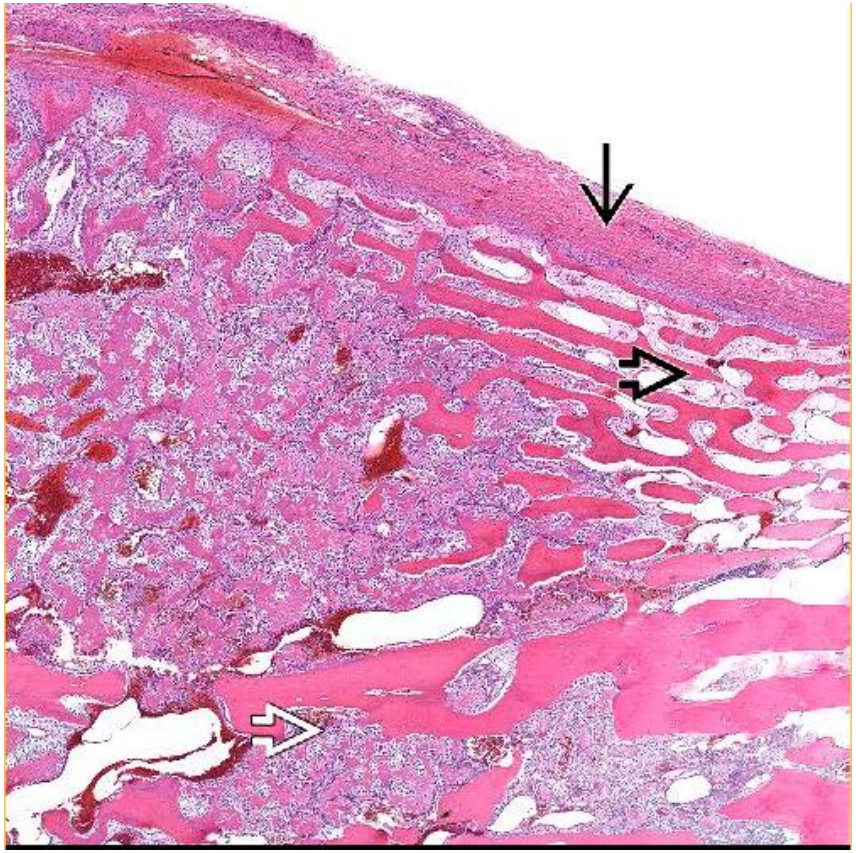
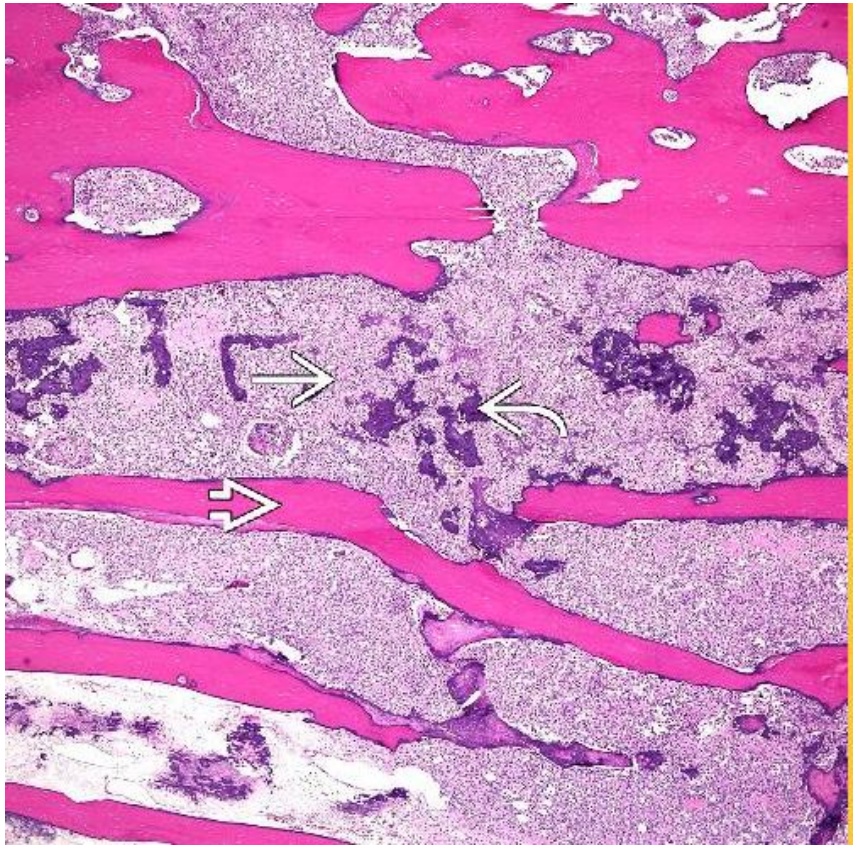
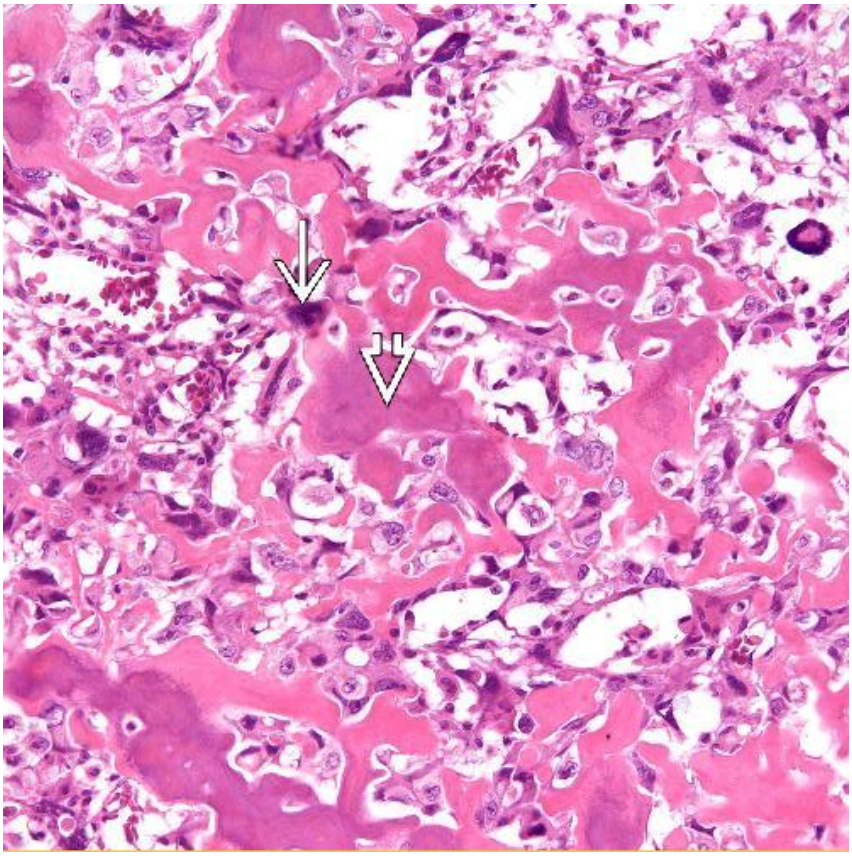
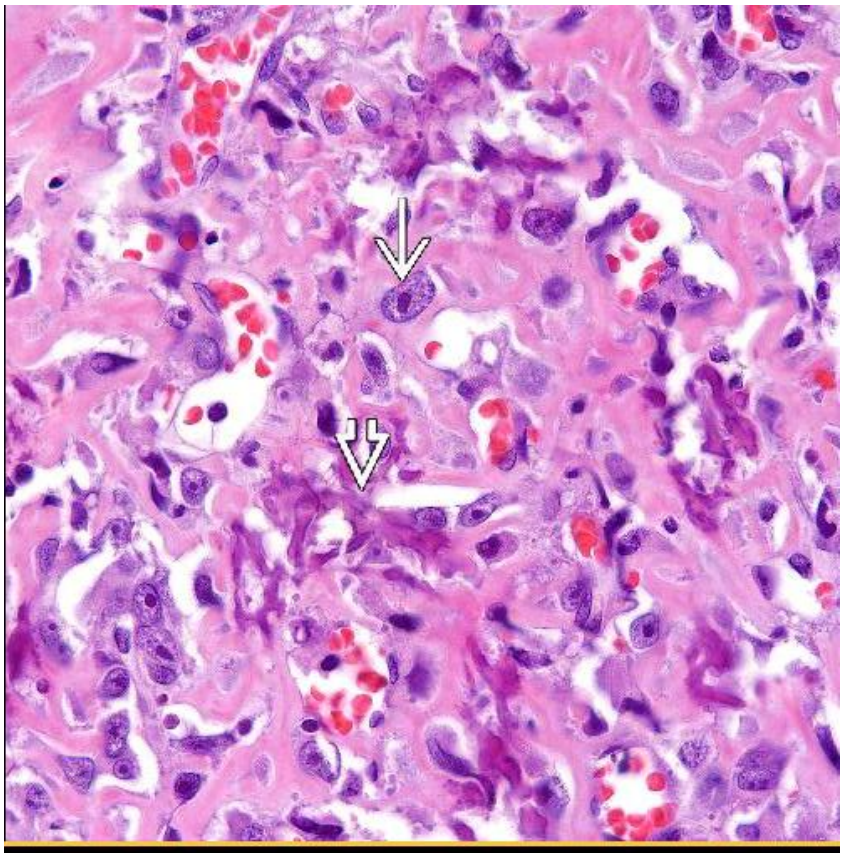
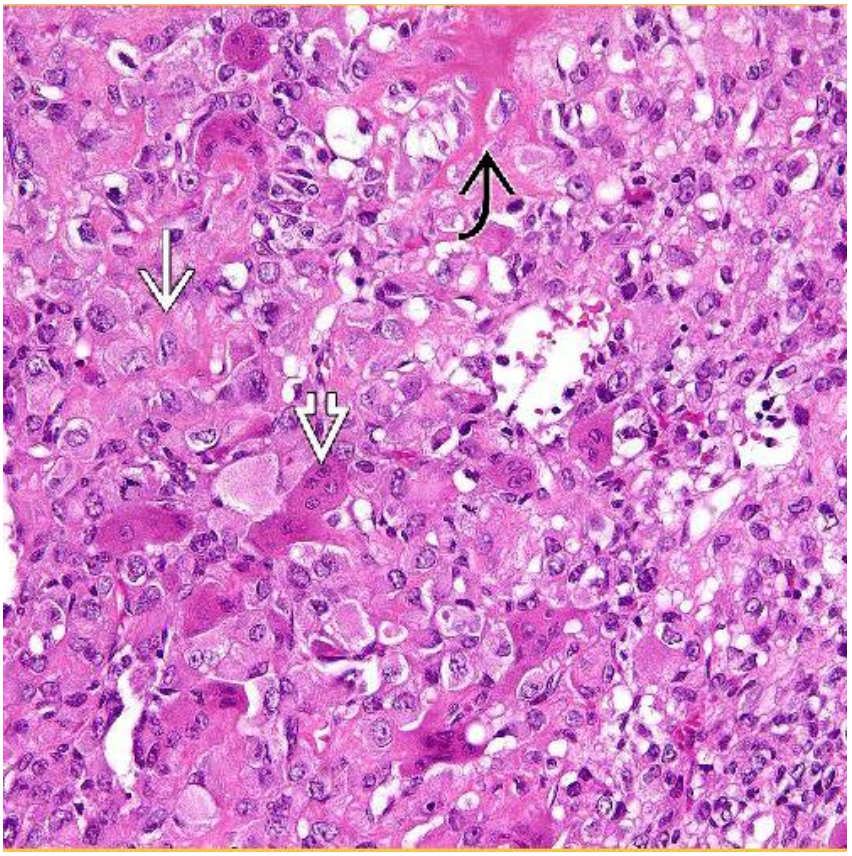










Differential diagnosis

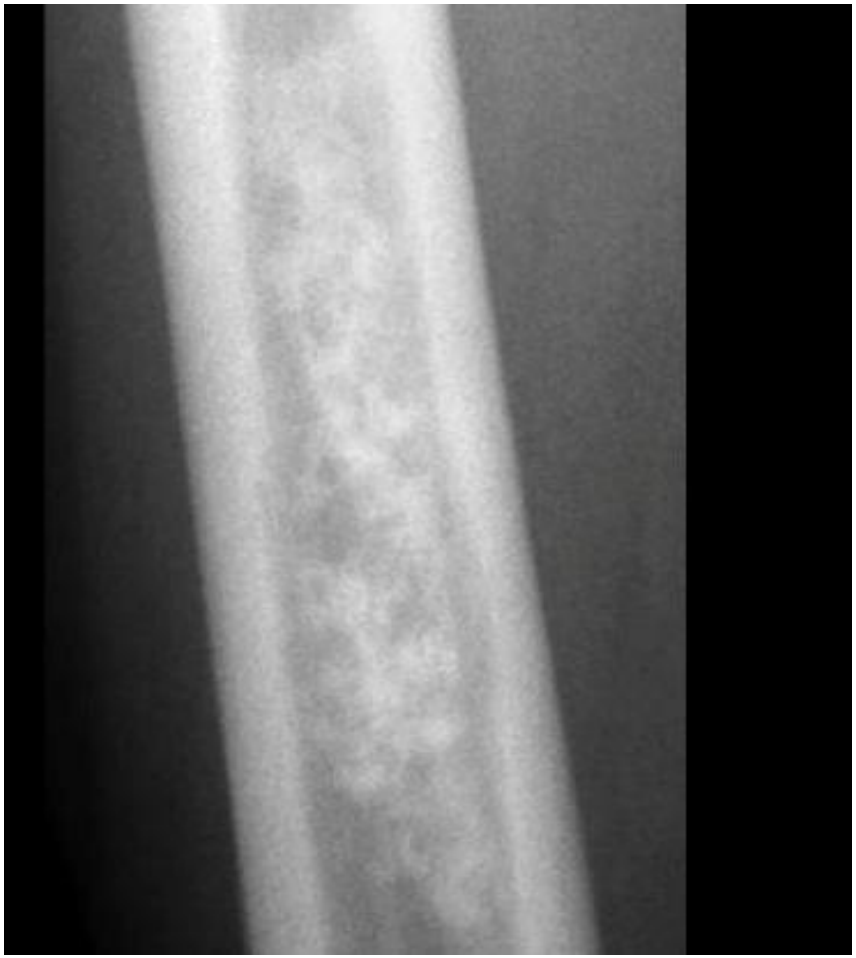
- Osteoblastoma
- Chondrosarcoma
- Myositis ossificans

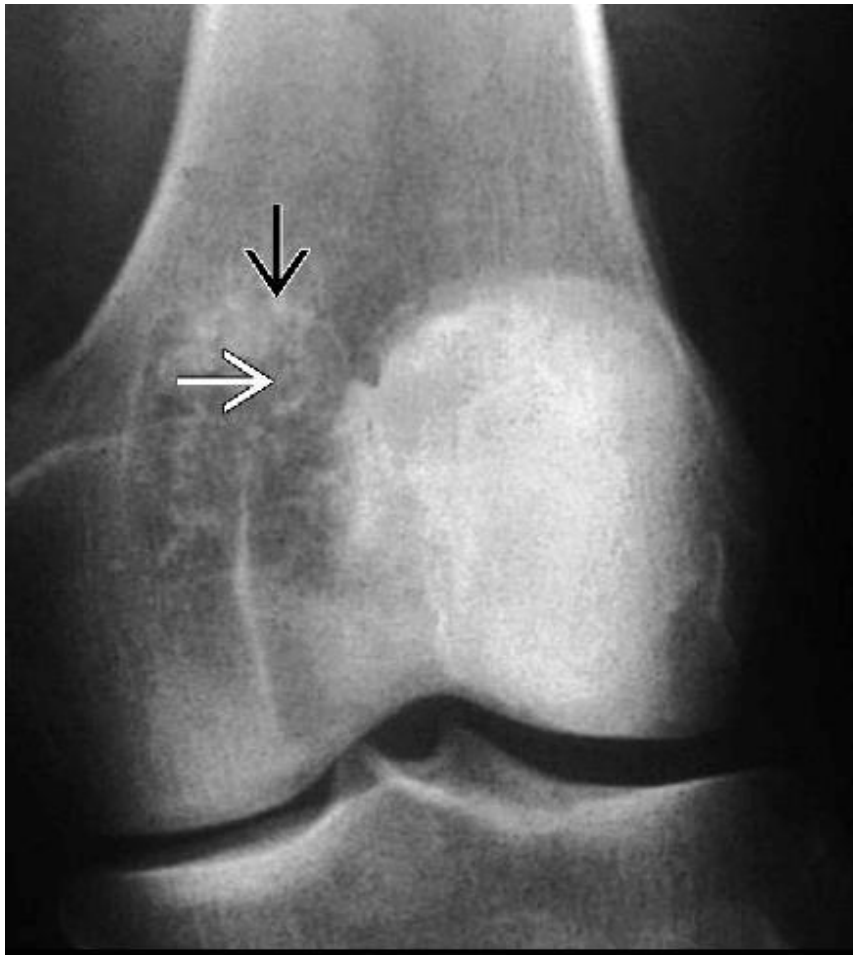
Benign Cartilage Tumors

Enchondroma

- Common benign primary bone tumor that accounts for approximately 3-10% of all bone tumors
- Usually in 3rd to 4th decade
- Almost 90% solitary
- Predominates in distal appendicular skeleton
- Solitary enchondromas can be followed
- Tumors with questionable radiographic findings should be curetted

Image findings





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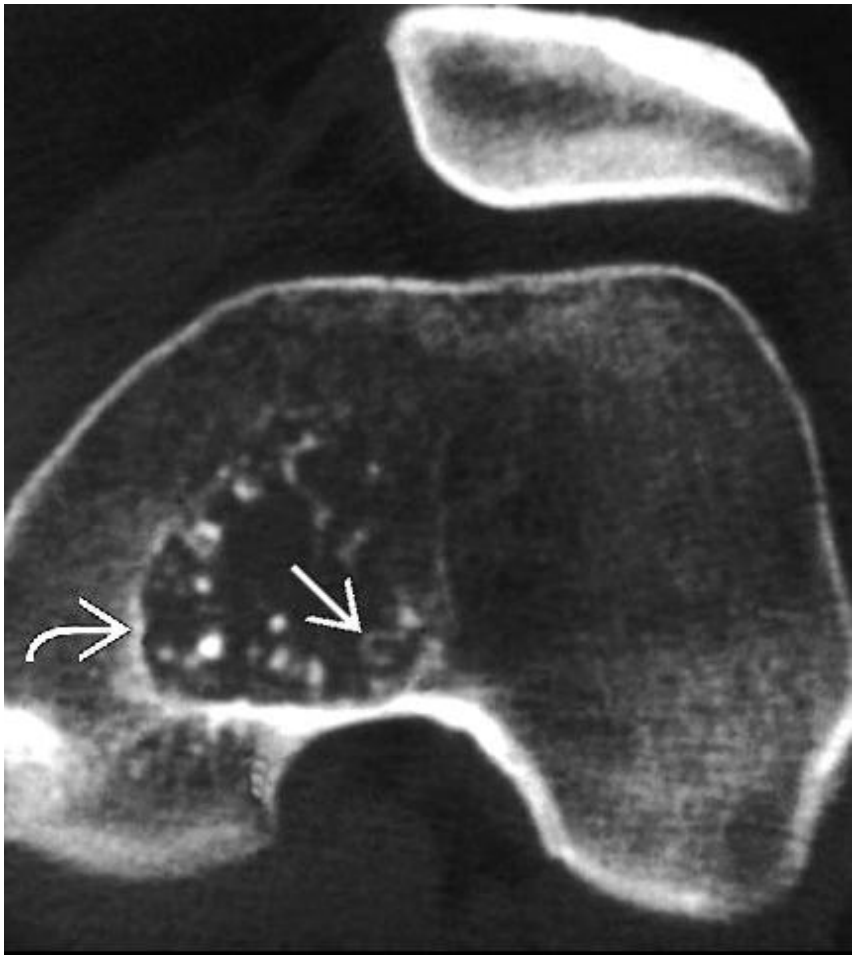
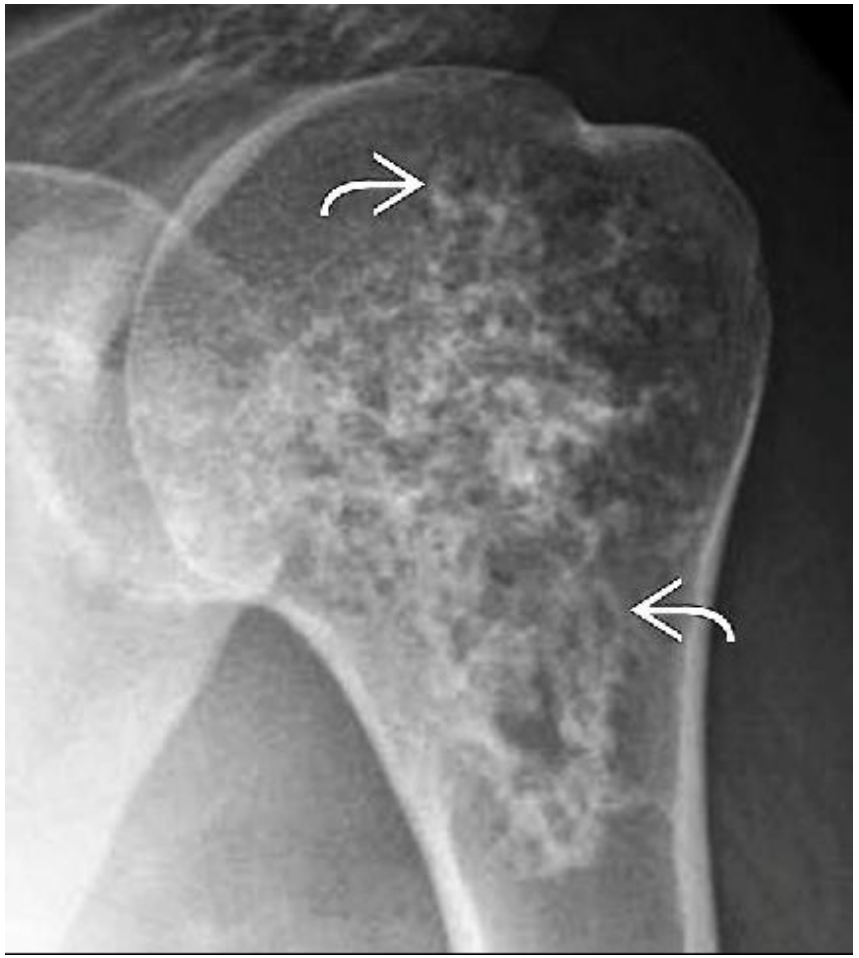
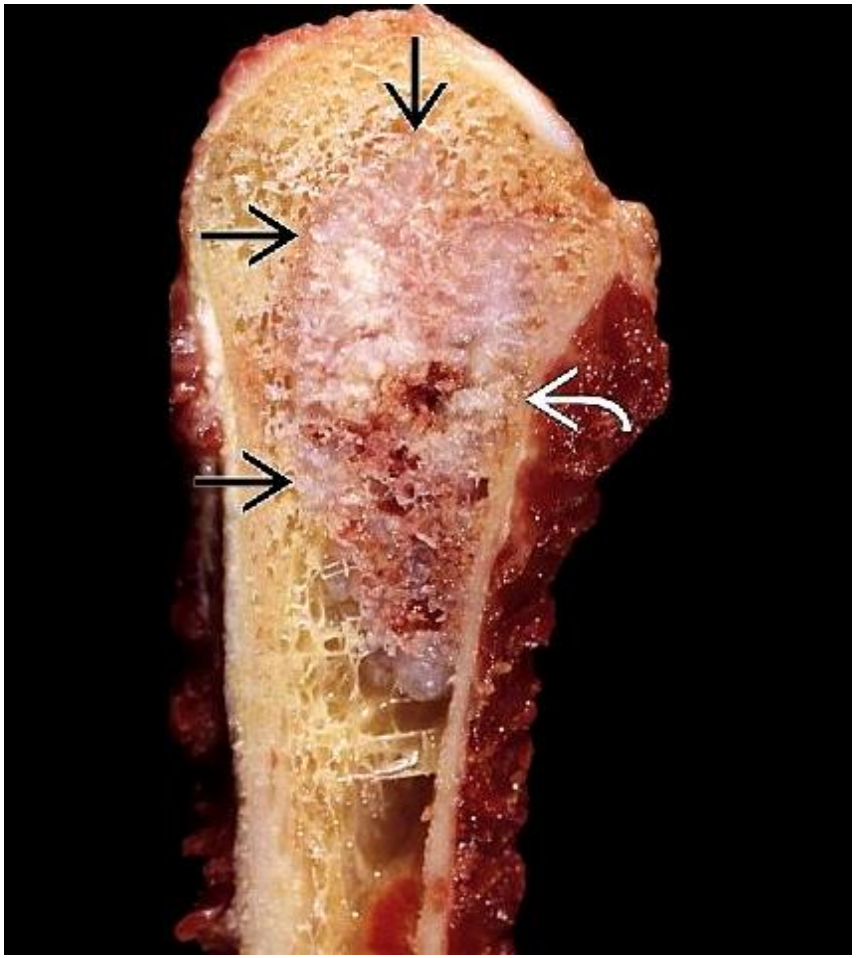
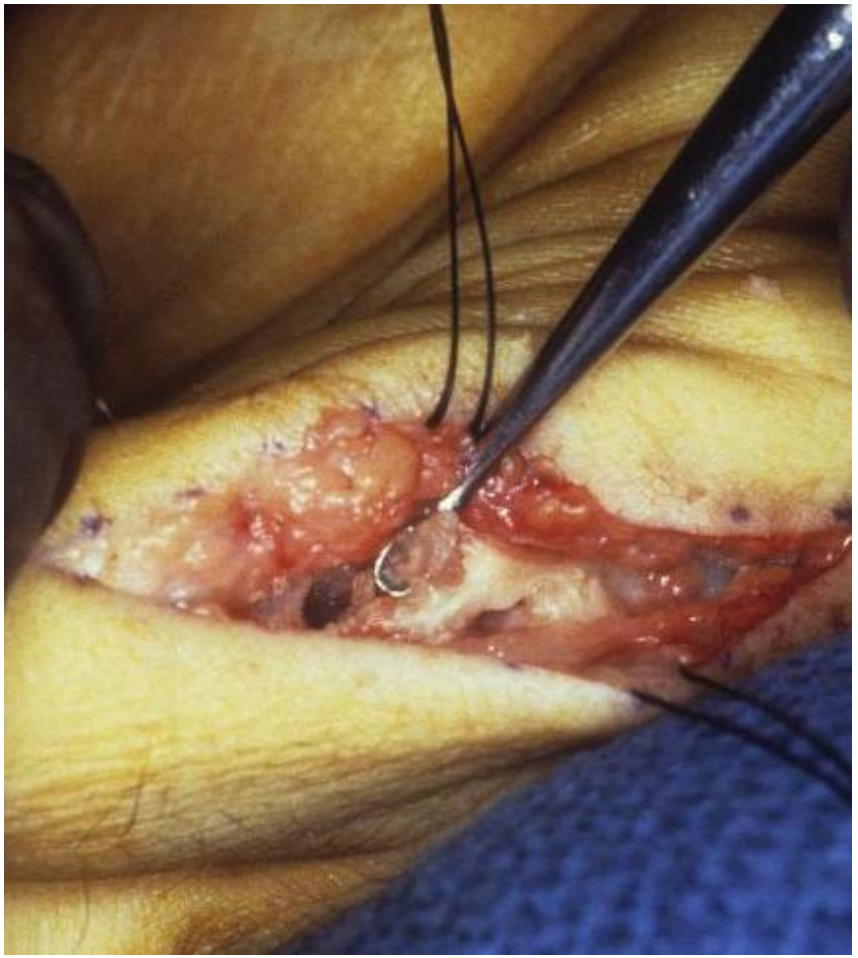


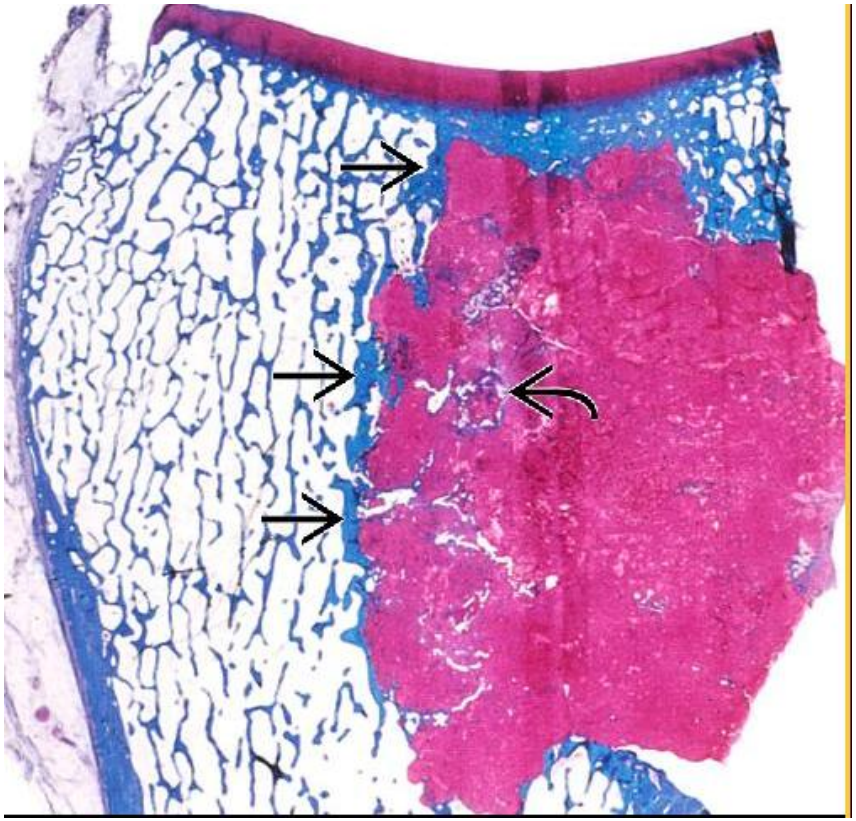


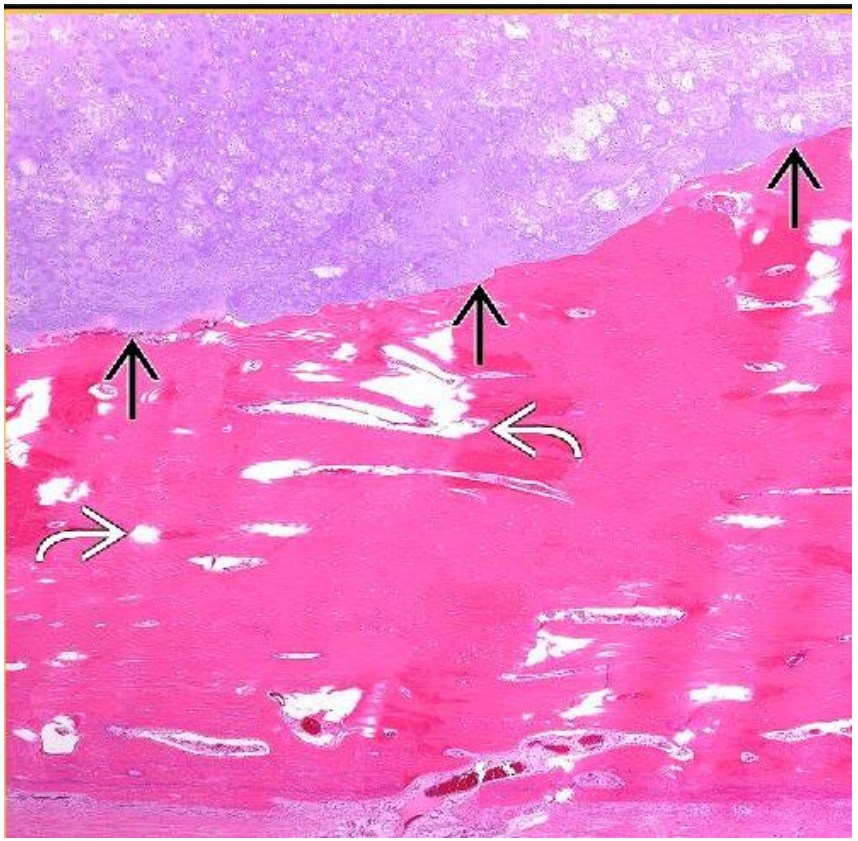
Macroscopic features





Microscopic Pathology





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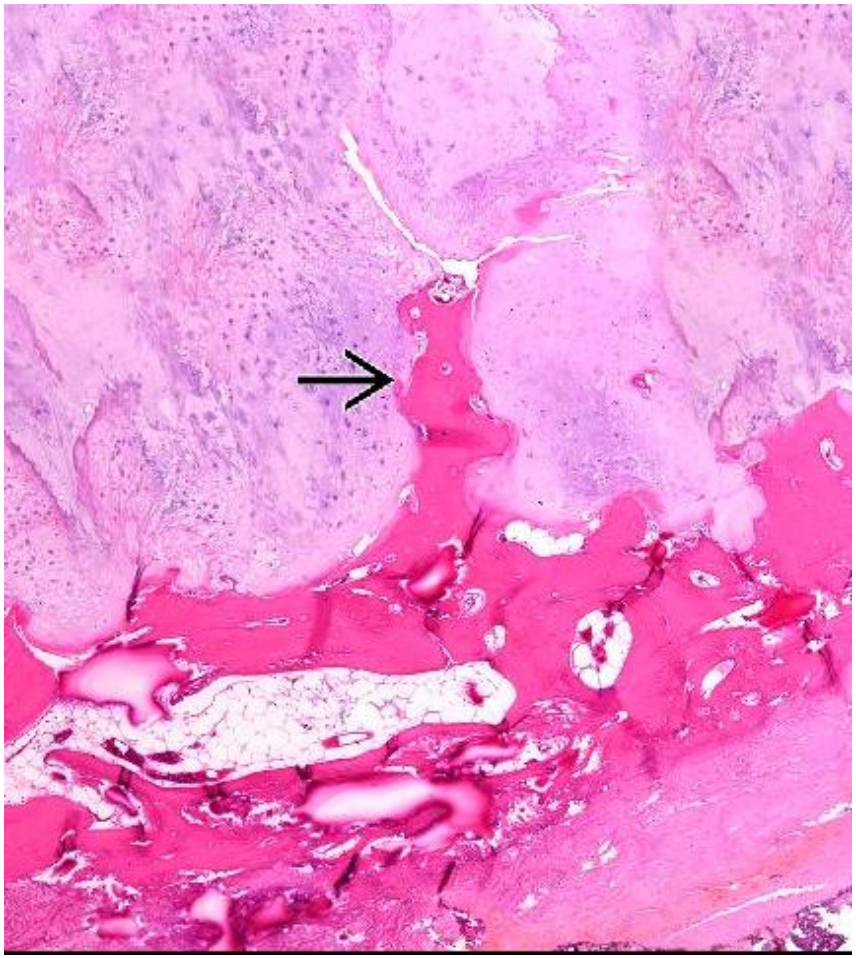

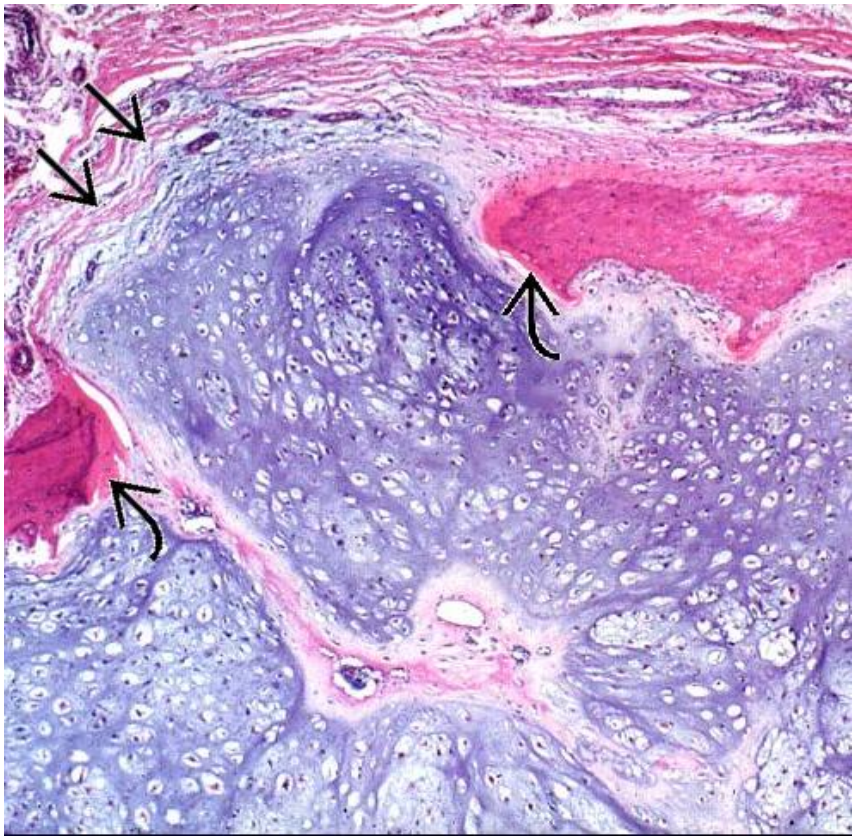

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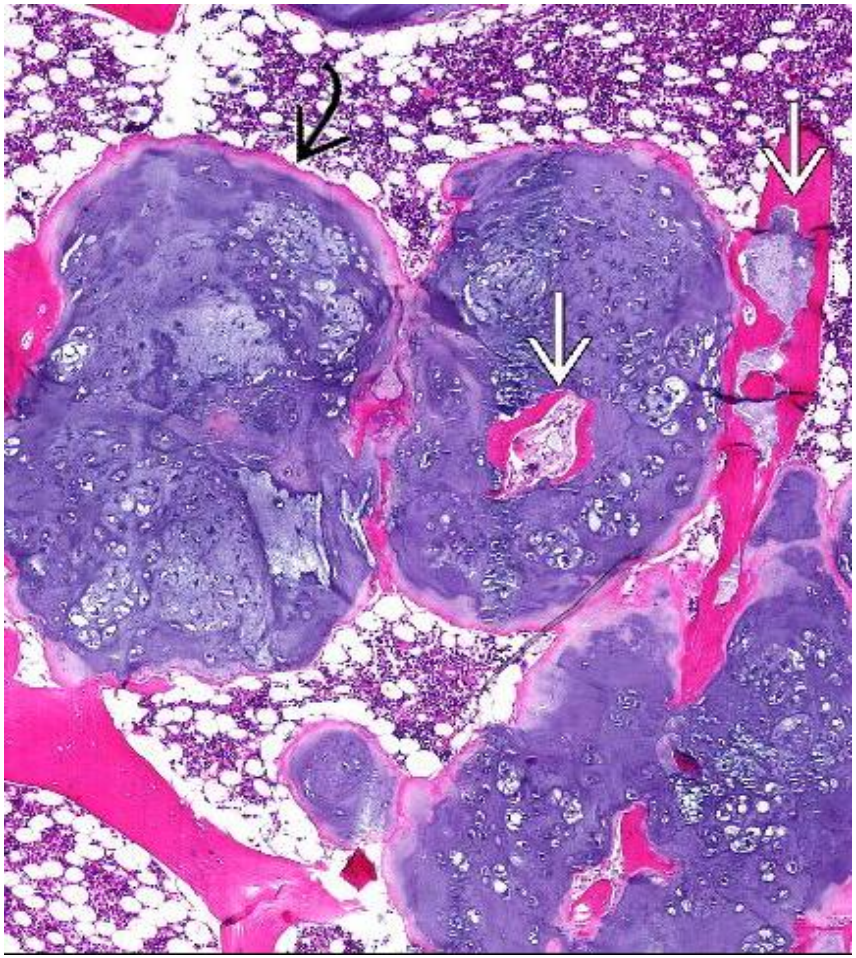
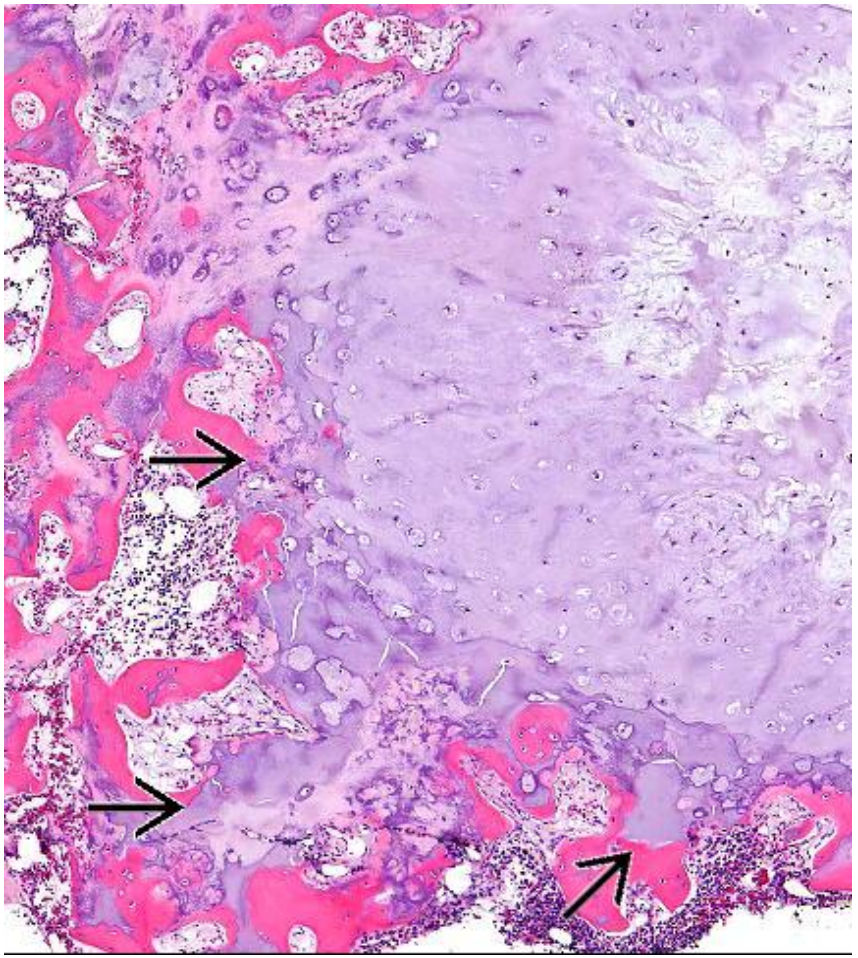




Differential Diagnosis

- Low-Grade chondrosarcoma
  - Grows in infiltrative pattern
  - Greater degree of cellularity
  - Increased nuclear atypia
- Chondromyxoid fibroma
  - Contains myxoid and fibrous elements
  - Lacks well-formed hyaline cartilage

Enchodromatosis

- Definition
  - Multiple enchondromas may be a/w Ollier disease or Mafucci syndrome
    - 90% of patients with multiple enchondromas have Ollier disease
    - 10% are a/w Mafucci syndrome
- Ollier disease
  - >3 enchondromas affecting short and lobular bones
- Mafucci syndrome
  - >3 enchondromas a/w extraosseous hemangiomas (spindle cell hemangiomas)
- Etiology/Pathogenesis
  - In Ollier and Mafucci syndrome by somatic mutations involving IDH1 and IDH2

Epidemiology and Site

- Frequently 1st noted during childhood
  - In Ollier disease cartilage tumors may stabilize in size after puberty or continue to grow
- Enchondromas may involve
  - Only small bones of hands and feet
  - Only long bones, scapulae and pelvis
  - Small, long and flat bone
  - Involvement of skull and vertebrae is rare.
- Tends to affect 1 side of the body more severely
- Hemangiomas in Mafucci syndrome usually located in skin or soft tissue
  - May be centered in viscera

Presentation and Natural History

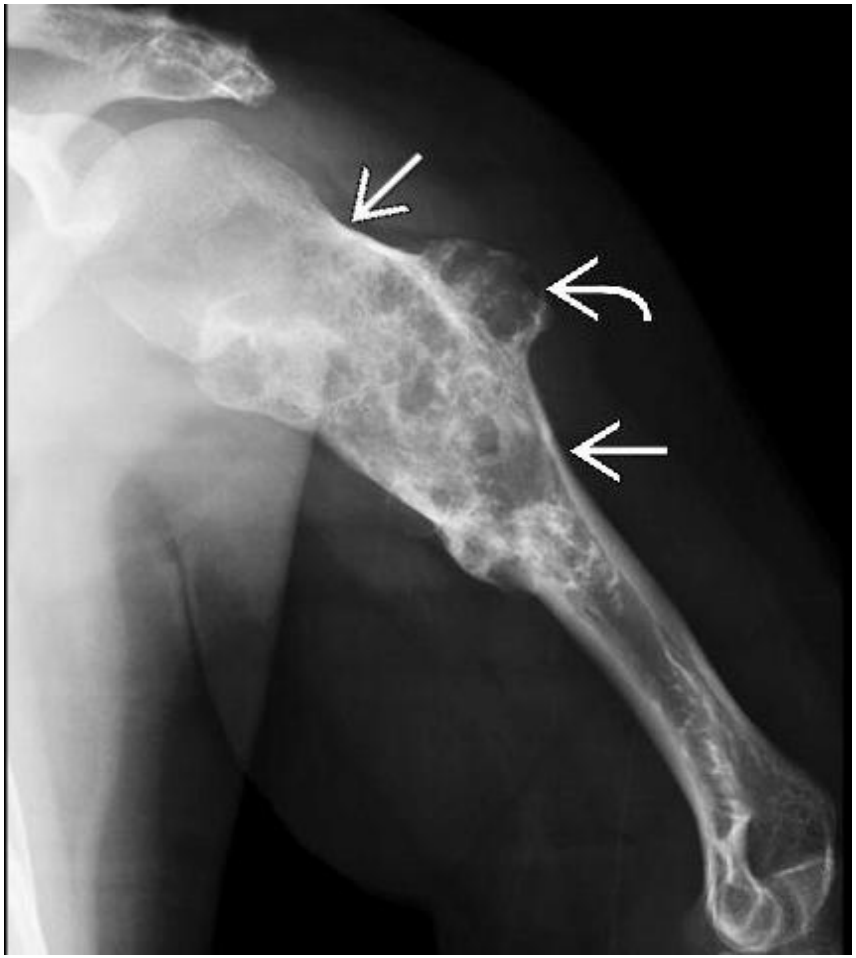
- Initial symptoms related to enlargement of fingers
- May have anywhere from 3 to hundreds of tumors
- In Ollier may stabilize in size after puberty or continue to grow
- Development within viscera as well as in enchondromas is an important aspect of Mafucci syndrome
  - Carcinomas of pancreas and malignancies of ovaries, brain and skeleton are commonplaces in Mafucci syndrome
- Chondrosarcoma is major malignancy a/w Ollier disease

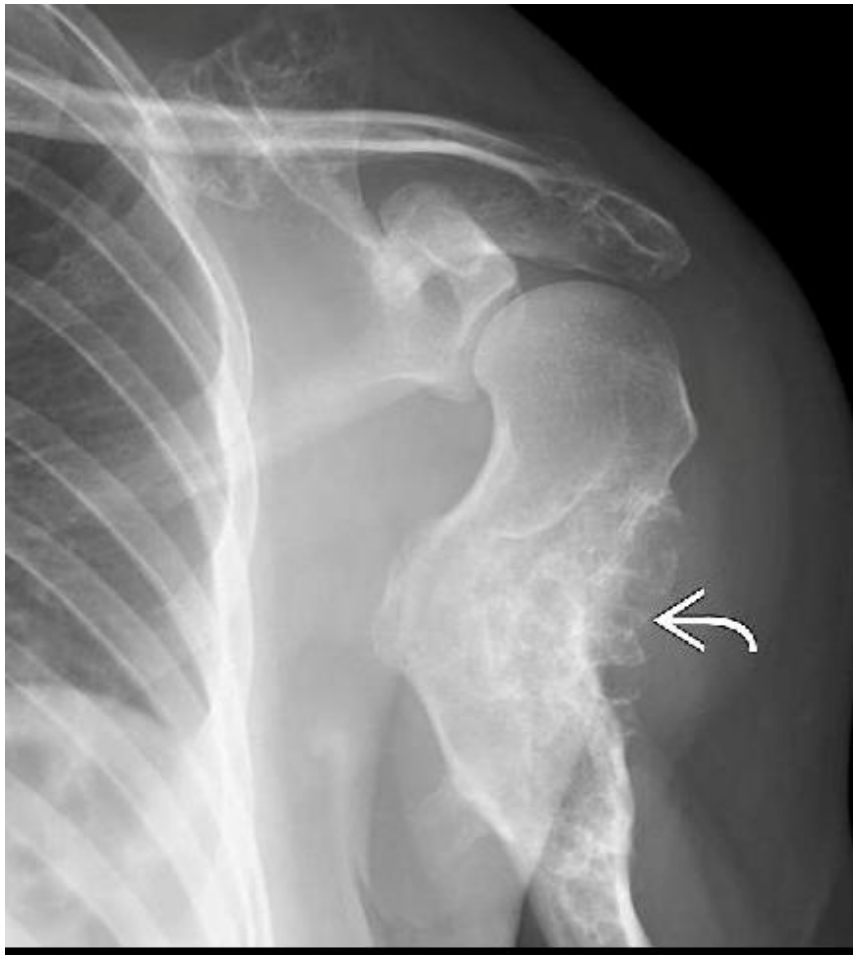
Treatment and Prognosis

- No specific treatment

- Overall risk of malignant transformation into chondrosarcoma is 40%
  - More common in patients with severe skeletal involvement or involvement of long and flat bones

Image findings





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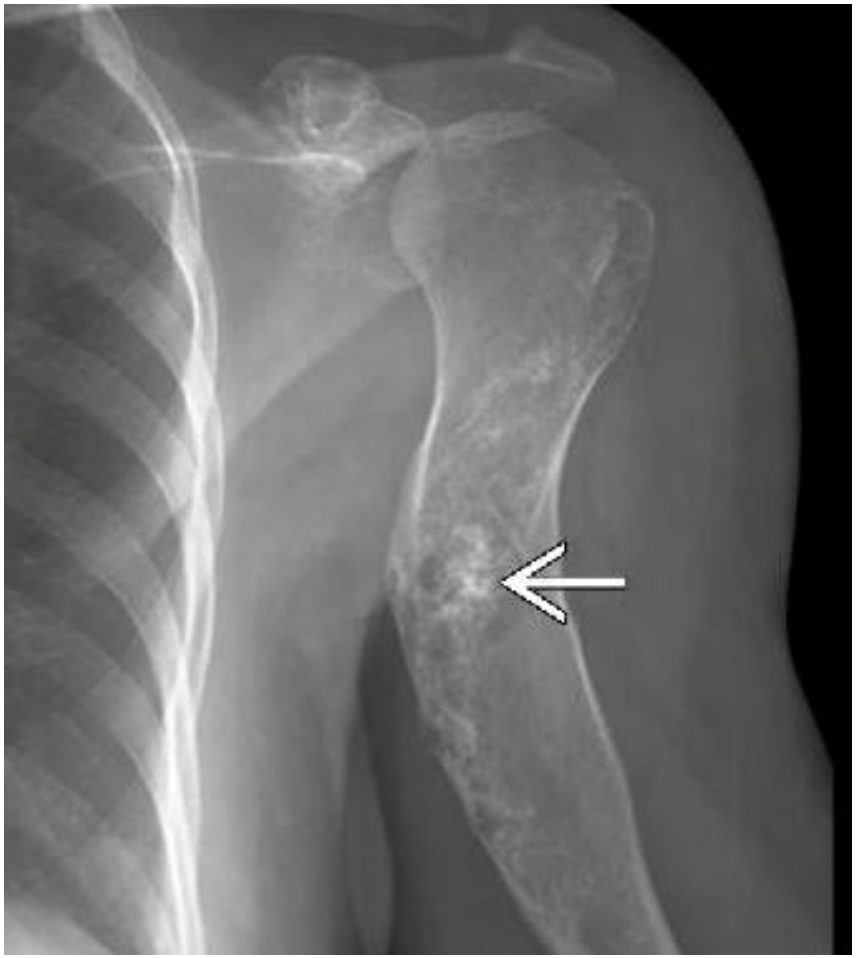

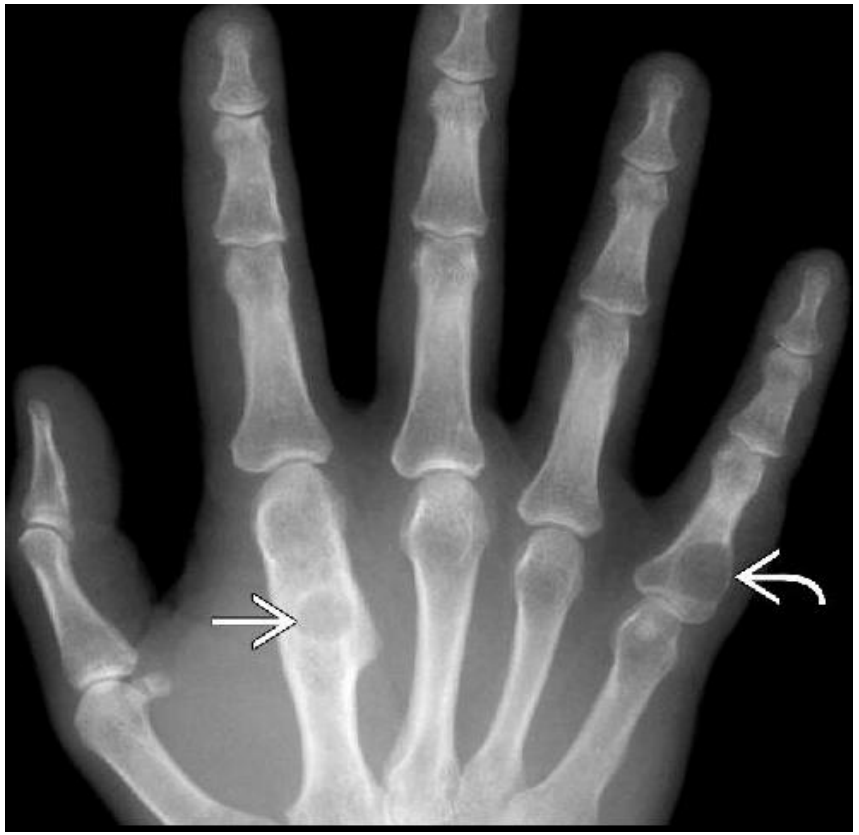

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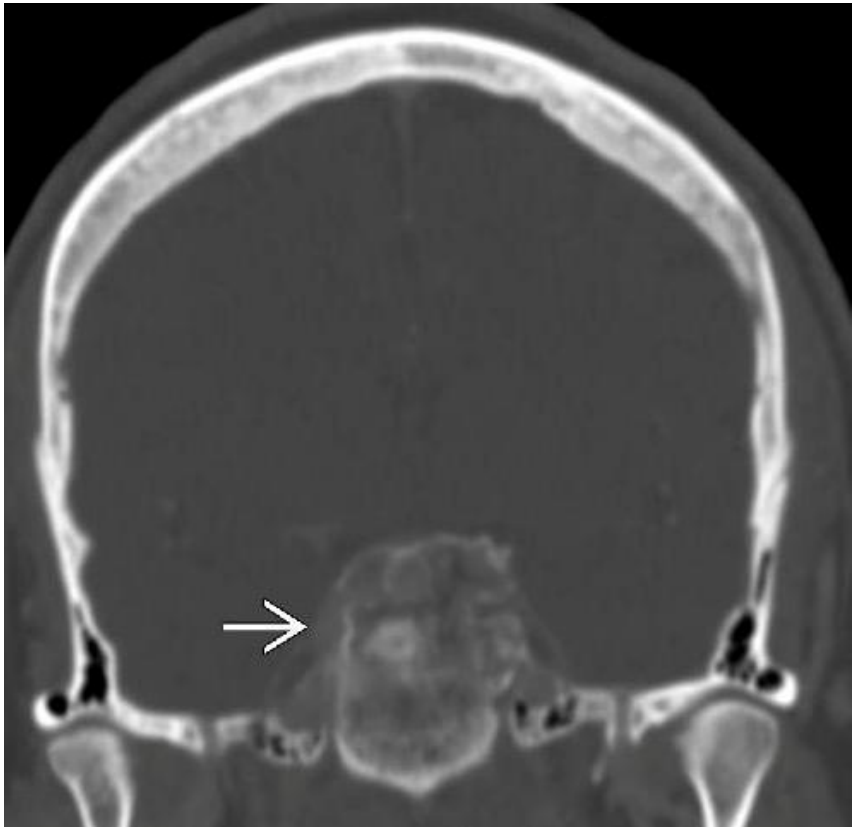

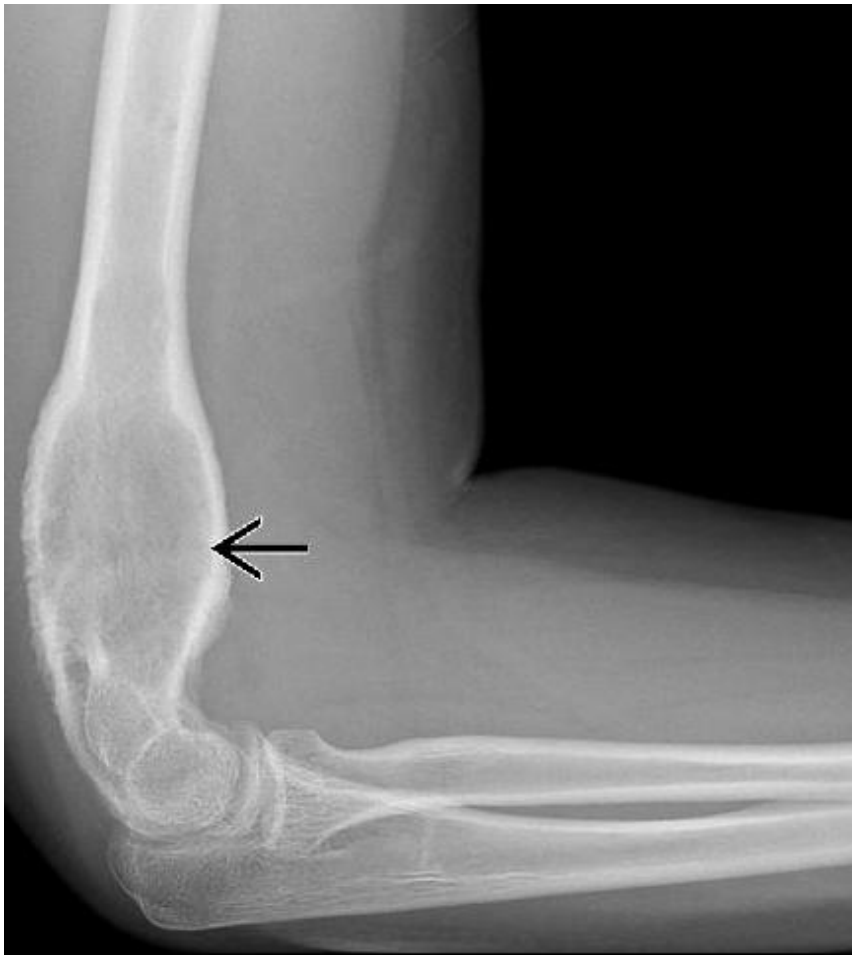

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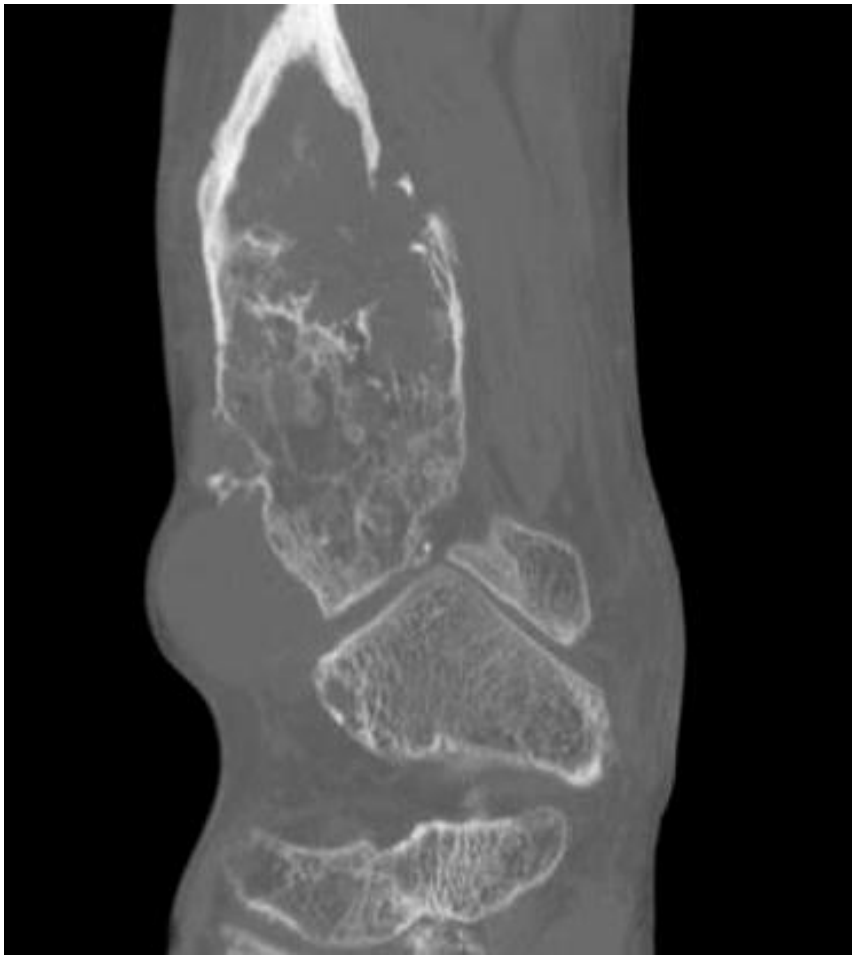
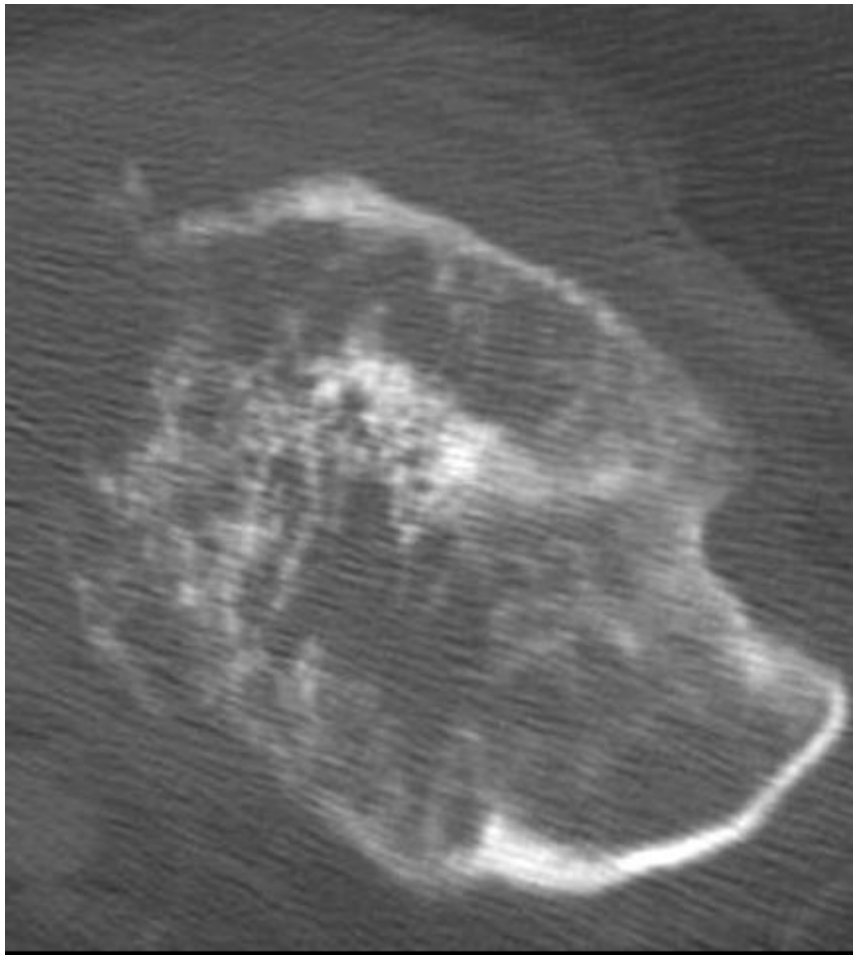
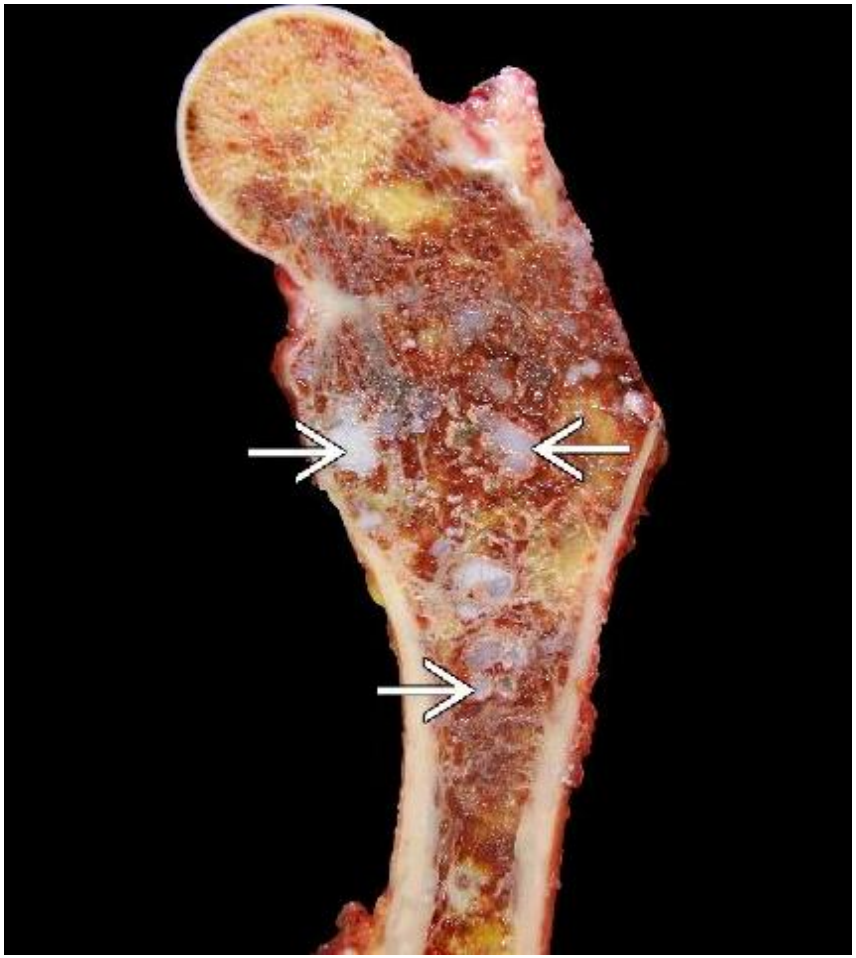
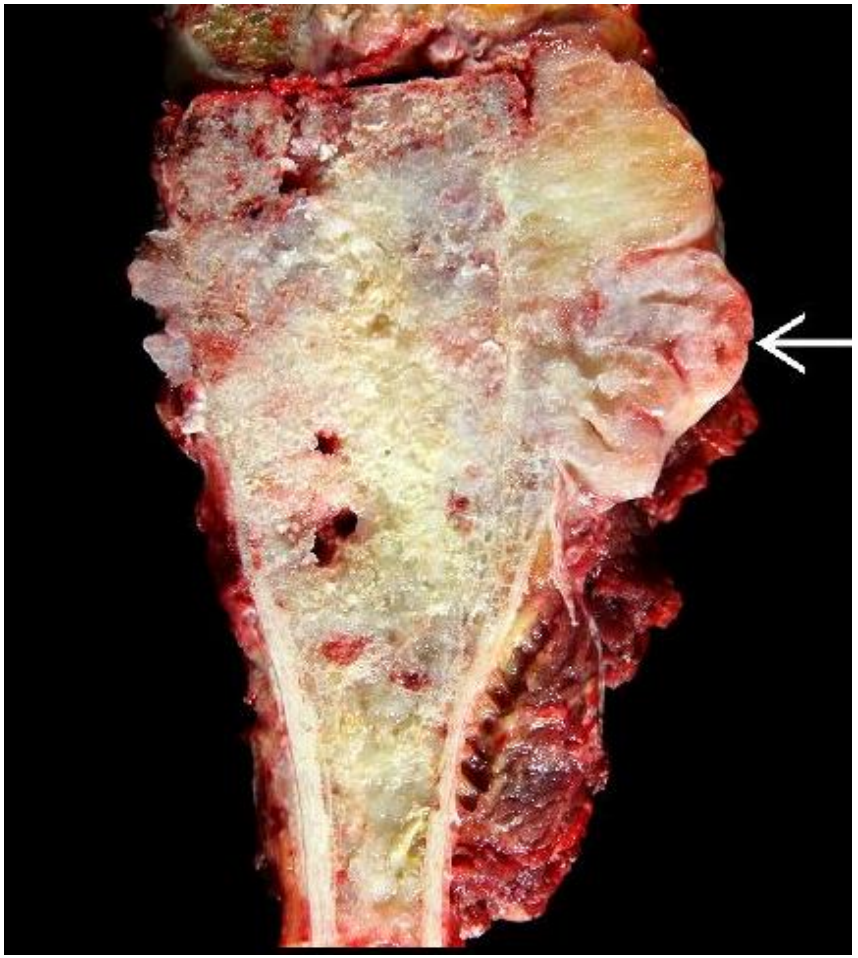




Macroscopic features





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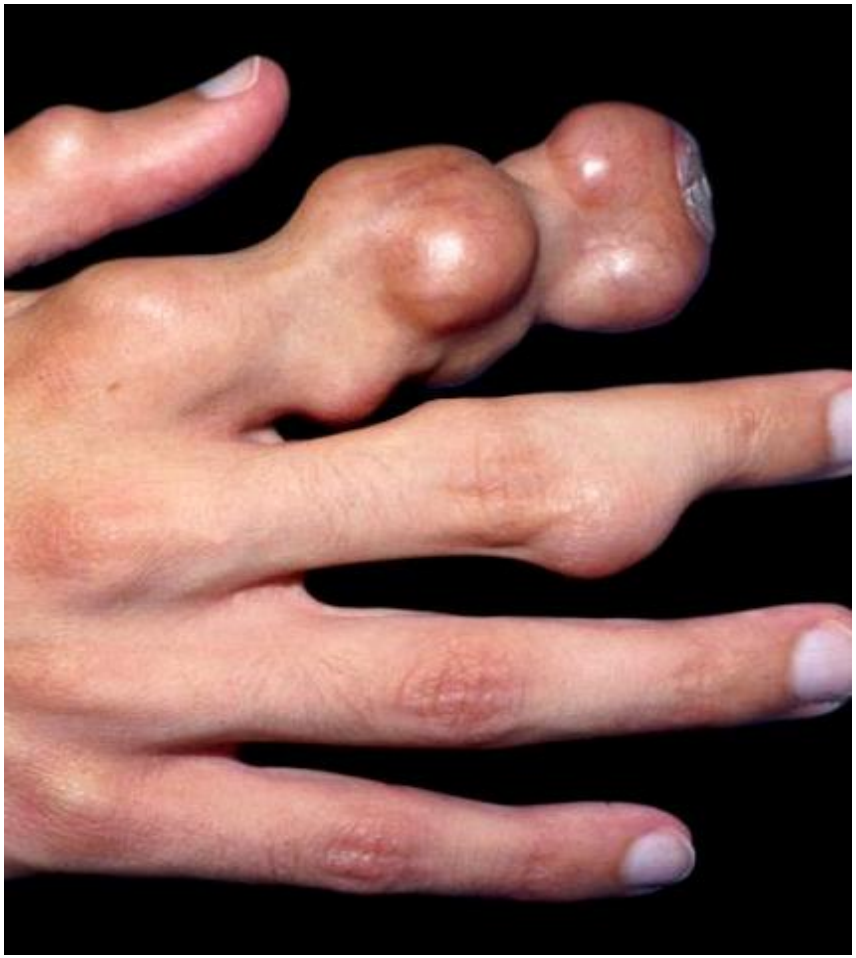

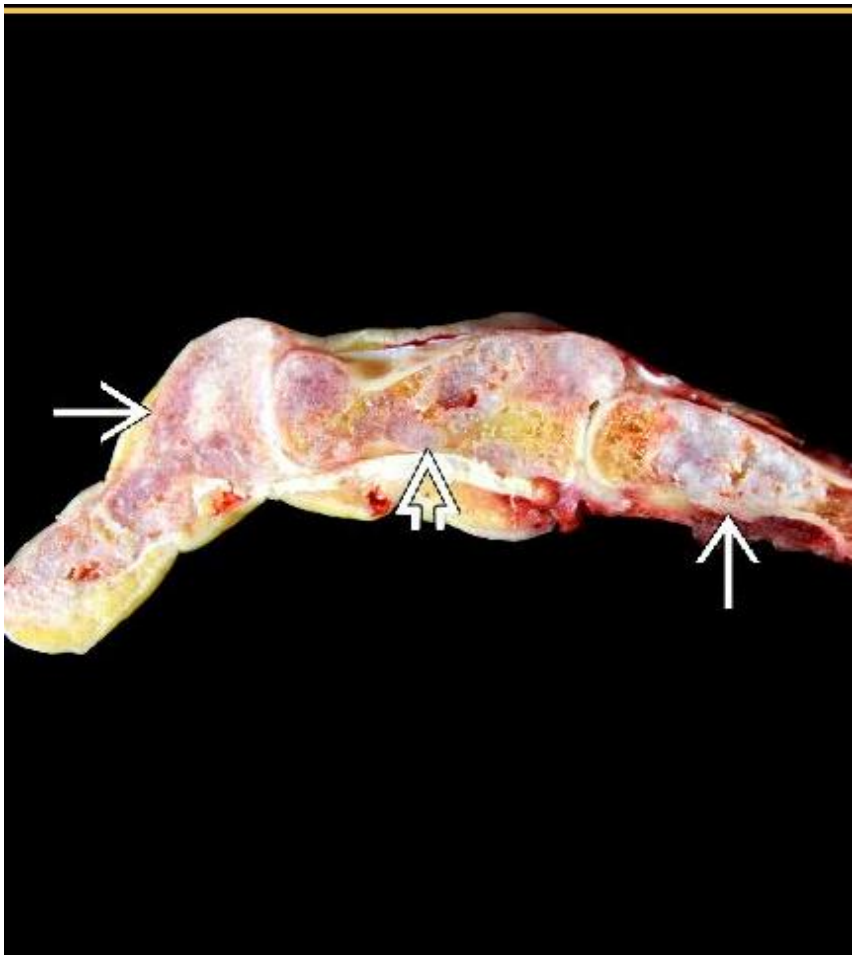

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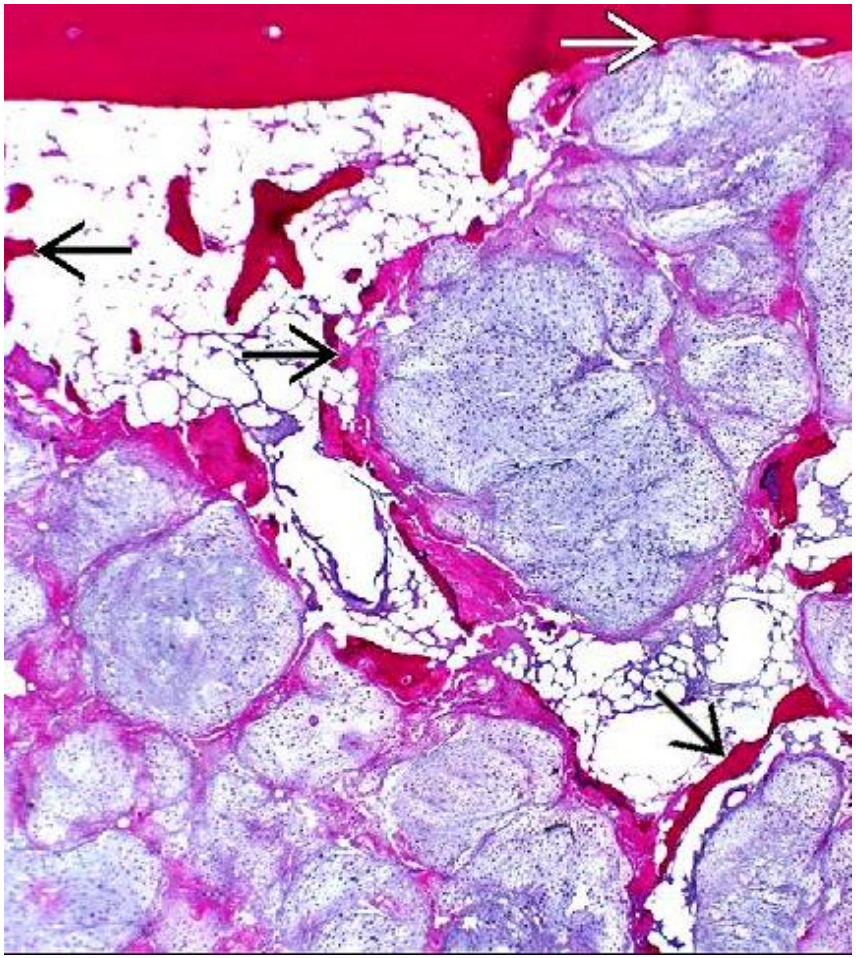
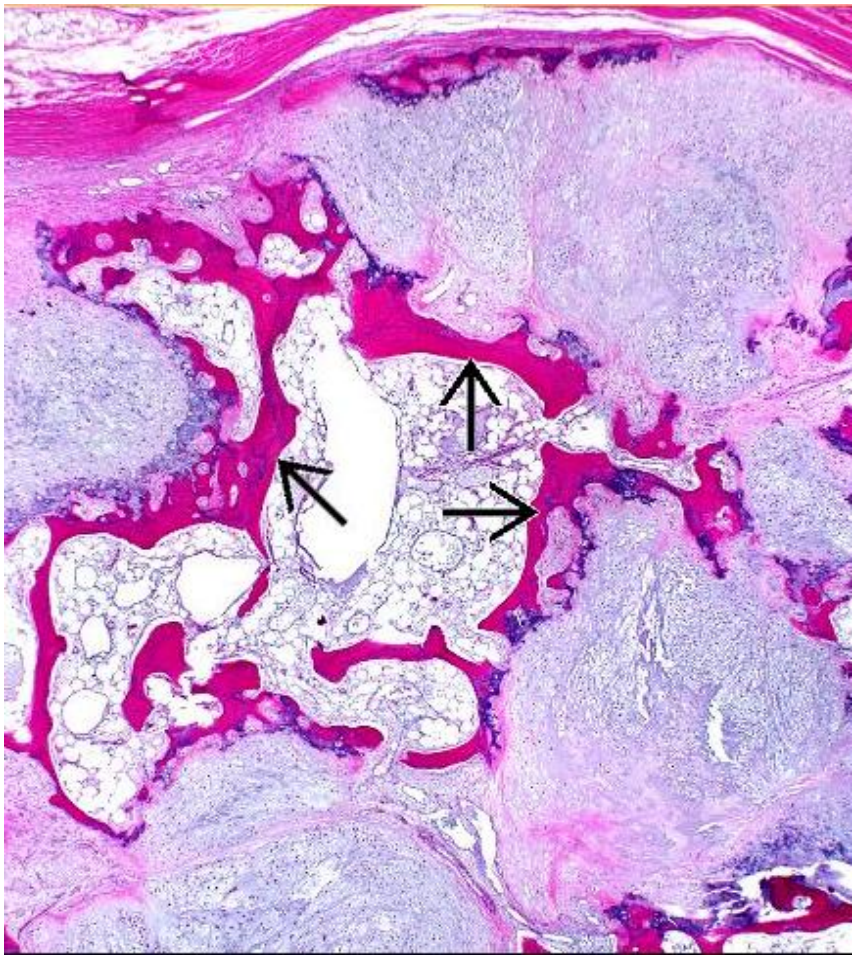
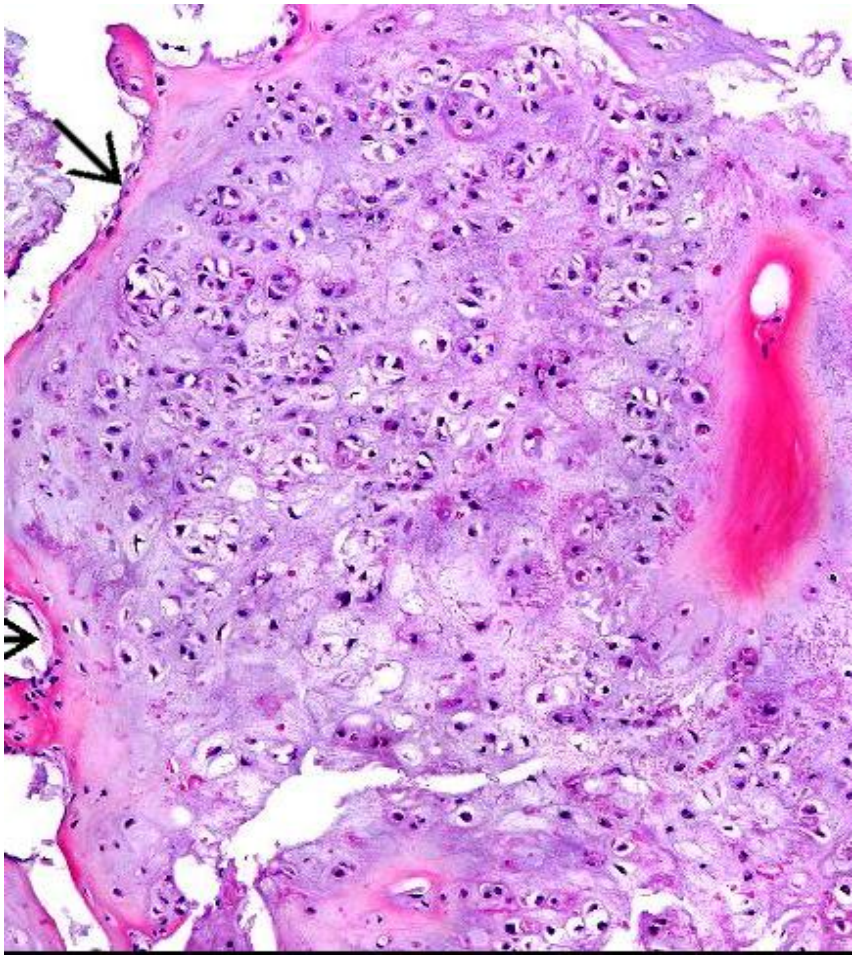
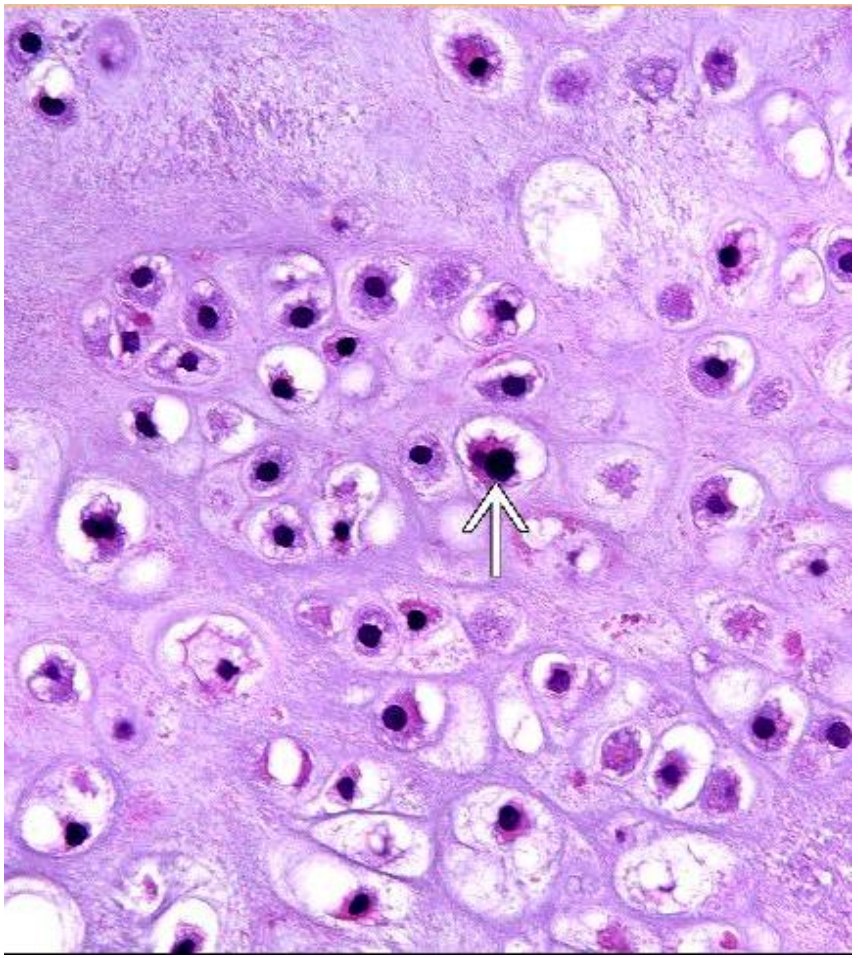




Microscopic Pathology





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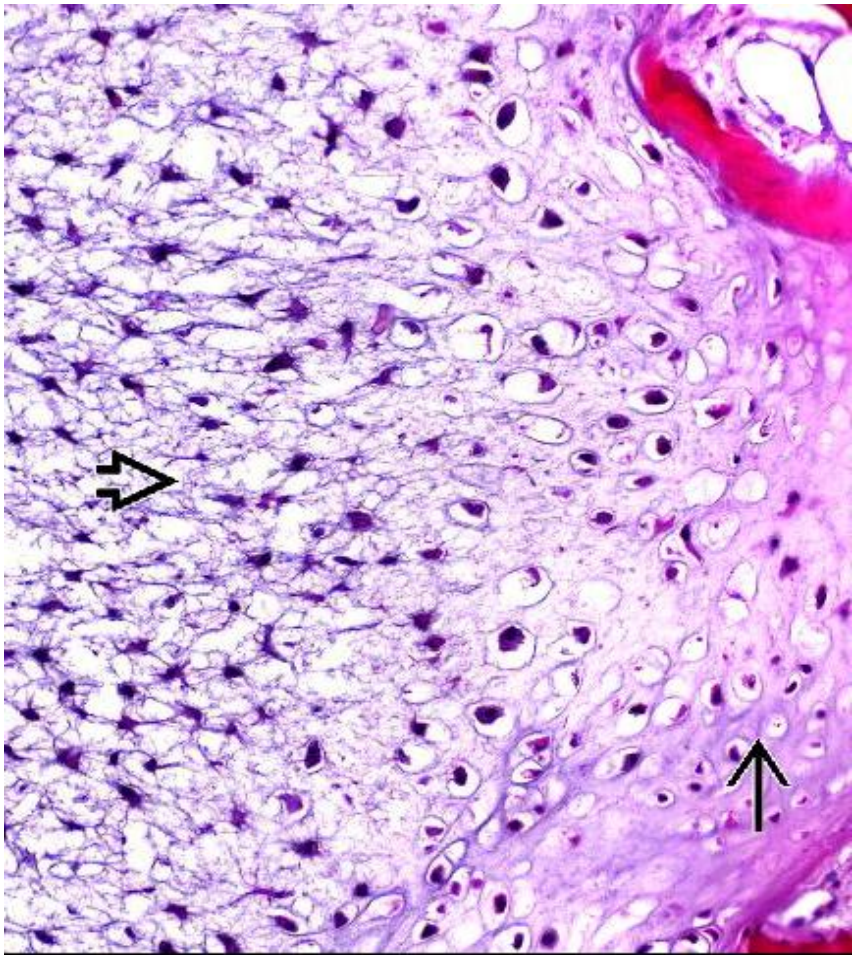
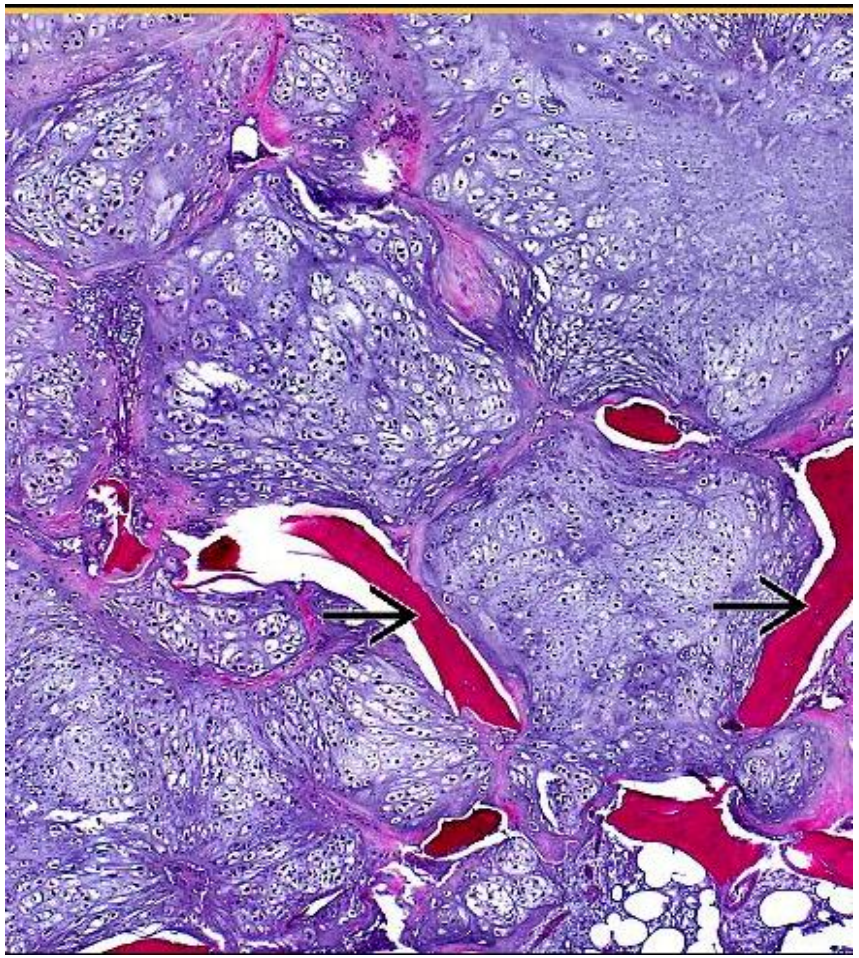
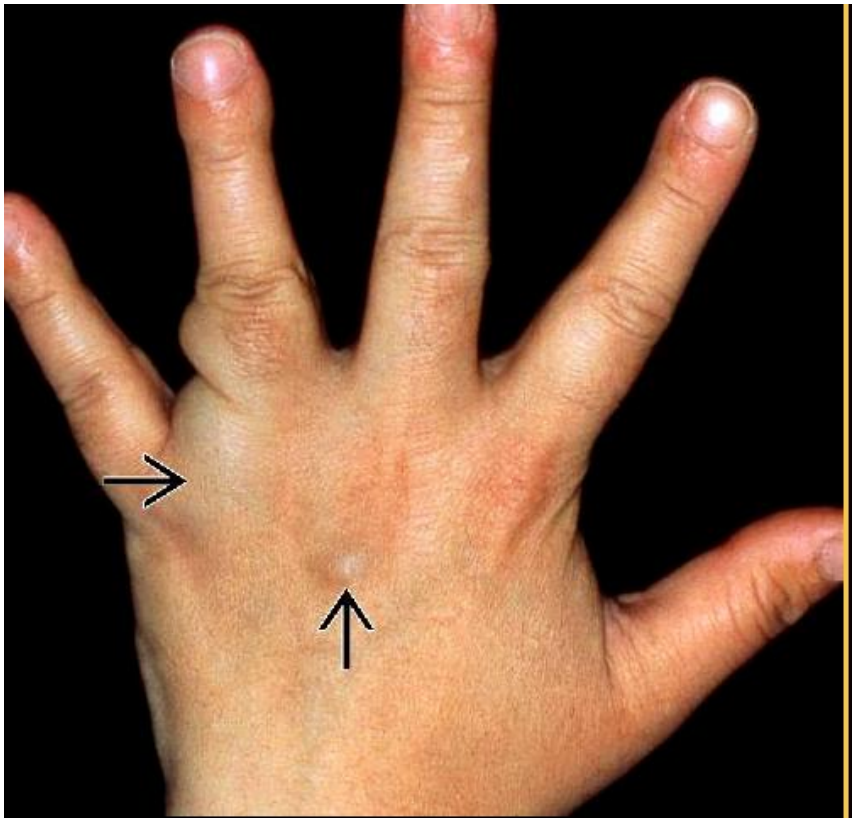
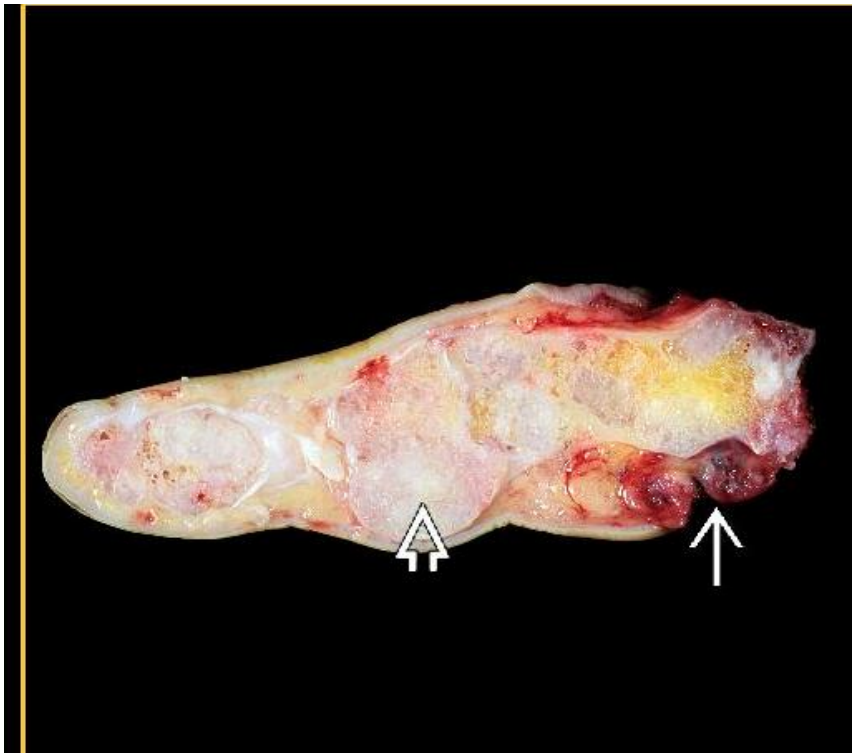
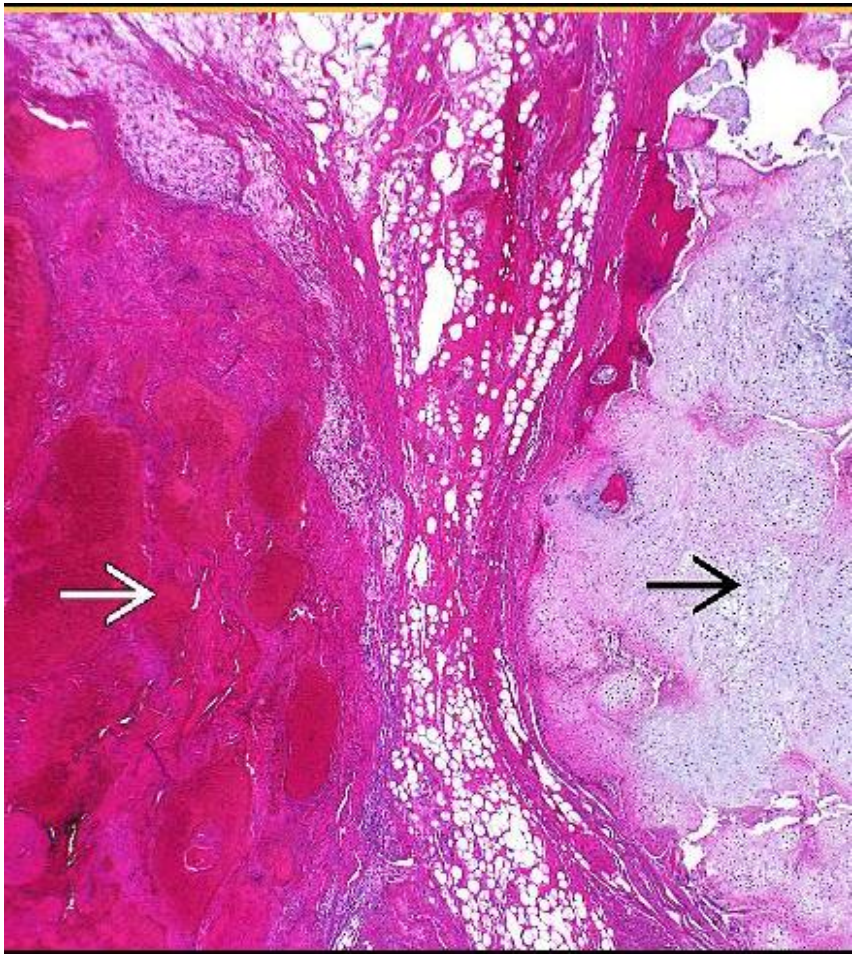


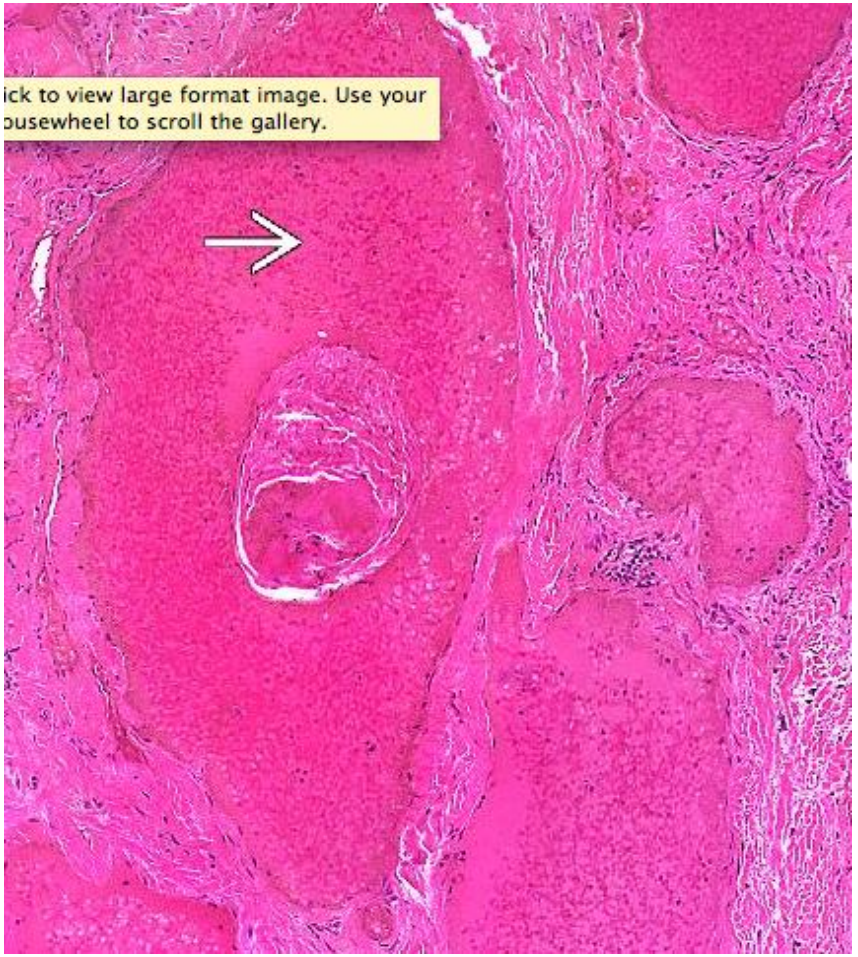


Mafucci syndrome





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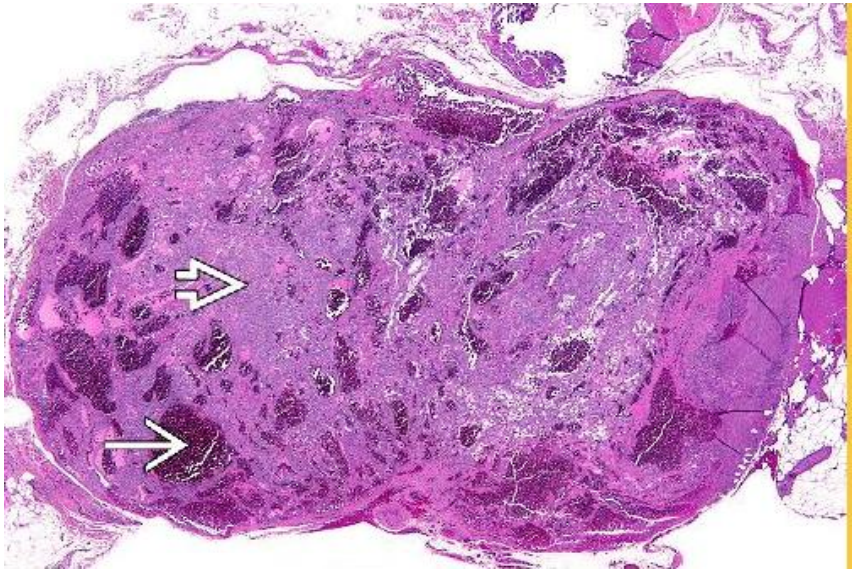
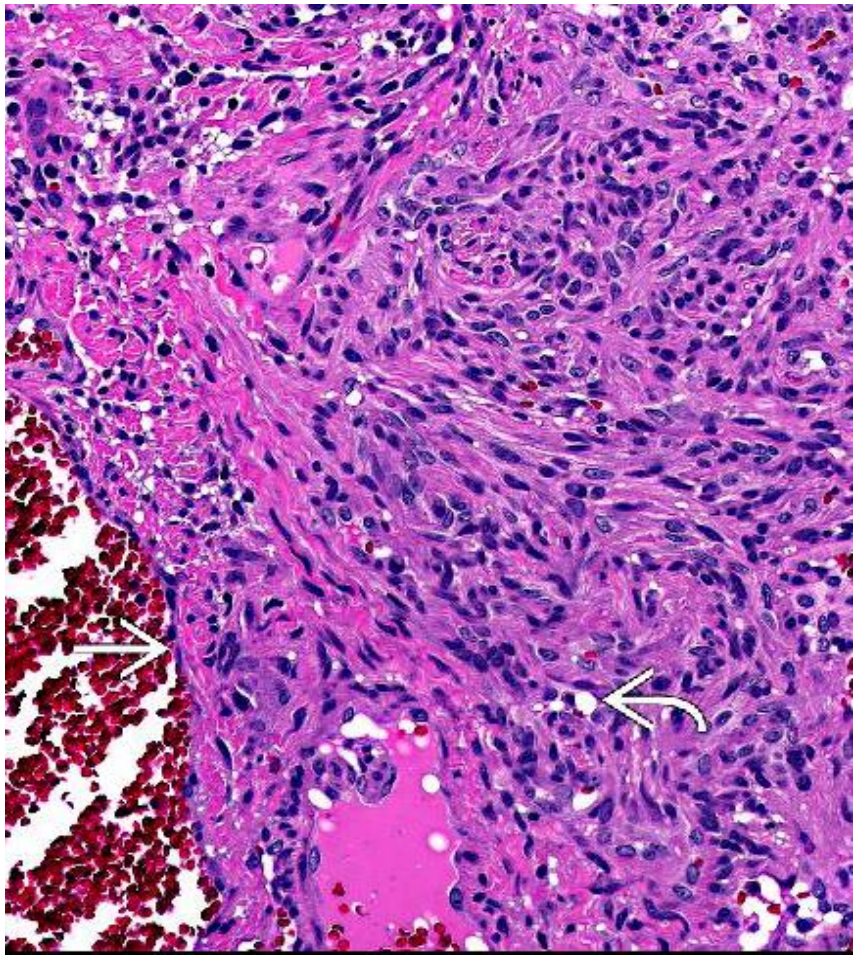
Spindle cell hemangioma





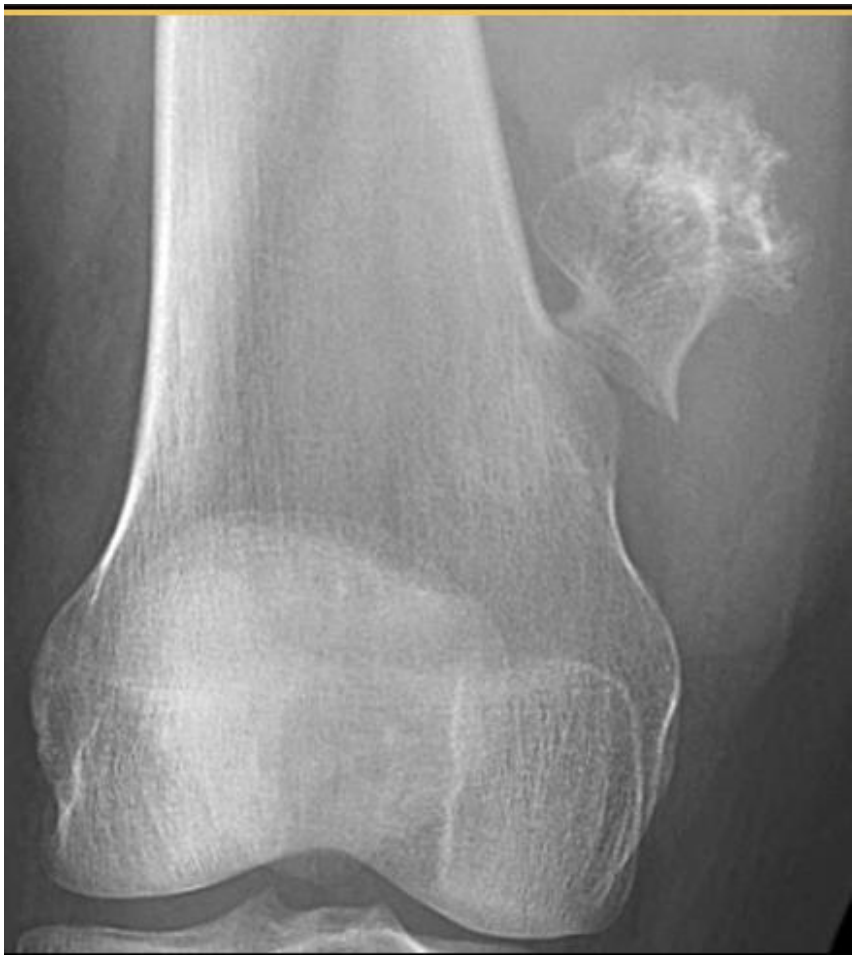
Osteochondroma

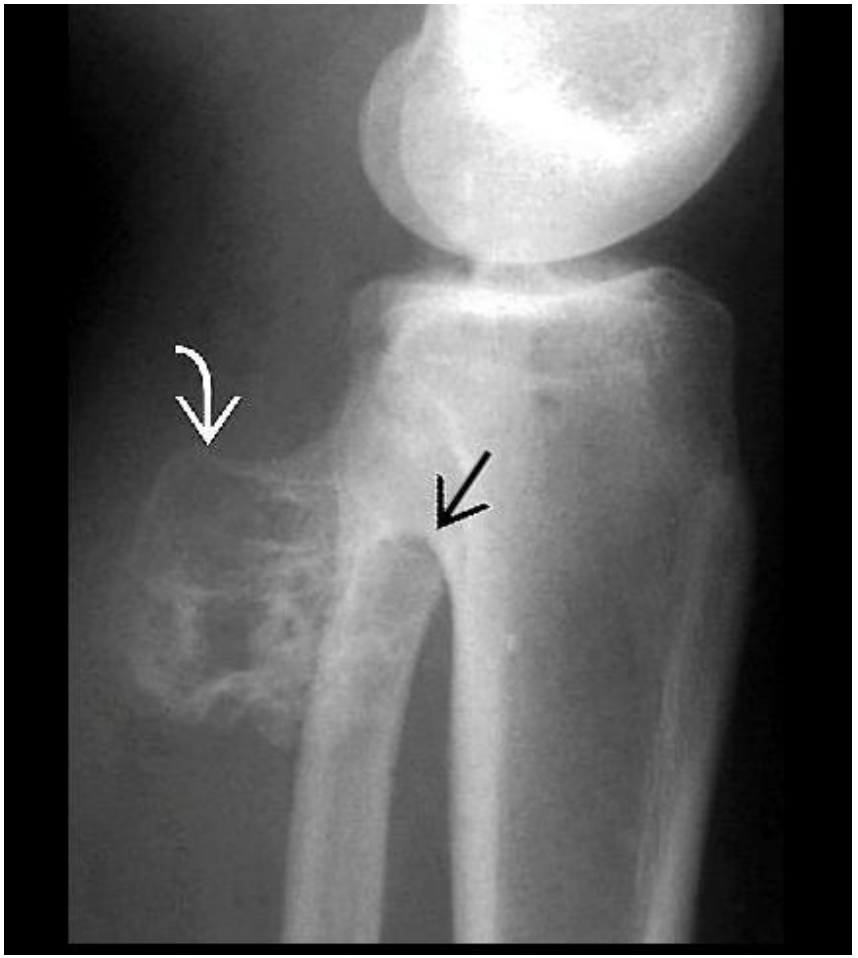
- Benign cartilage-capped tumor that originates in metaphysis or apophysis
- Account up to 50% of benign tumors
- Neoplastic process
  - Associated with mutations involving EXT genes
- Majority occurs sporadically

Clinical Issues

- Most patients in 2nd decade of life at time of diagnosis
- Typically arises in metaphysis of bones derived from enchondral ossification
- Treated with observation or simple excision

Image findings





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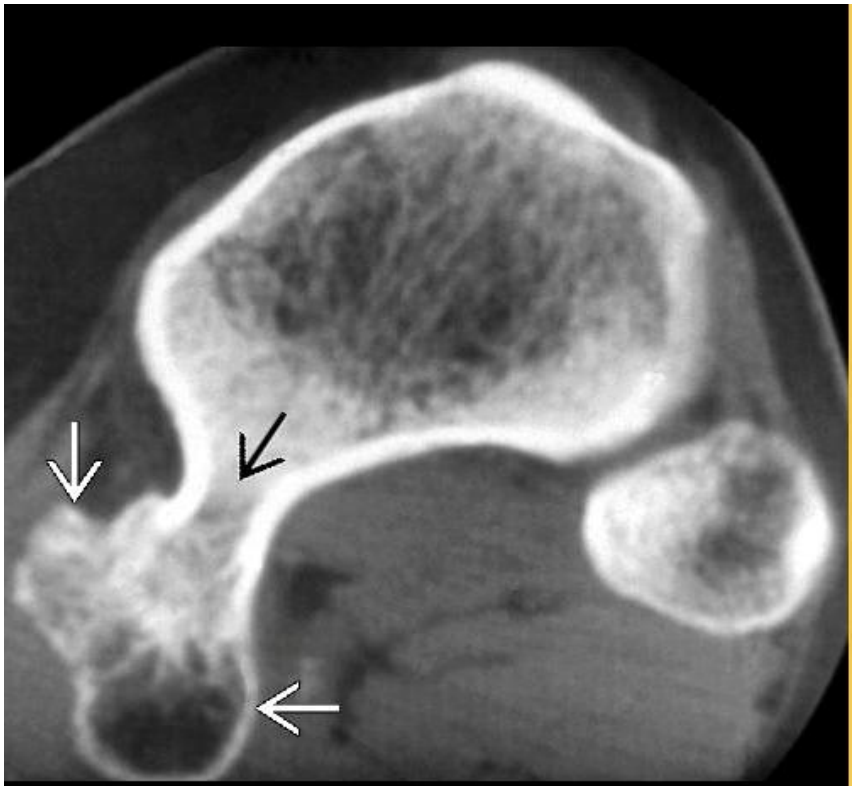
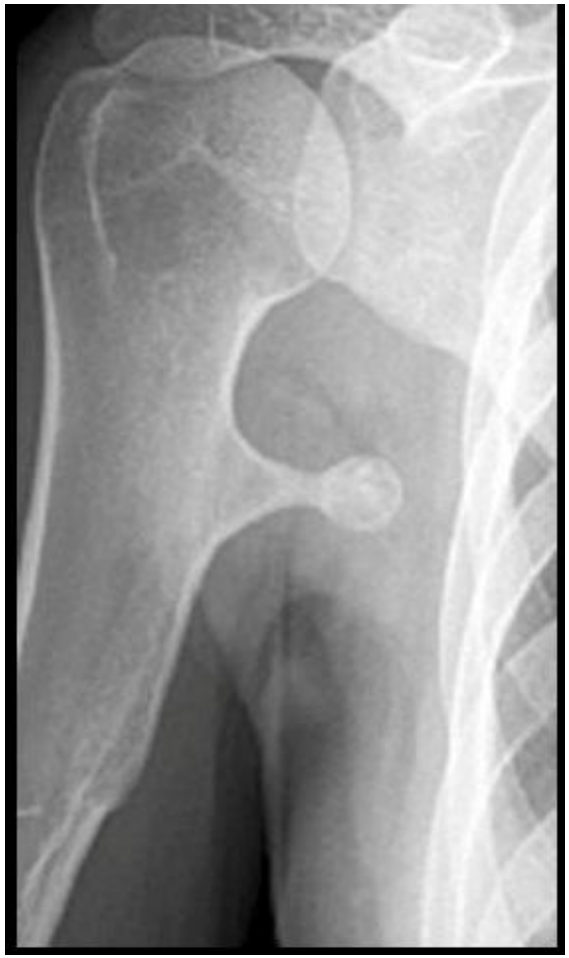
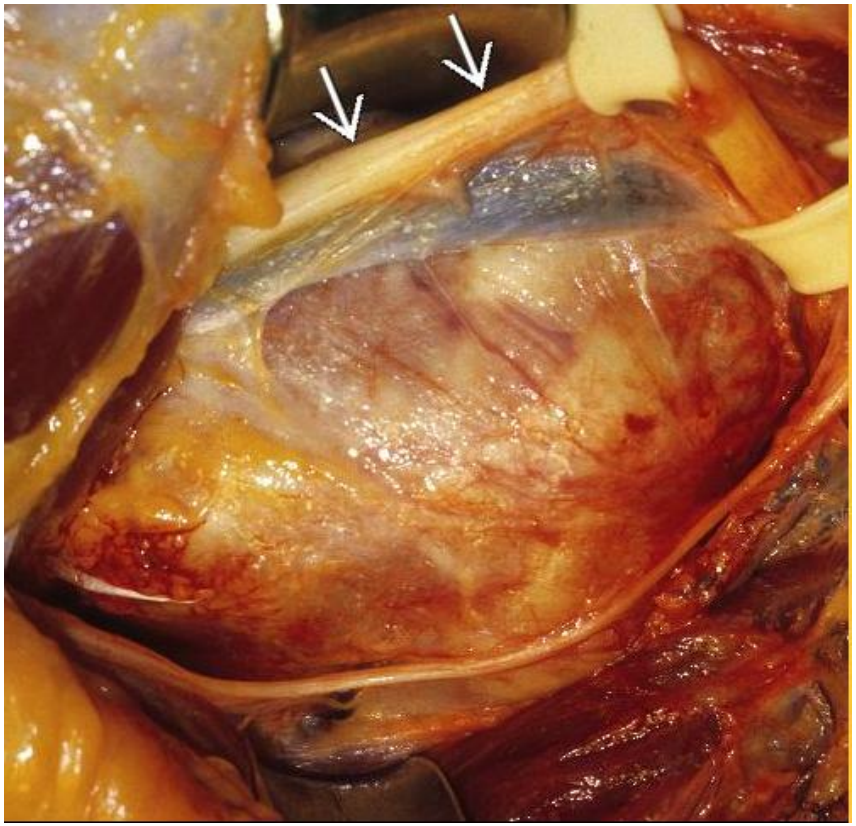




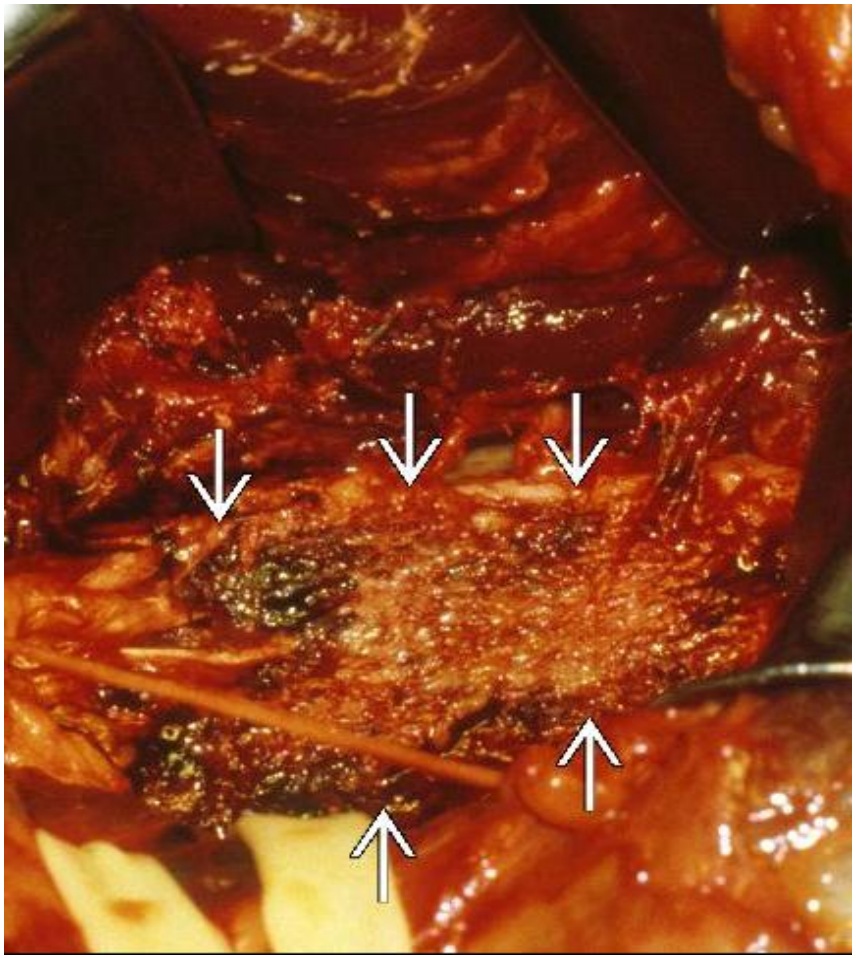
Differential diagnosis

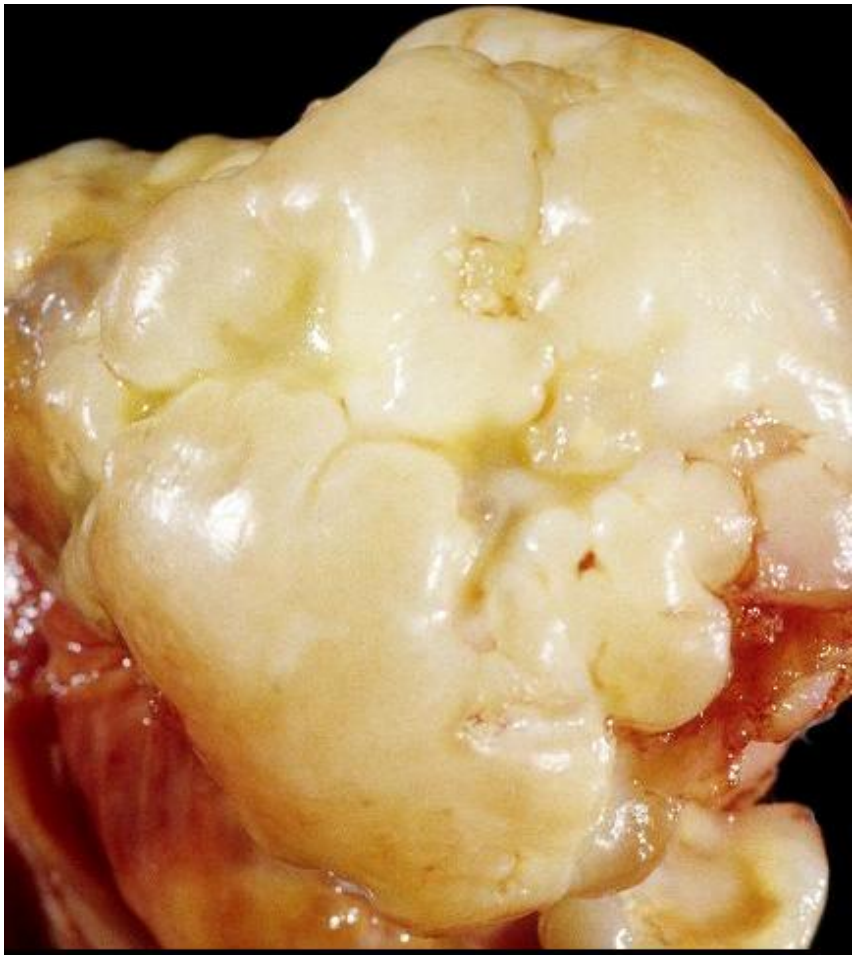
- Bizarre Parosteal Osteochondromatous Proliferation
- Periosteal Myositis Ossificans
- Surface periostal chondroma
- Surface osteosarcoma (Parosteal osteosarcoma)

Macroscopic features



Macroscopic features





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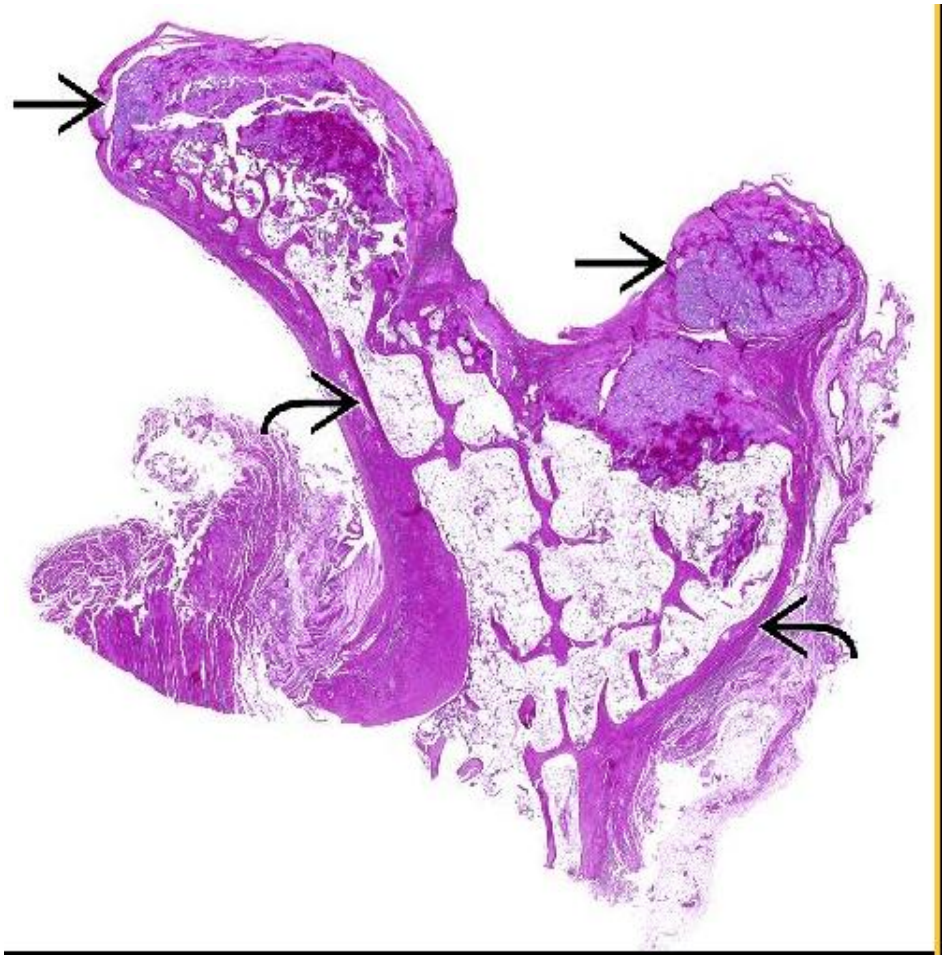

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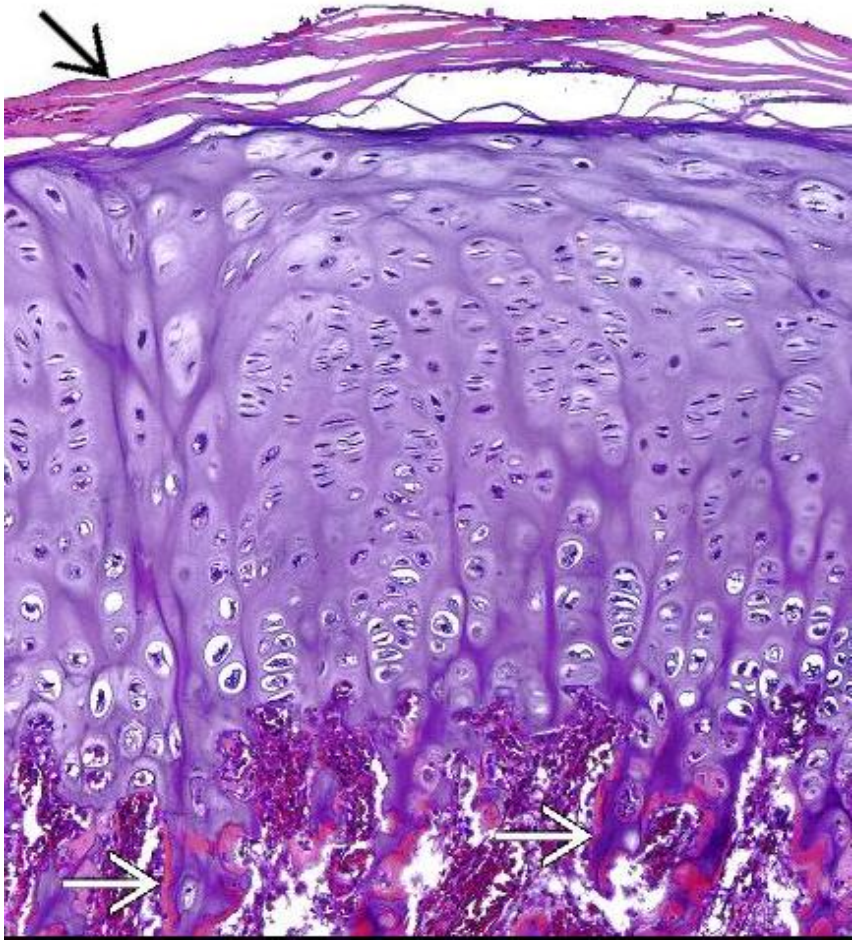

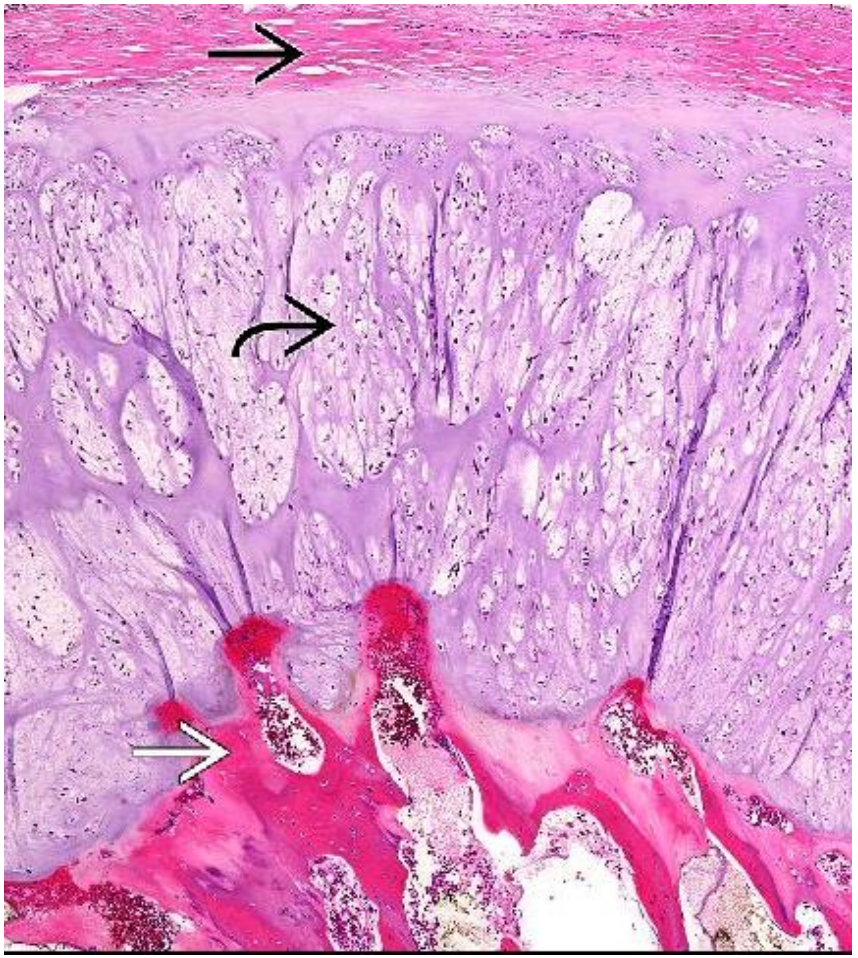

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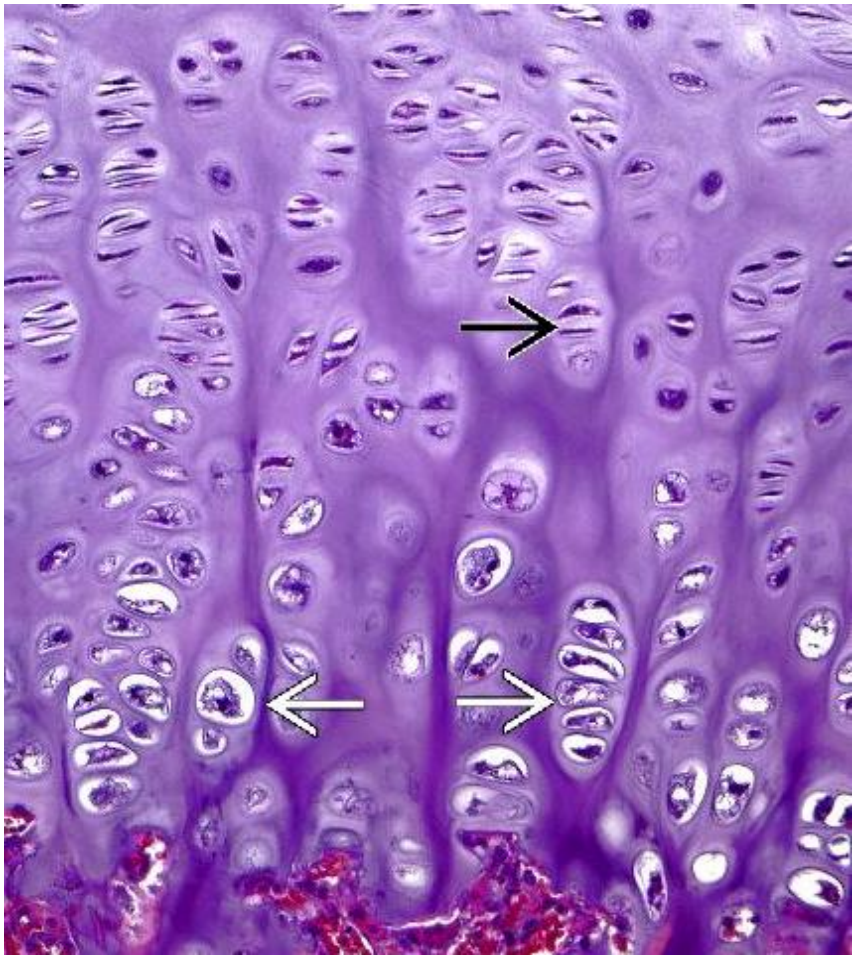
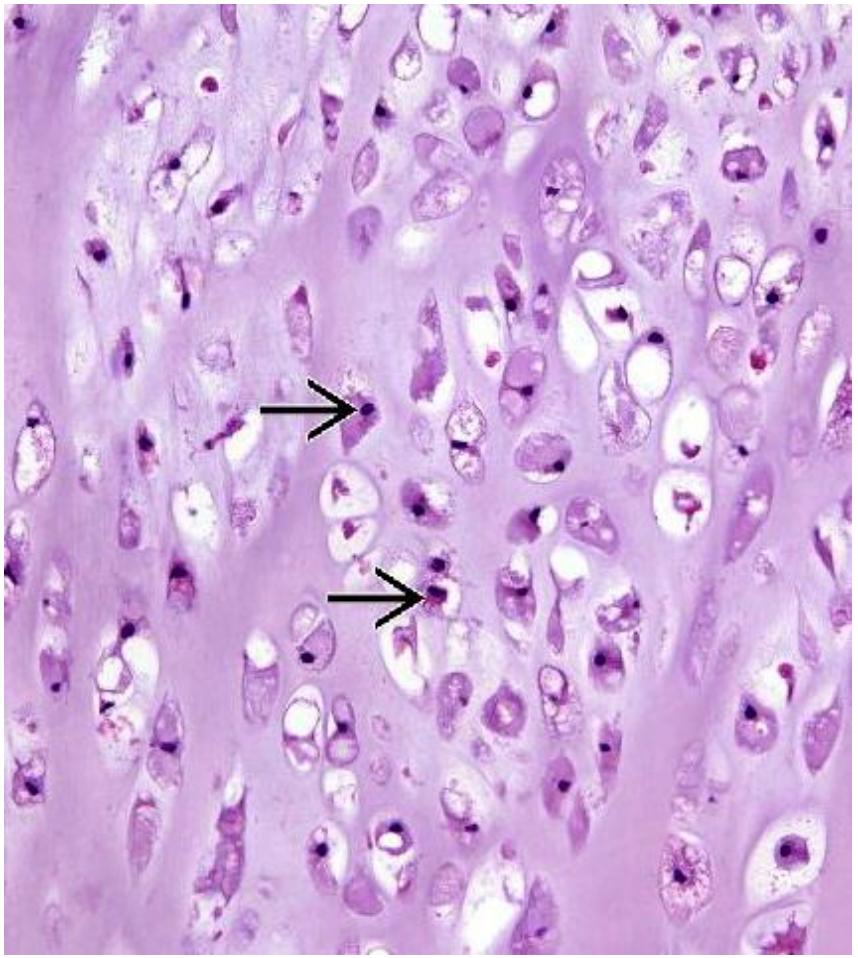




Multiple hereditary osteochondromatosis

- Synonyms: Diaphyseal aclasis, multiple cartilaginous exostoses, hereditary multiple exostoses

- Definition
  - Autosomal dominant condition caused by mutations in 1 of the EXT genes
  - > 2 osteochondromas of juxtaepiphyseal region of long bones are required for diagnosis

Epidemiology and Site

- Incidence
  - 1 ~ 50.000 persons
  - Solitary osteochondromas are 6X more common
  - Most patients are in the second decade of life

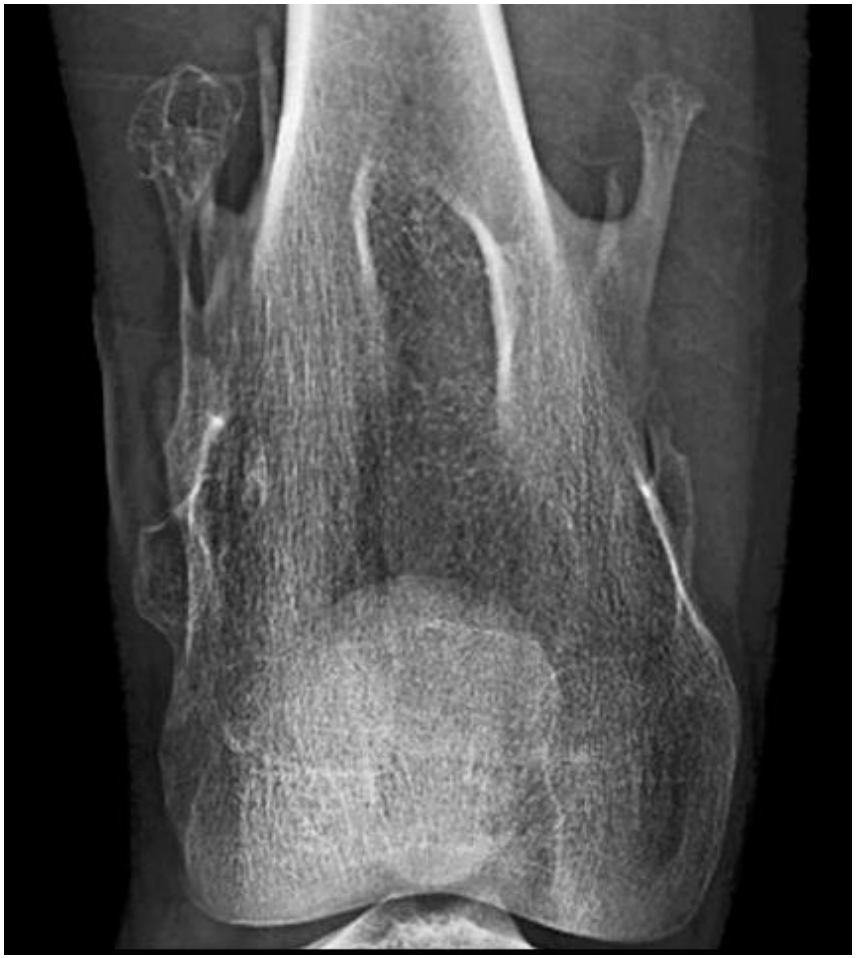
- Site
  - Typically in appendicular skeleton
  - Distal femur, proximal tibia, proximal humerus
  - Can involve flat bones such ilium and scapula

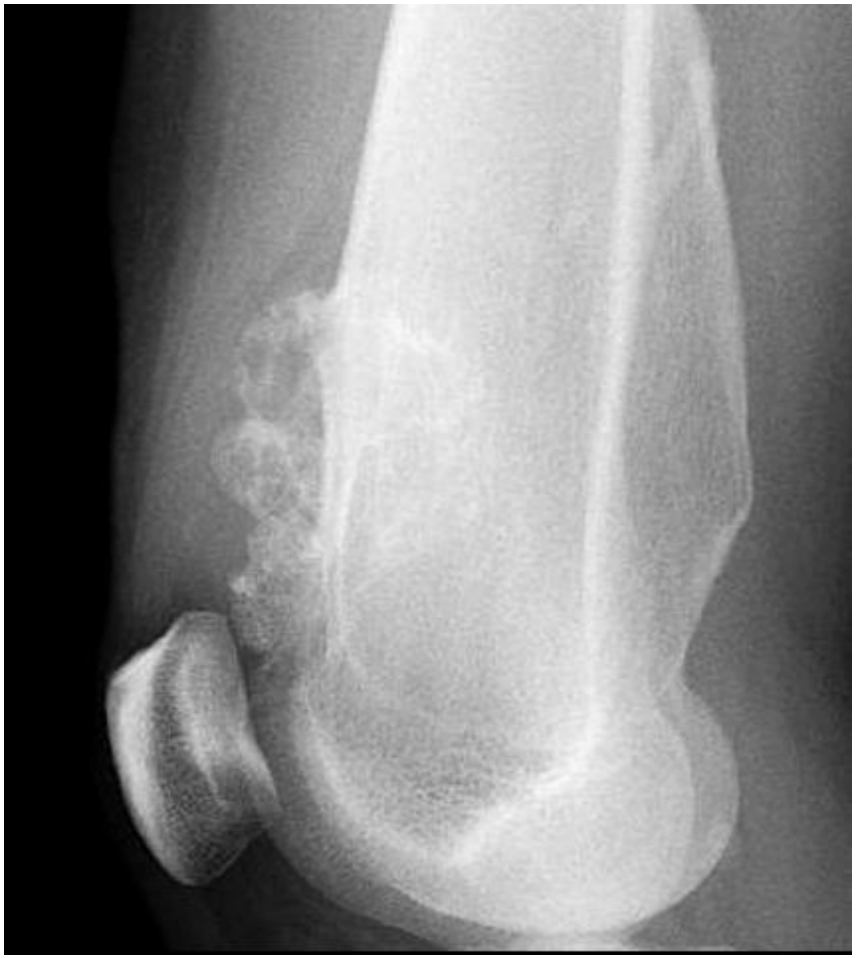
Presentation and Prognosis

- Presentation
  - 60% have family history
  - Slowing enlarging firm lesions present for many years
  - Can be painful, related to bursitis or impingement upon neurovascular bundles

- Malignant transformation of osteochondroma to chondrosarcoma occurs in 0.5-5%
  - Rarely osteosarcoma and dedifferentiated chondrosarcoma have also been reported

Image findings





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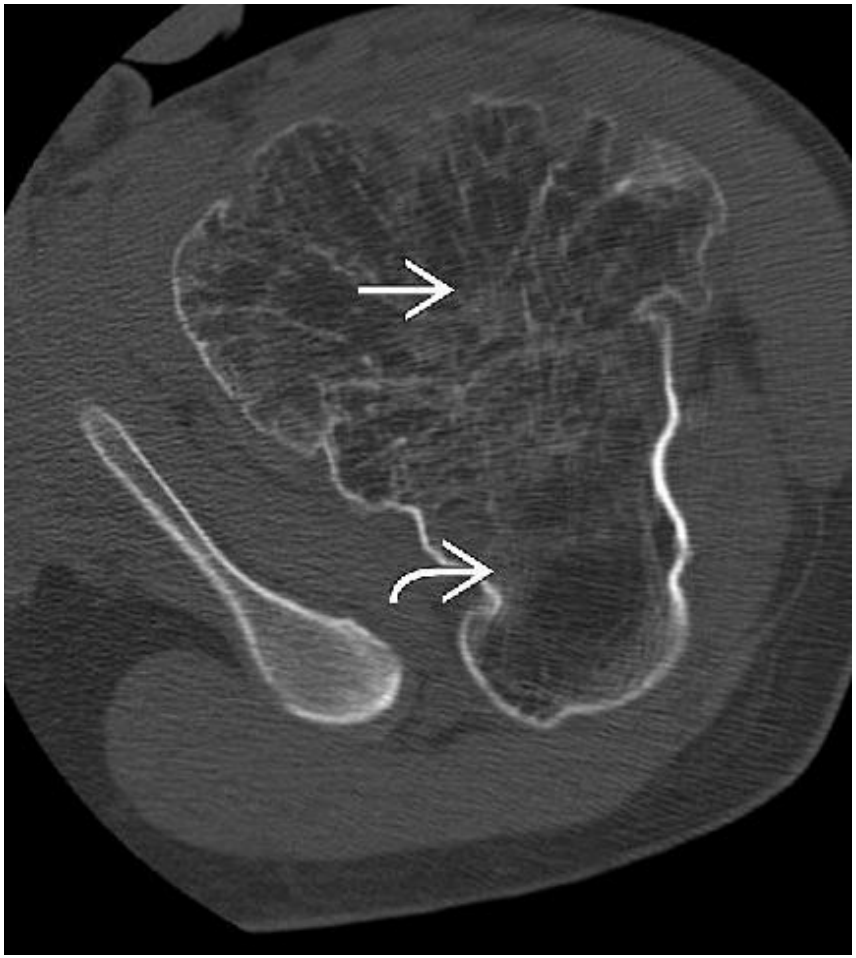

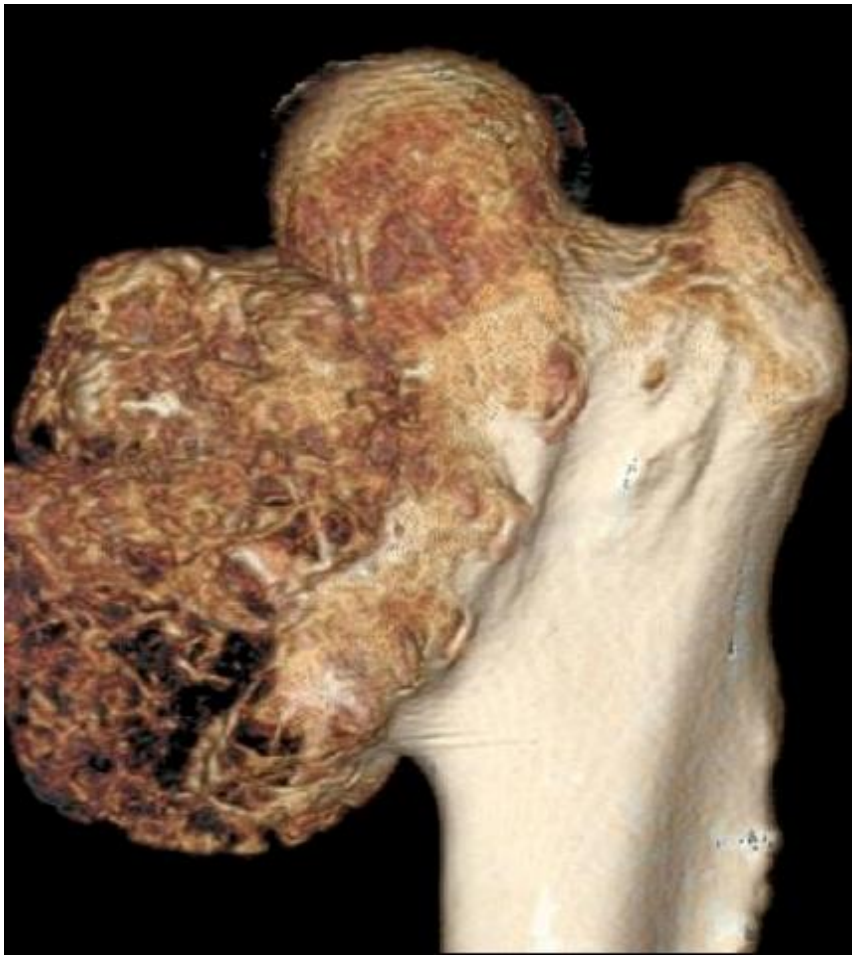

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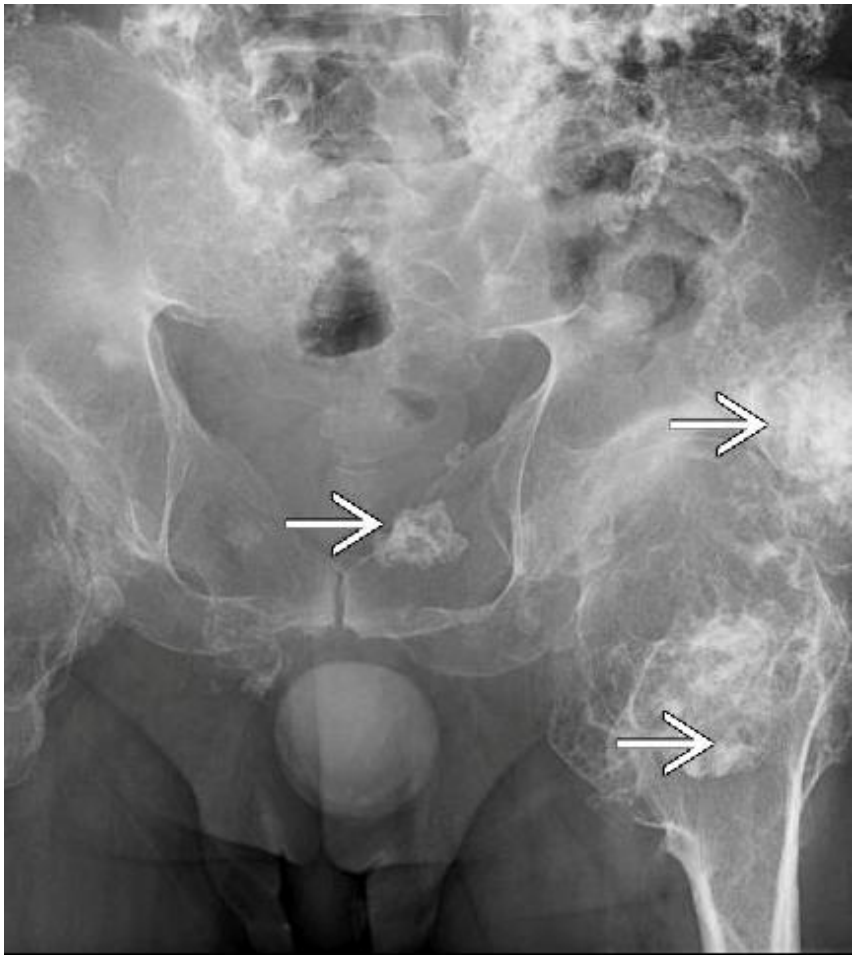

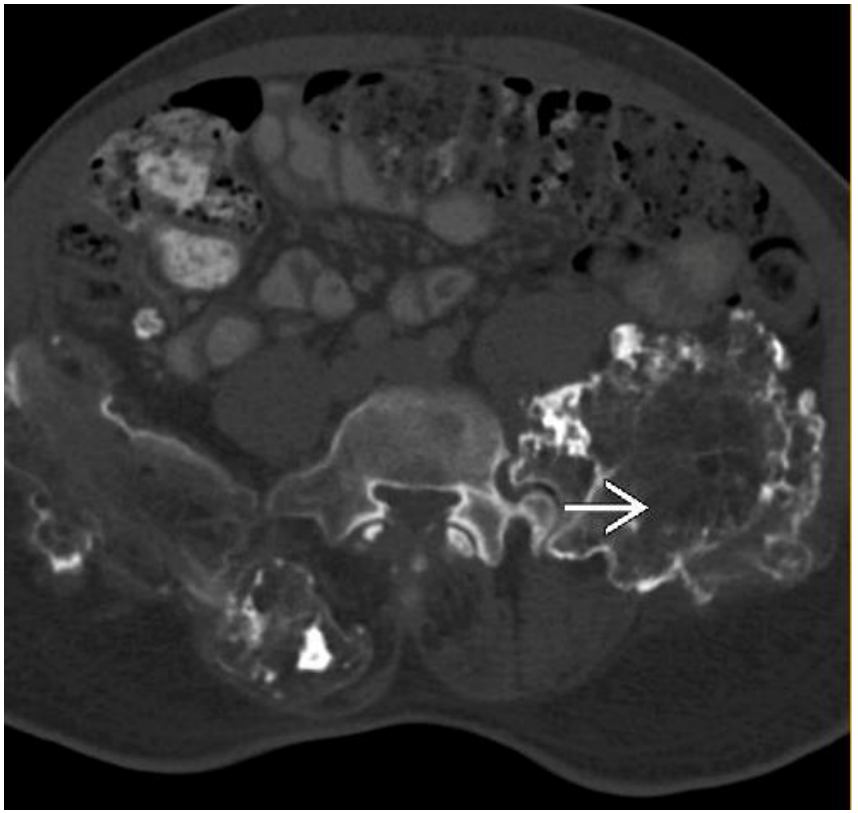

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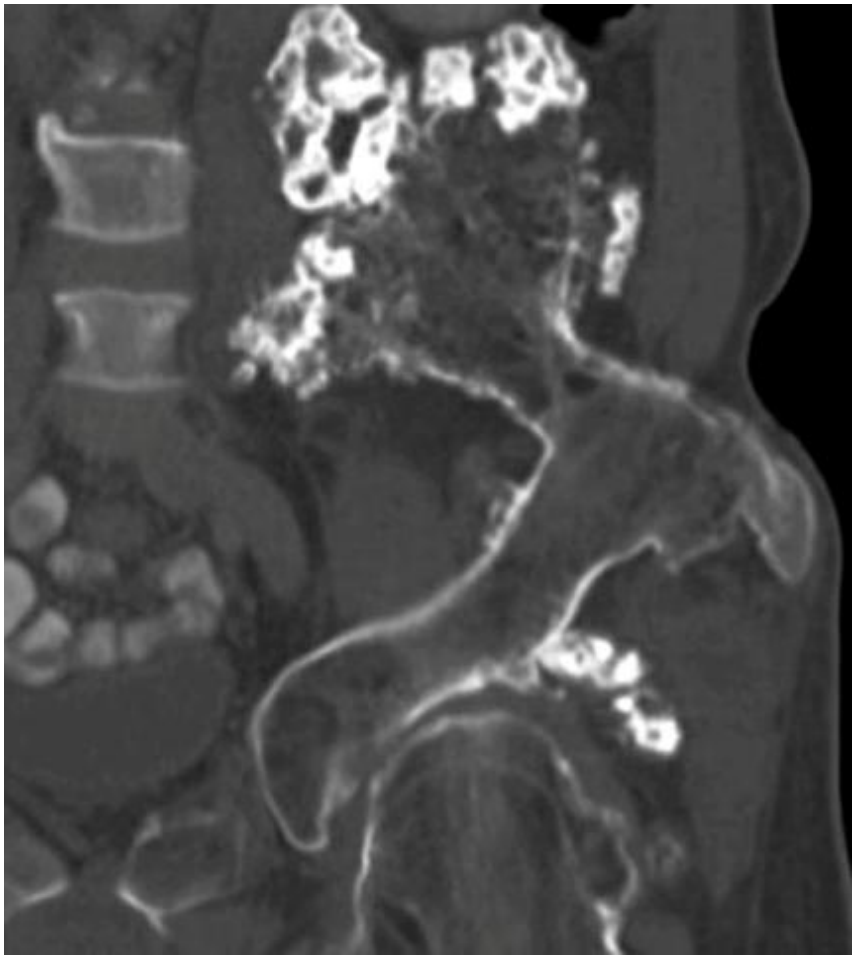

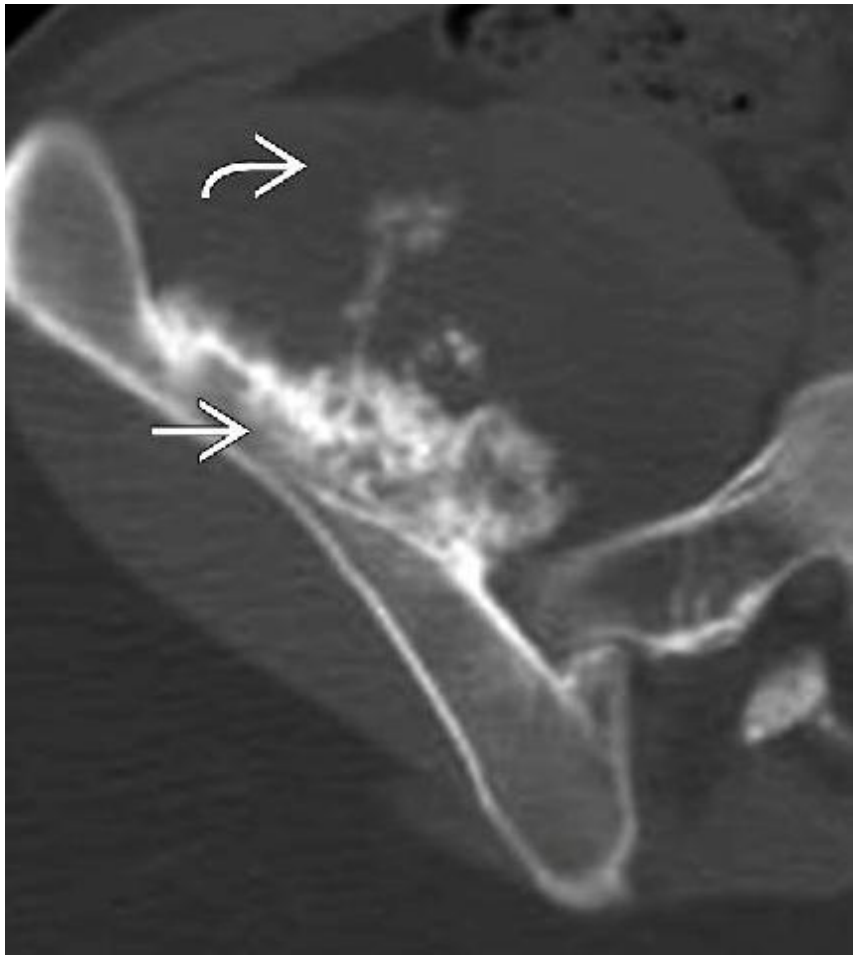

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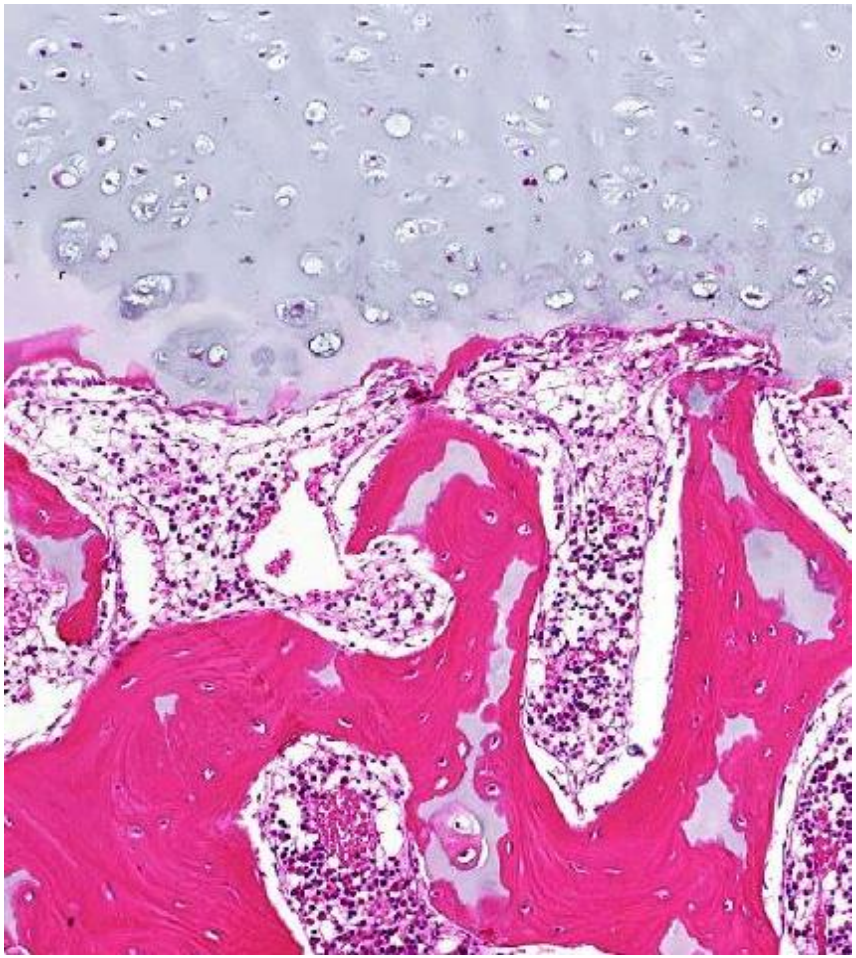

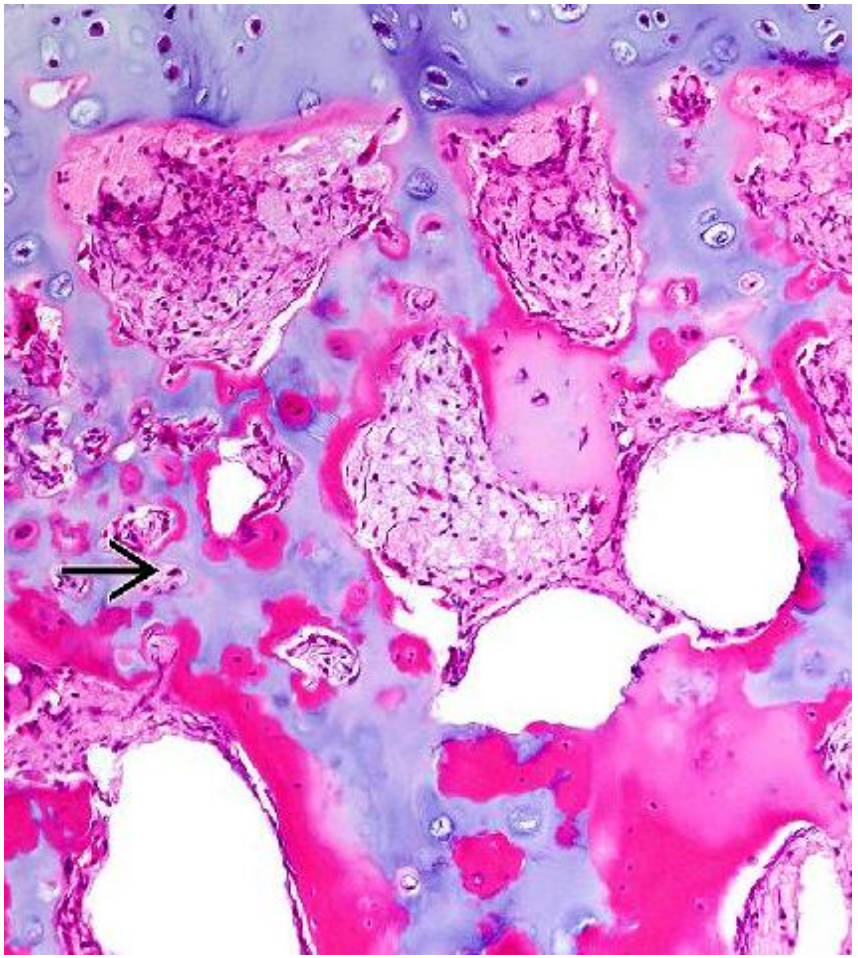

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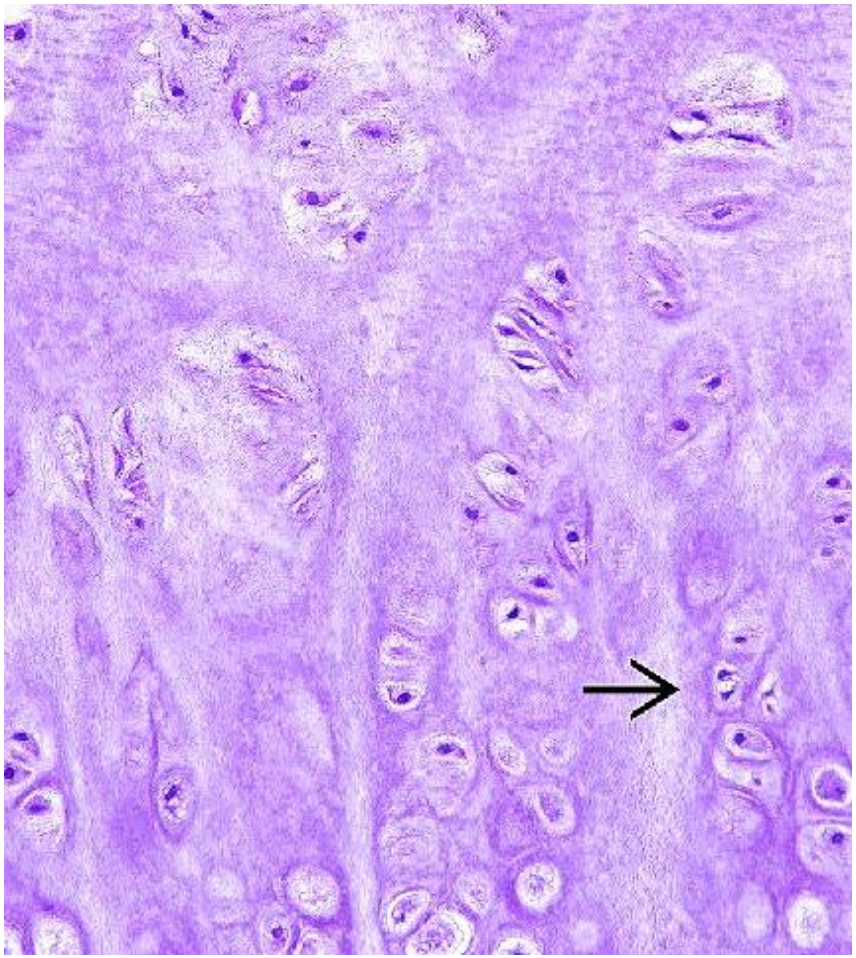

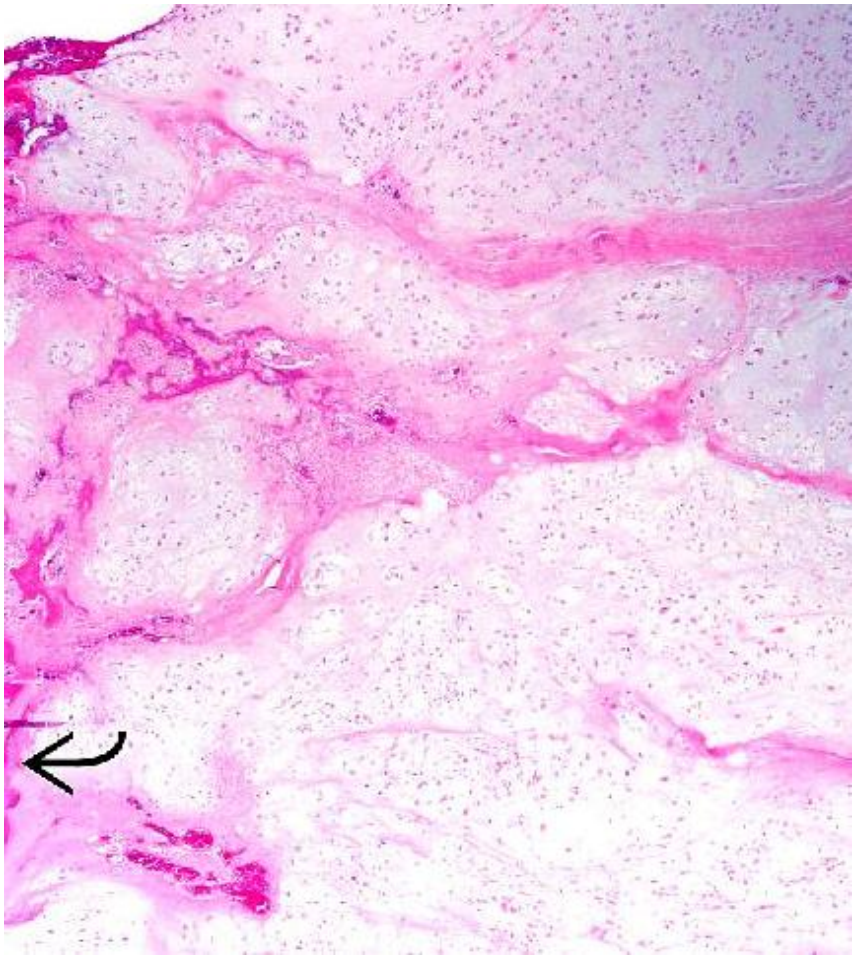

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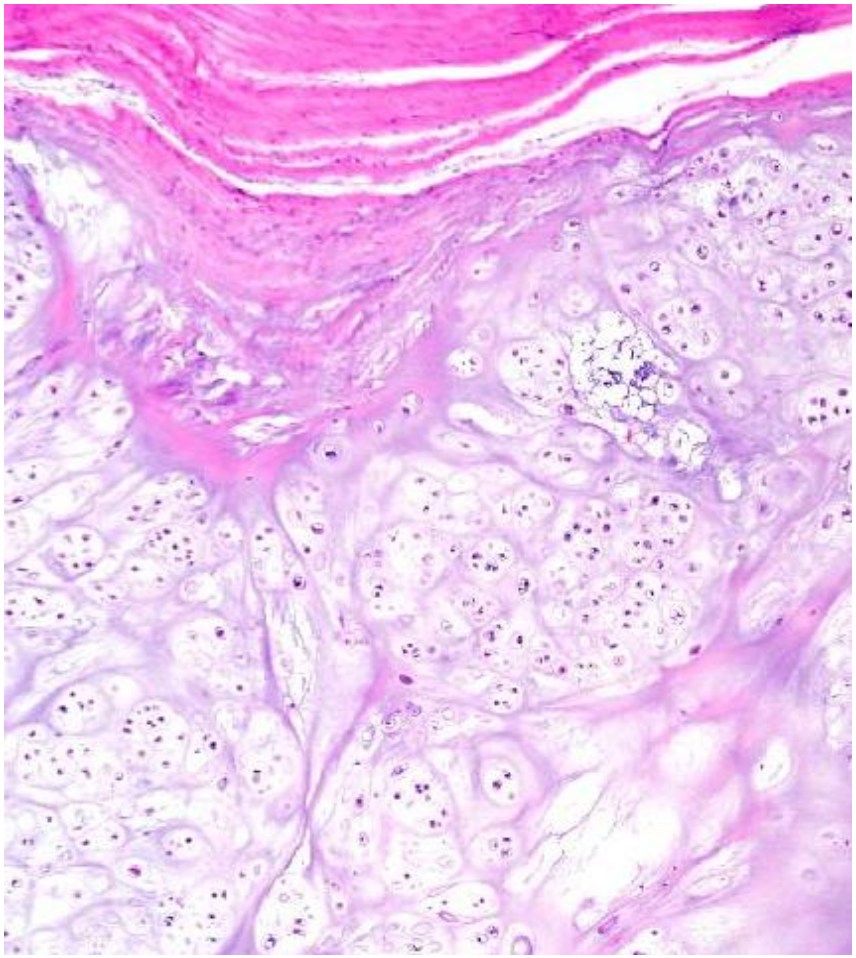
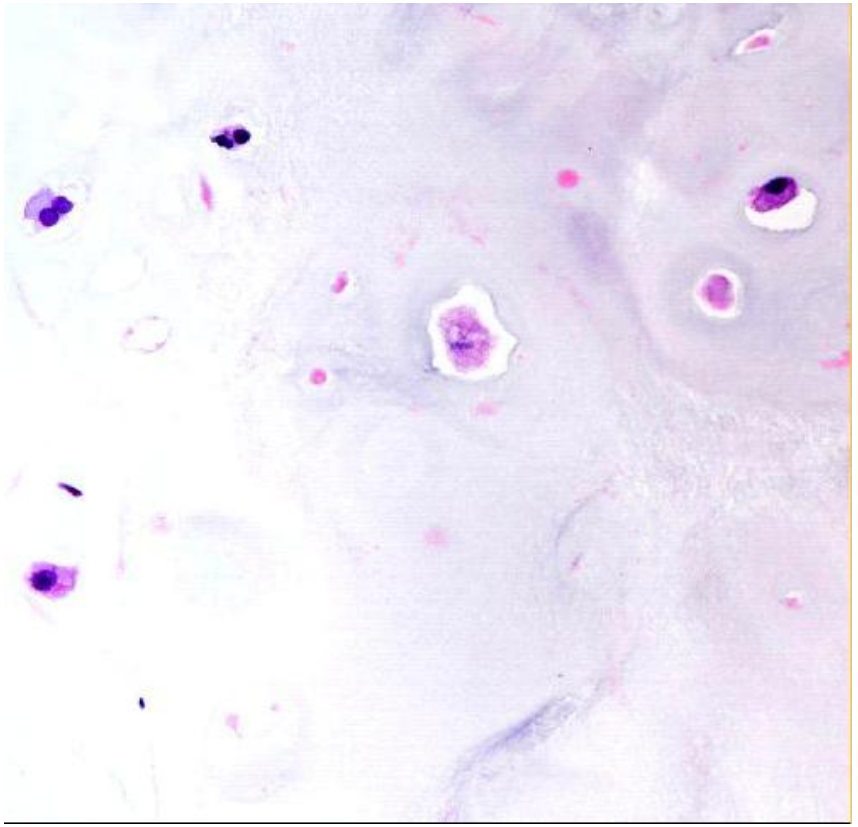




Ancillary tests

- Molecular genetics
  - Germline alterations in EXT1 (8q24) and EXT2 (11p11-p12)
  - Most of these mutations are predicted to result in truncated or nonfunctional protein

Malignant cartilage tumors

Conventional Chondrosarcoma

- Definition
  - Malignant cartilaginous matrix-producing tumor
  - Primary chondrosarcoma arises in normal bone
  - Secondary chondrosarcoma arises in association with
    - Preexisting benign tumor
      - Enchondroma, osteochondroma, fibrous dysplasia
    - Diseased bone
      - Radiation, Paget disease
  - Periosteal chondrosarcoma arises on surface of bone
    - Also known as juxtacortical chondrosarcoma

Etiology/Pathogenesis

- Etiology of most chondrosarcomas is unknown
- In some preexisting enchondroma can be found
  - Likely malignant transformation
  - Risk in sporadic enchondromas very low (<1%)
- In patients with Ollier's disease or Mafucci syndrome the risk of malignant transformation is 35-40%
- In patients with osteochondromatosis the risk is 5-25%
- Rarely it arises in solitary osteochondroma
  - Estimated incidence 0.4-2%

Clinical issues

- Incidence
  - 2nd most common primary malignant bone tumor after osteosarcoma
  - >90% are conventional intramedullary chondrosarcoma
- Age
  - Primary chondrosarcoma usually in adults 5th-7th decade
  - Very rare in children

Clinical issues

- Site
  - Can arise in any bone derived from enchondral ossification
  - Most originate in pelvic
    - Followed by proximal femur, proximal humerus, distal femur
    - In long bones chondrosarcoma usually involves metaphysis or diaphysis
  - Infrequently in small bones of hands and feet (1%)
  - Chondrosarcoma of cranium usually involve skull base

Treatment

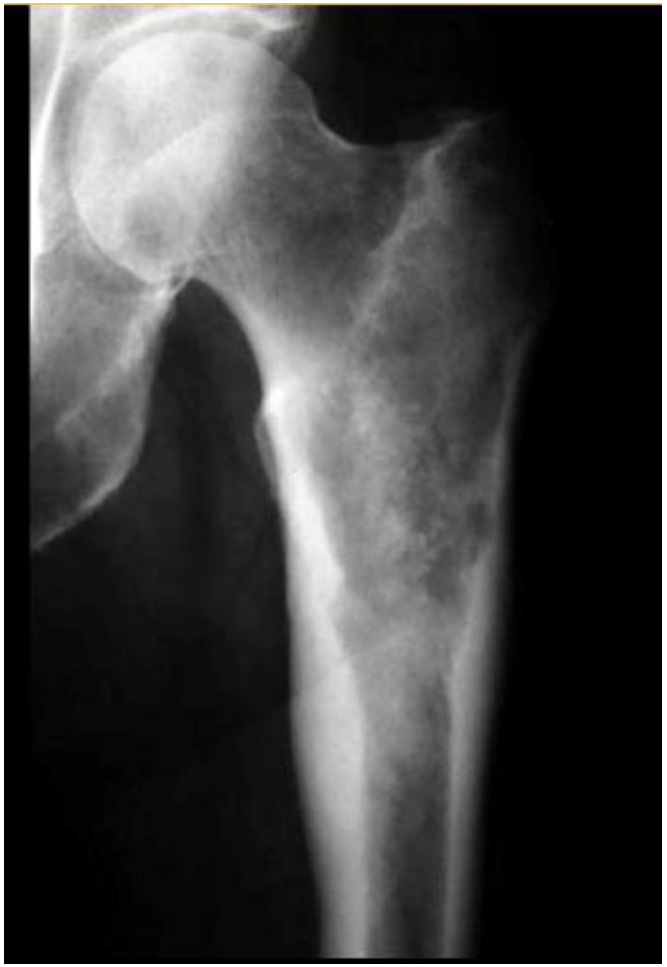
- Aggressive curettage for low grade (grade 1/3)
- High grade chondrosarcomas (grades 2/3 and 3/3) require wide surgical resection
- Chondrosarcomas in pelvis are treated with resection regardless of grade because local recurrence is very difficult to treat

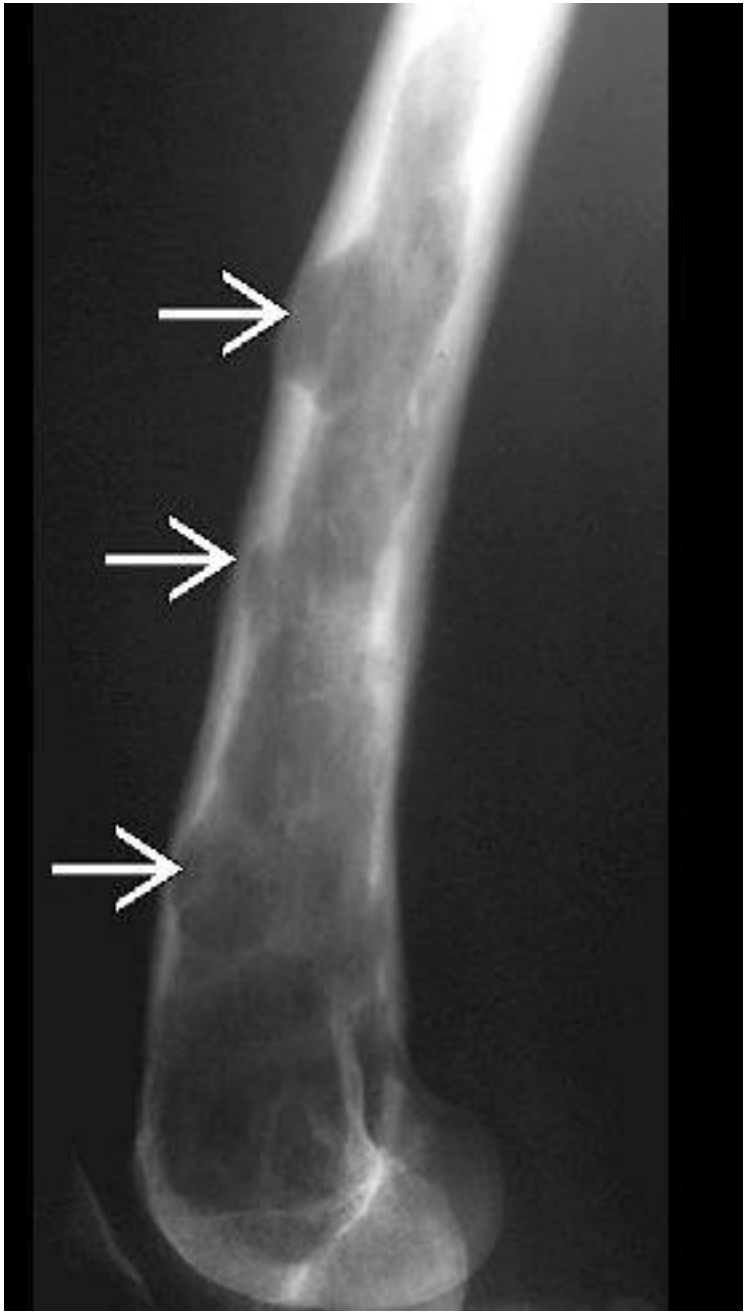
Prognosis

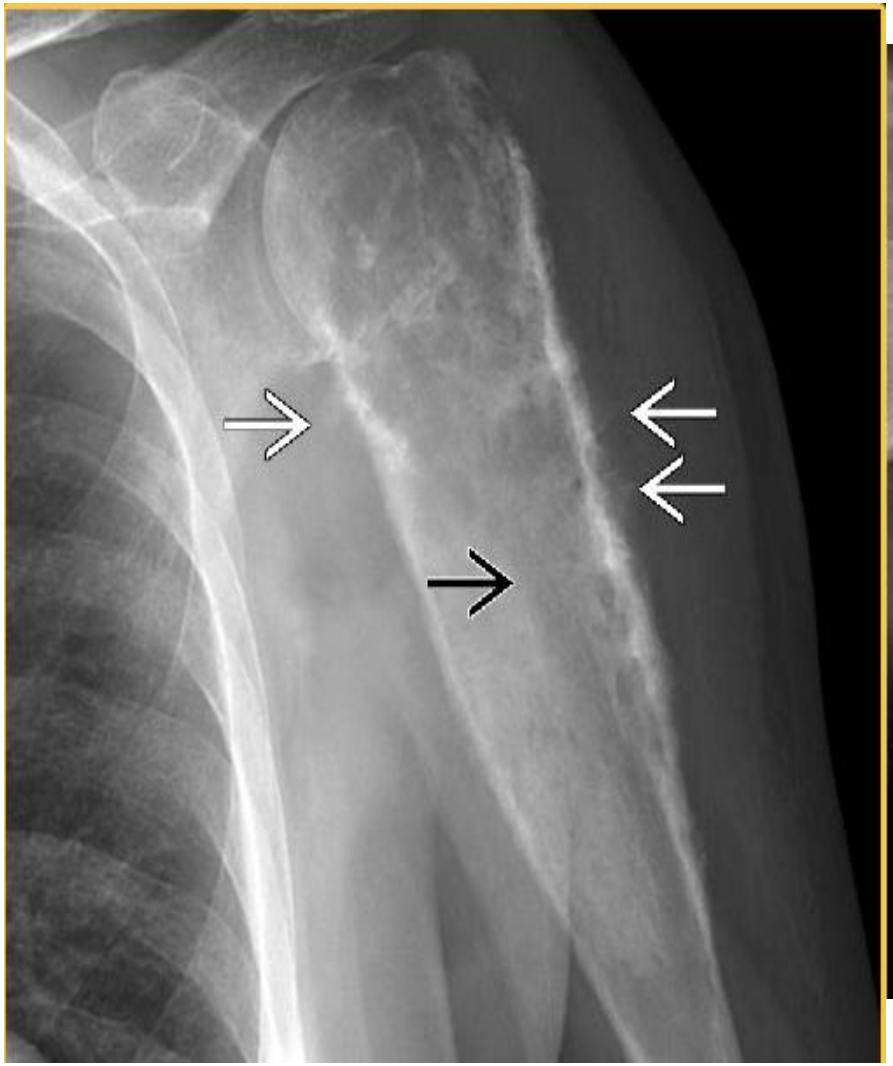
- **Histologic grade the single most important prognostic factor**
- Grade 1 behave in a locally aggressive manner
  - Deaths from local recurrence
  - Metastases rare
  - 5-year survival approximately 85%
- Grades 2 and 3 much worse prognosis
  - 5-year survival rate approximately 50%
- Recurrent tumors may have increase in histologic grade

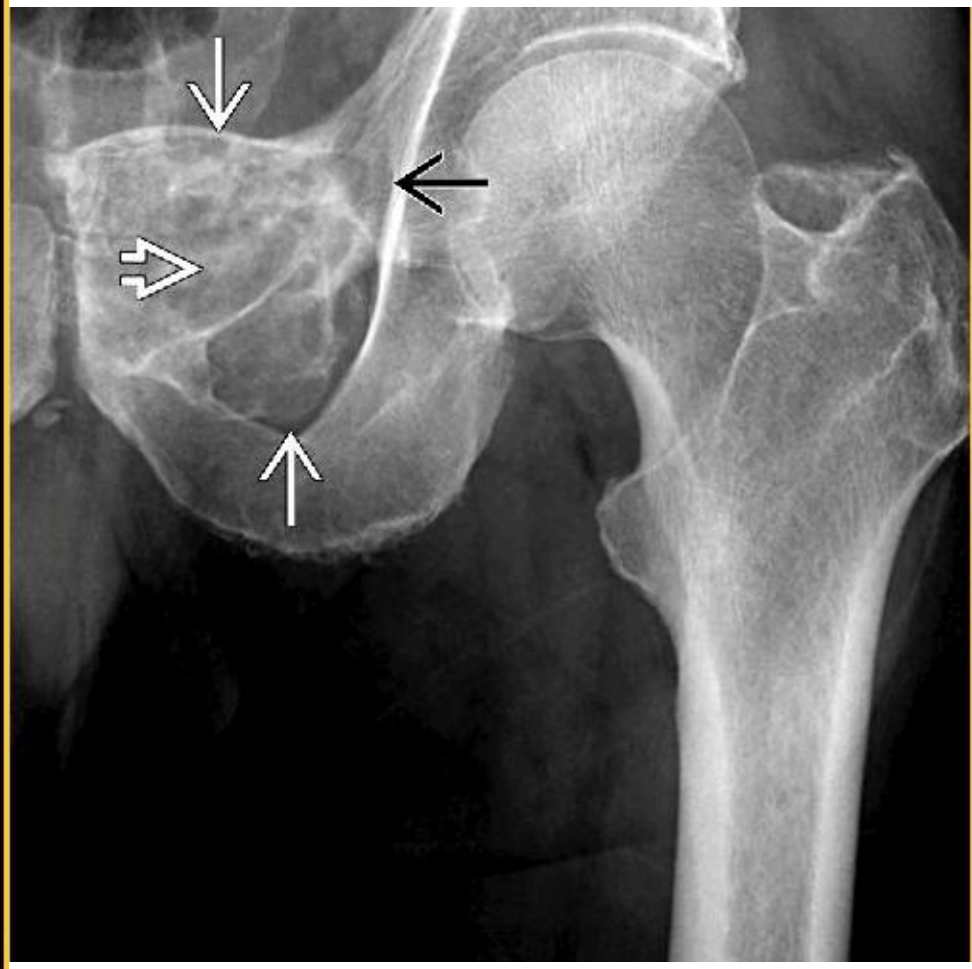
Prognosis

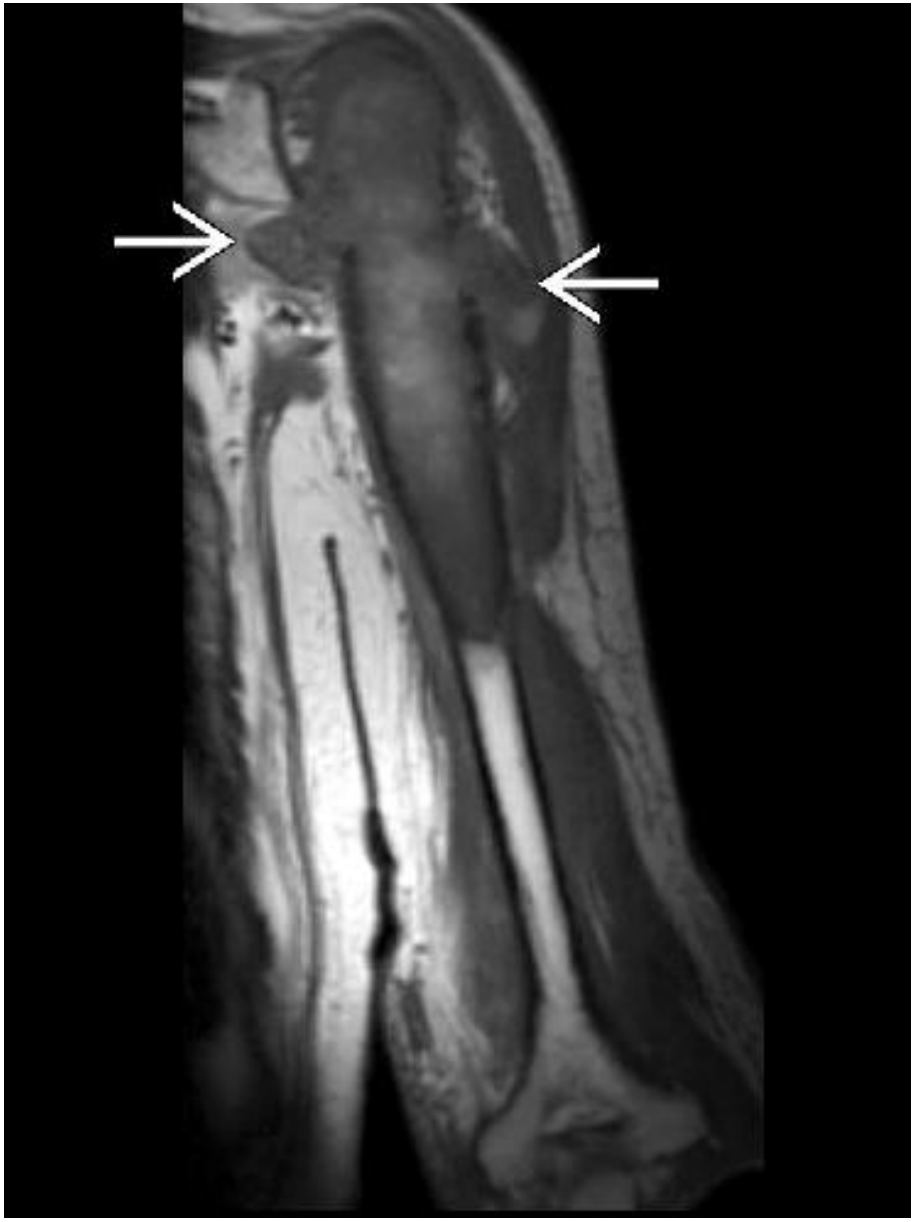
- Prognosis for secondary intramedullary chondrosarcomas is the same as primary chondrosarcomas
- Prognosis of chondrosarcoma arising in osteochondroma is excellent unless there is dedifferentiation
- Periostal chondrosarcomas tend to recur locally
  - Metastases are rare

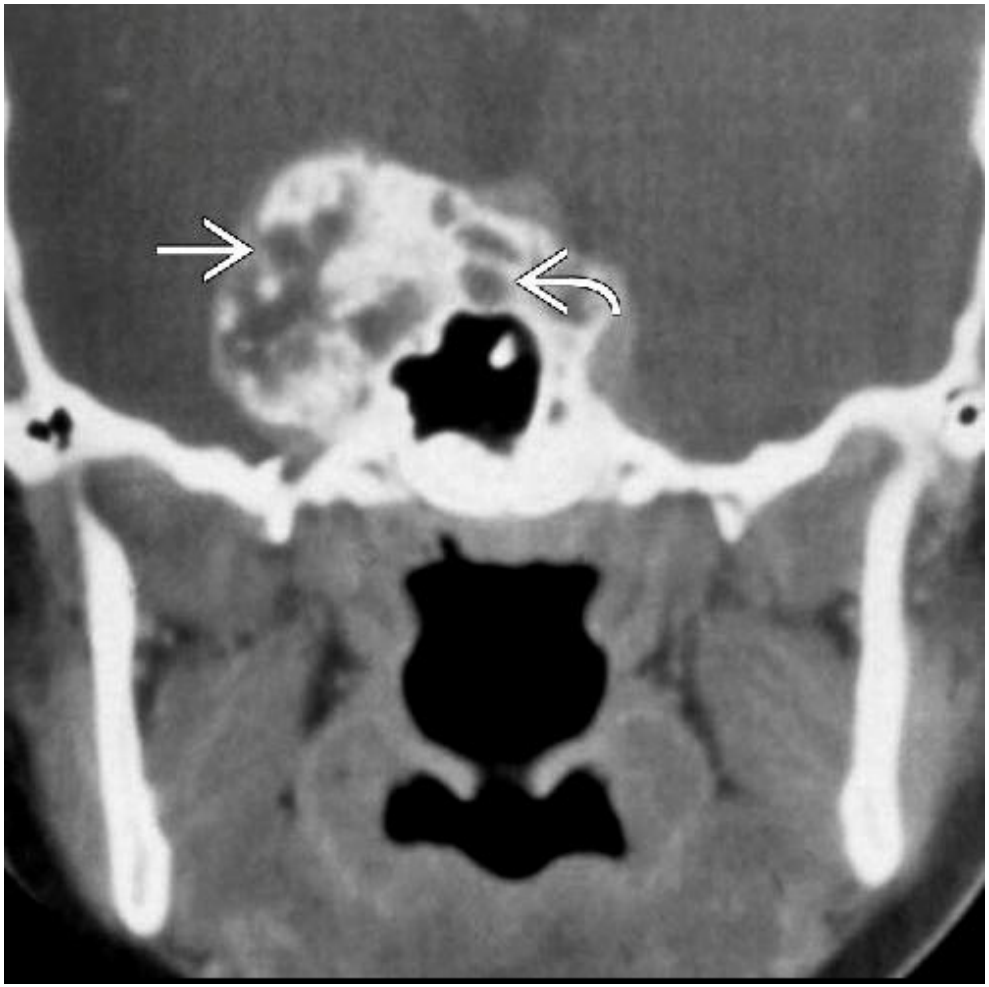


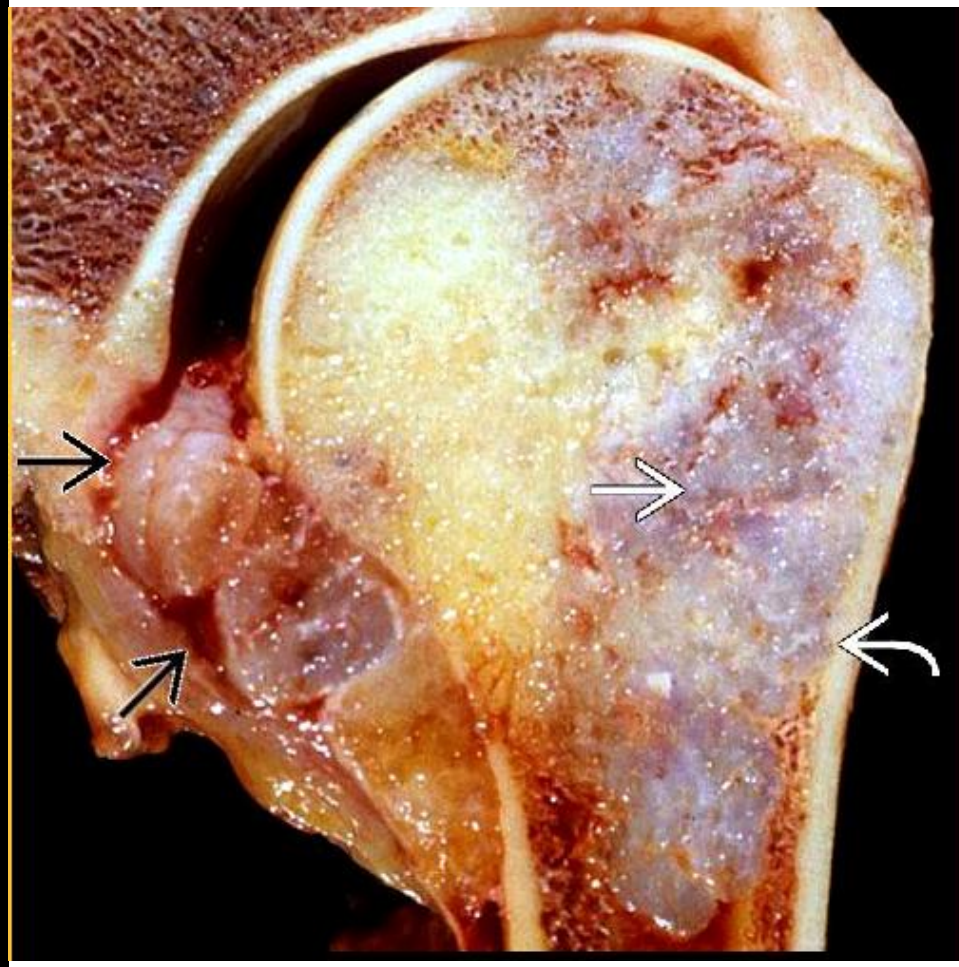


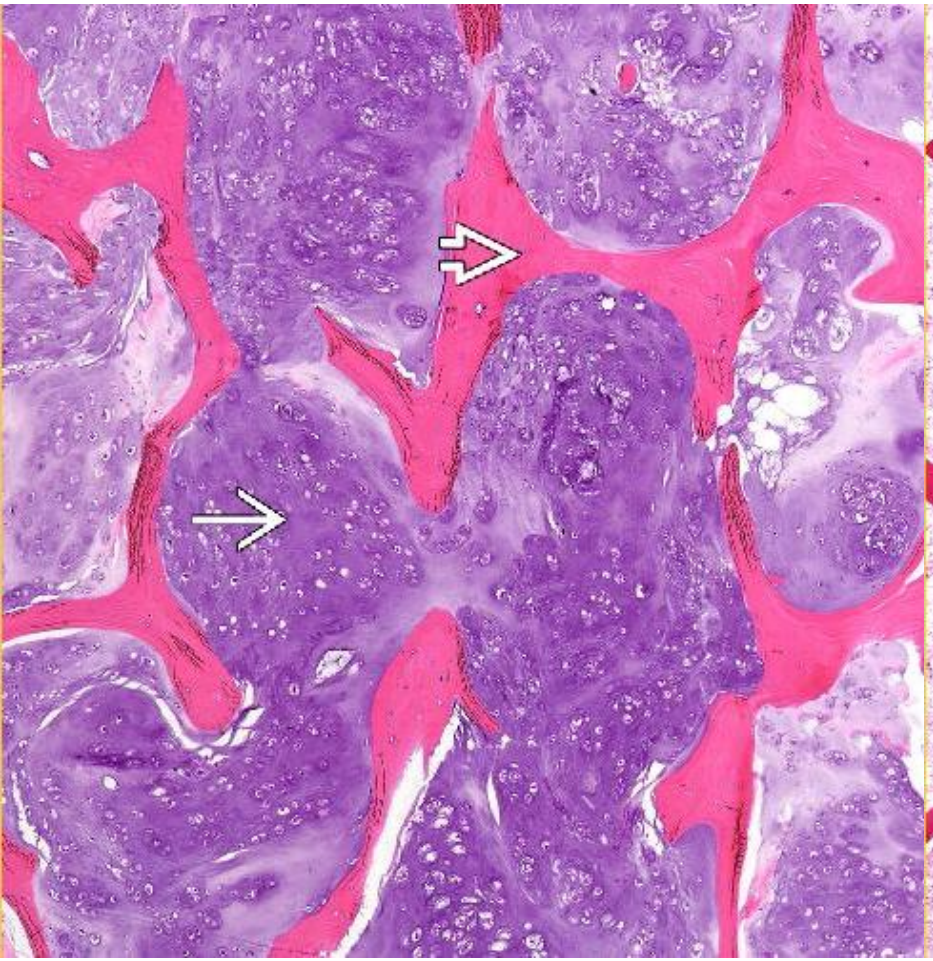


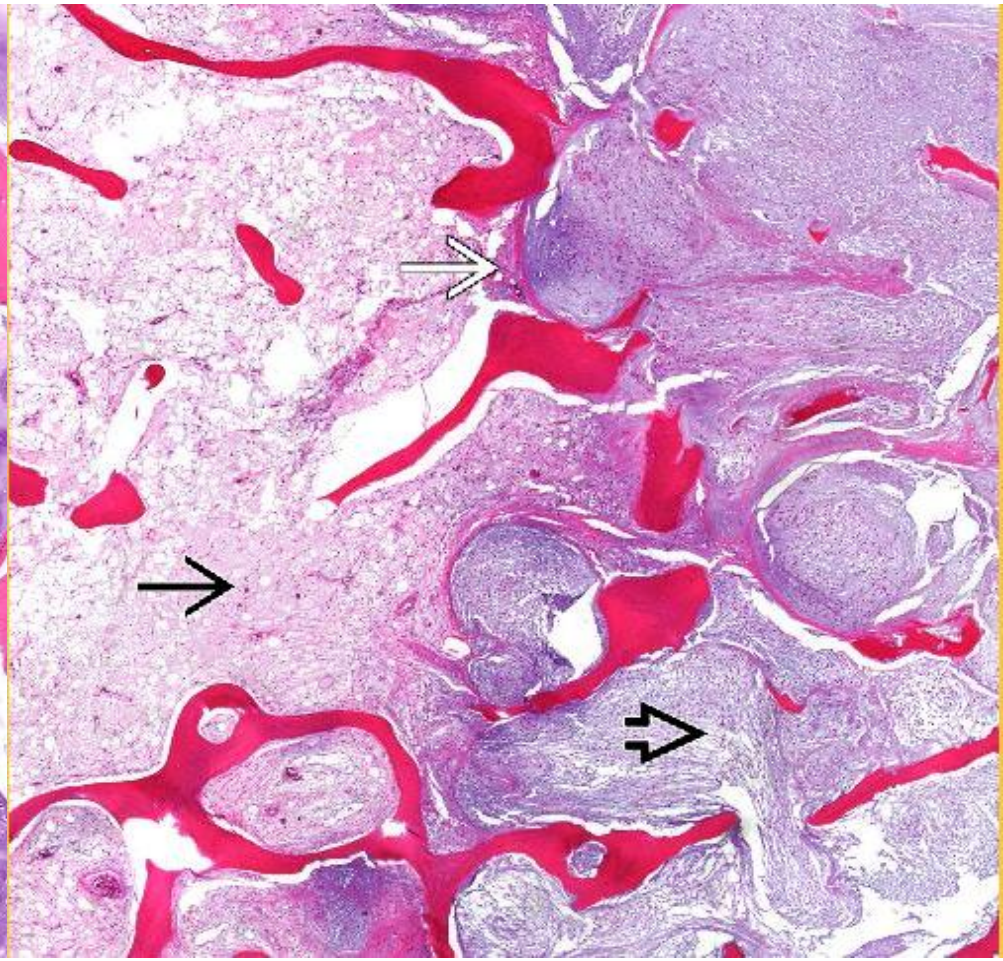


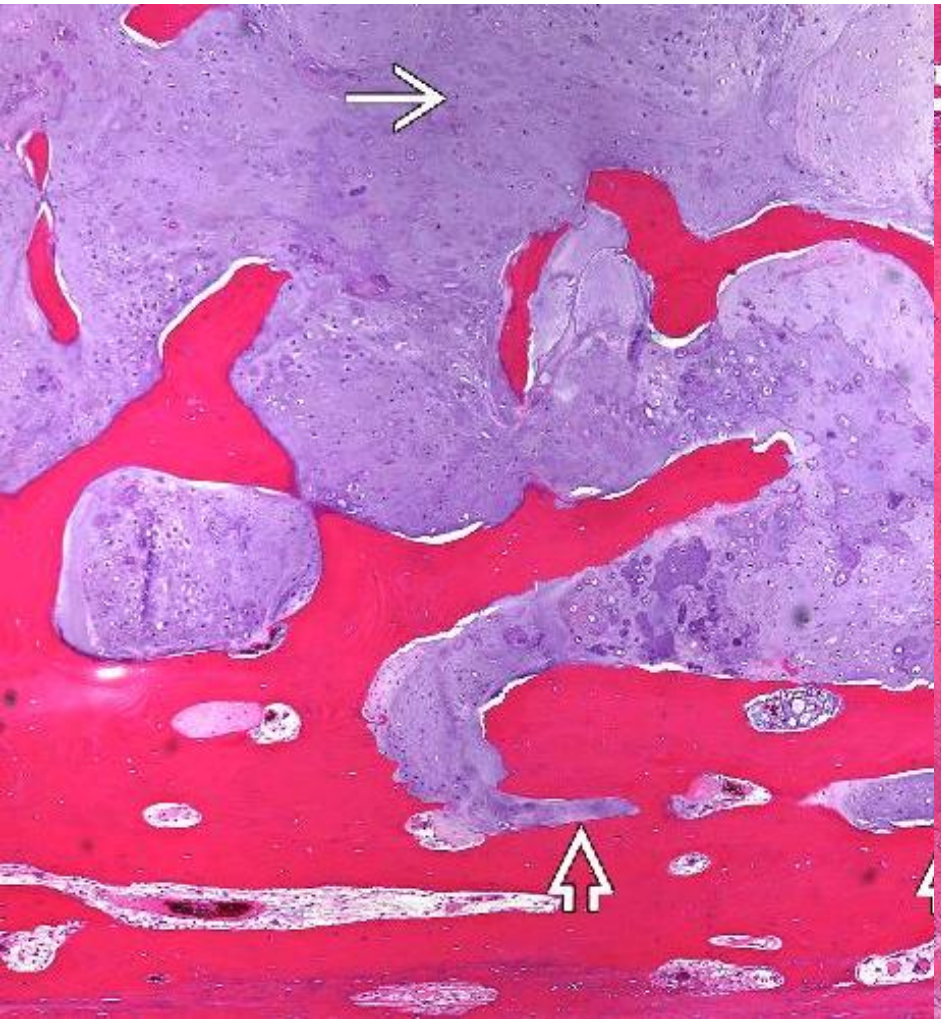


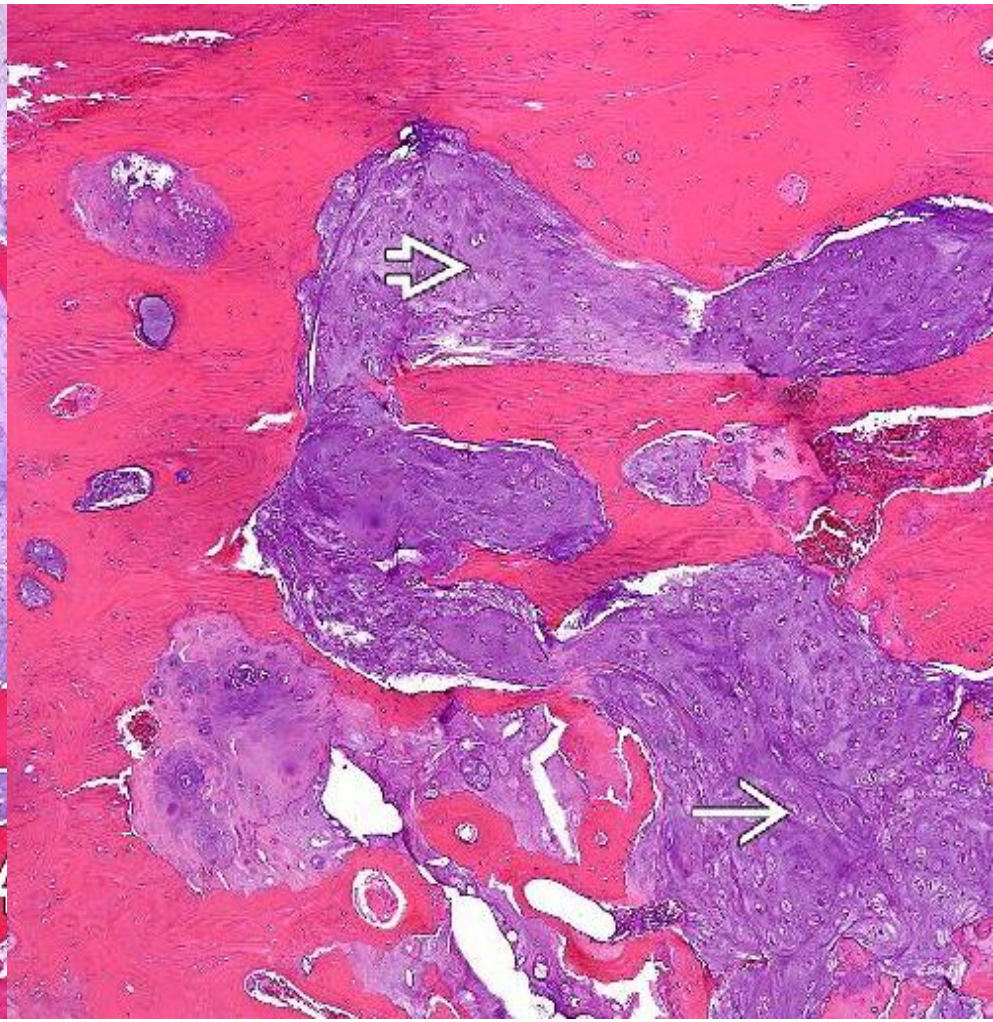


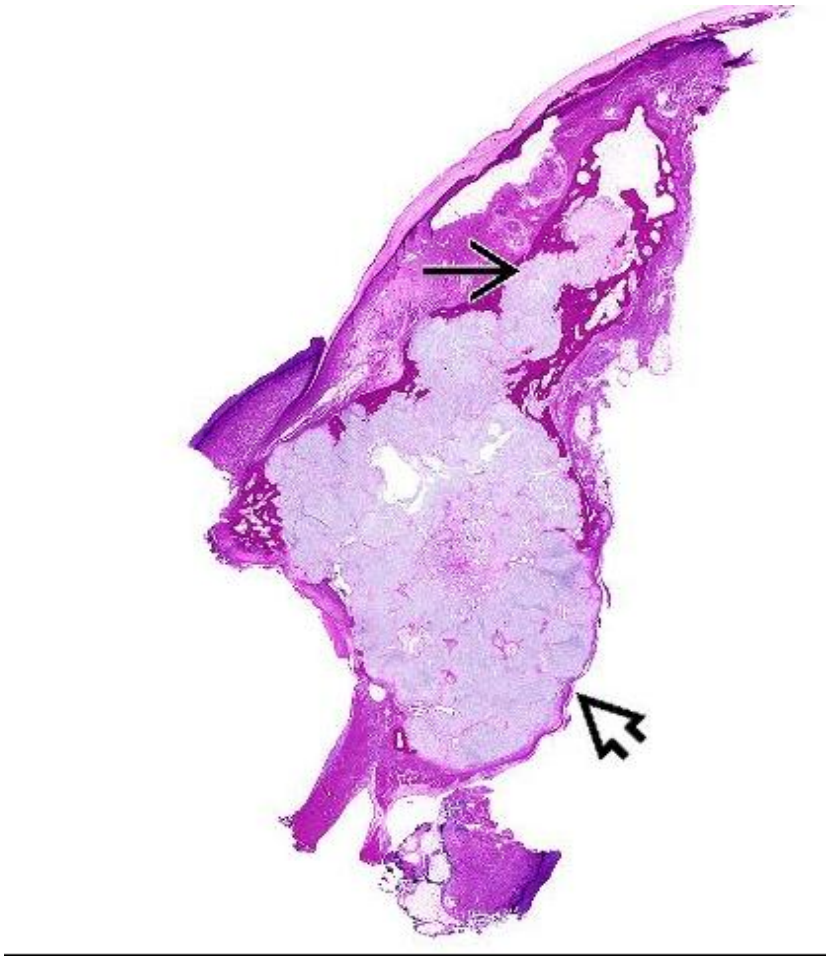


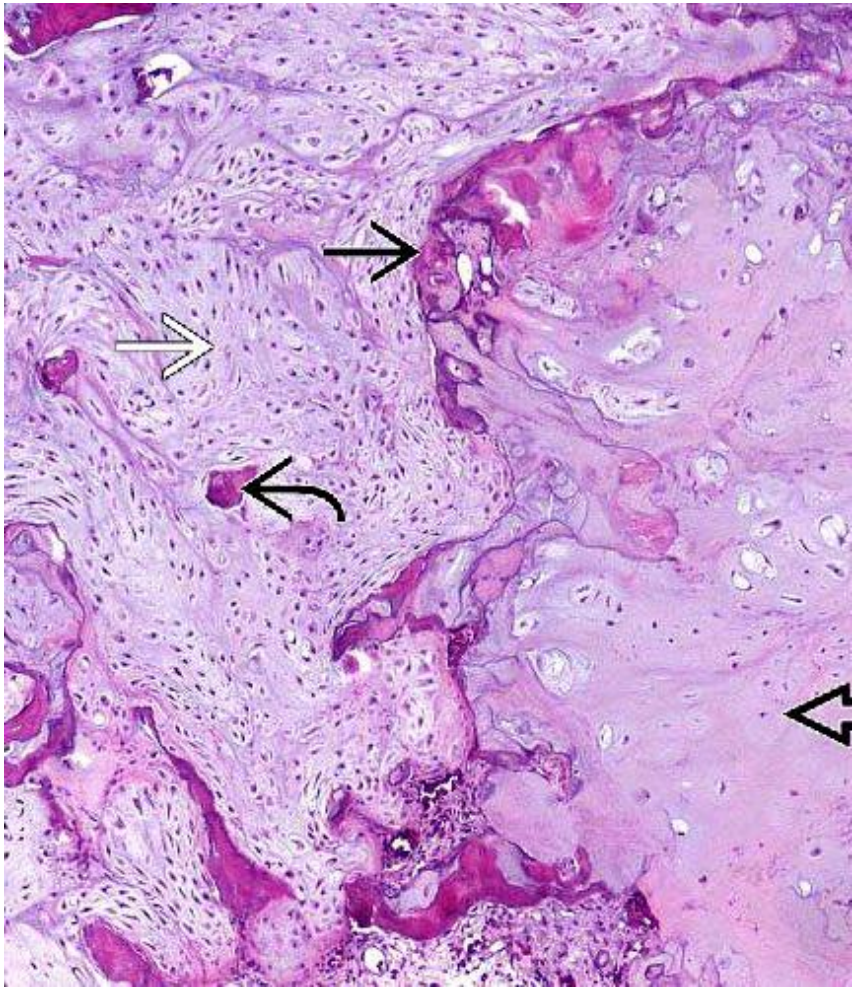


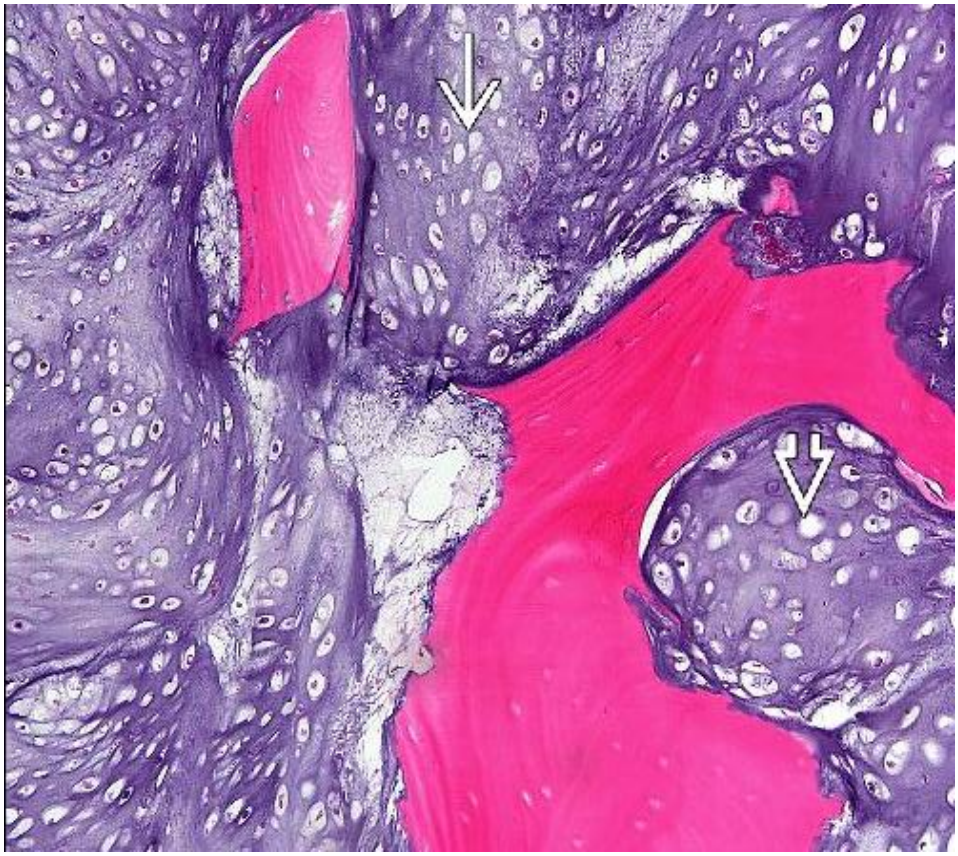


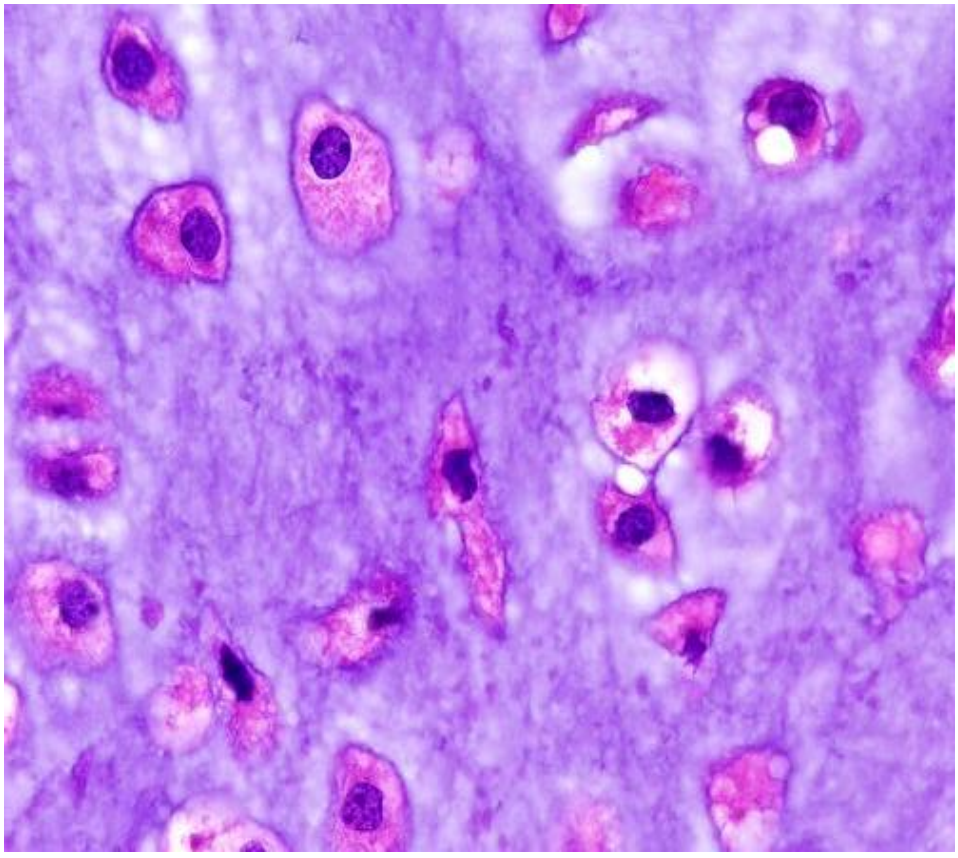


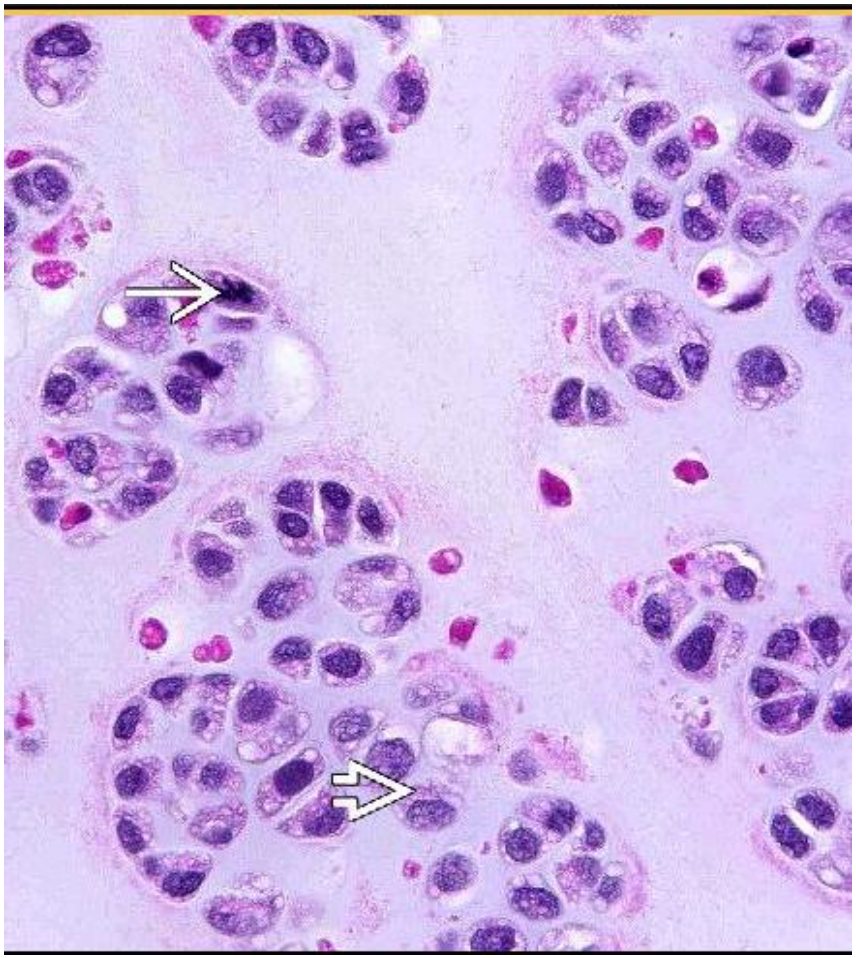


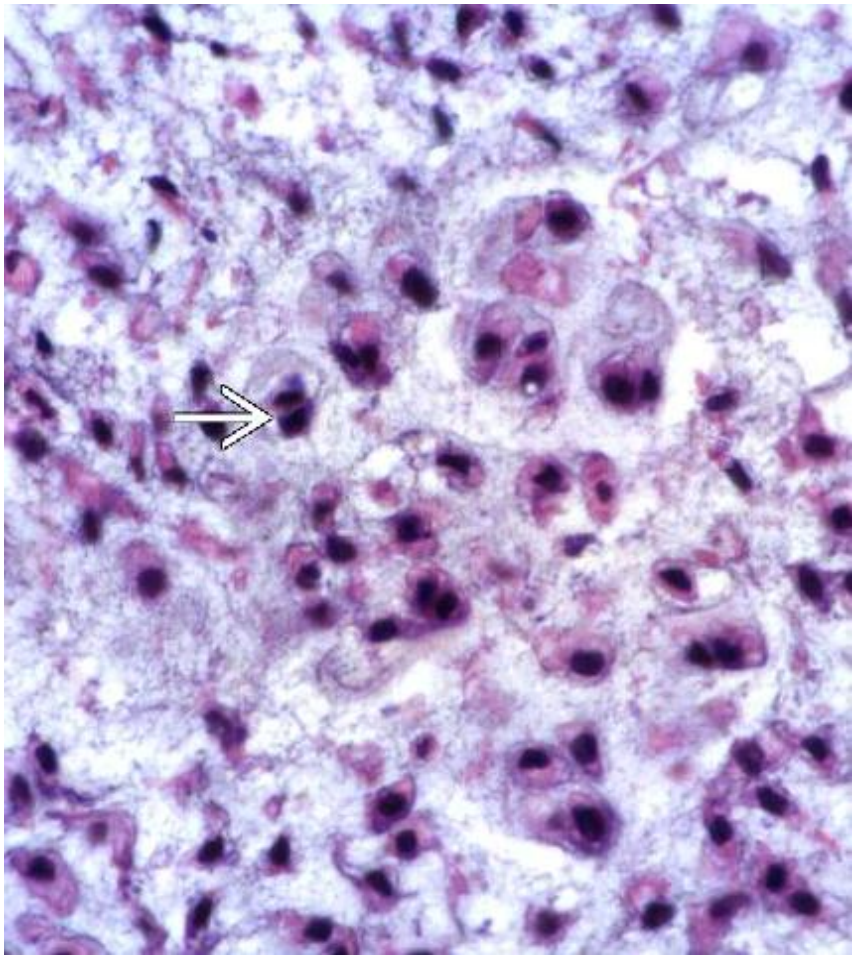


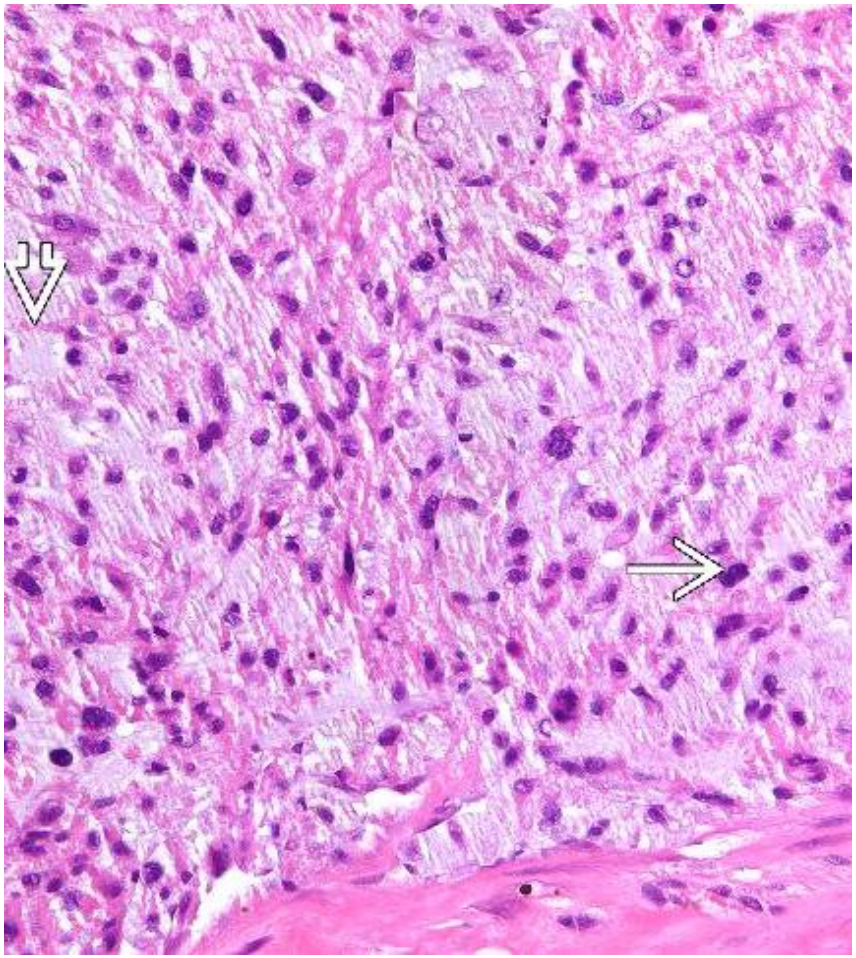


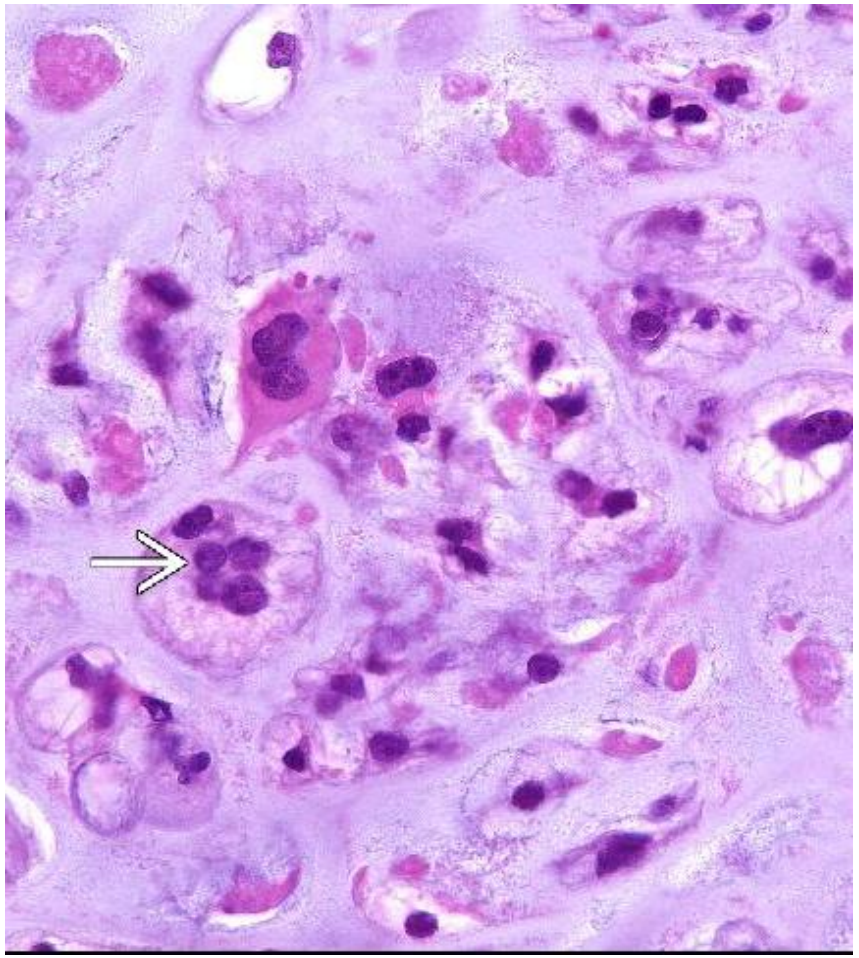


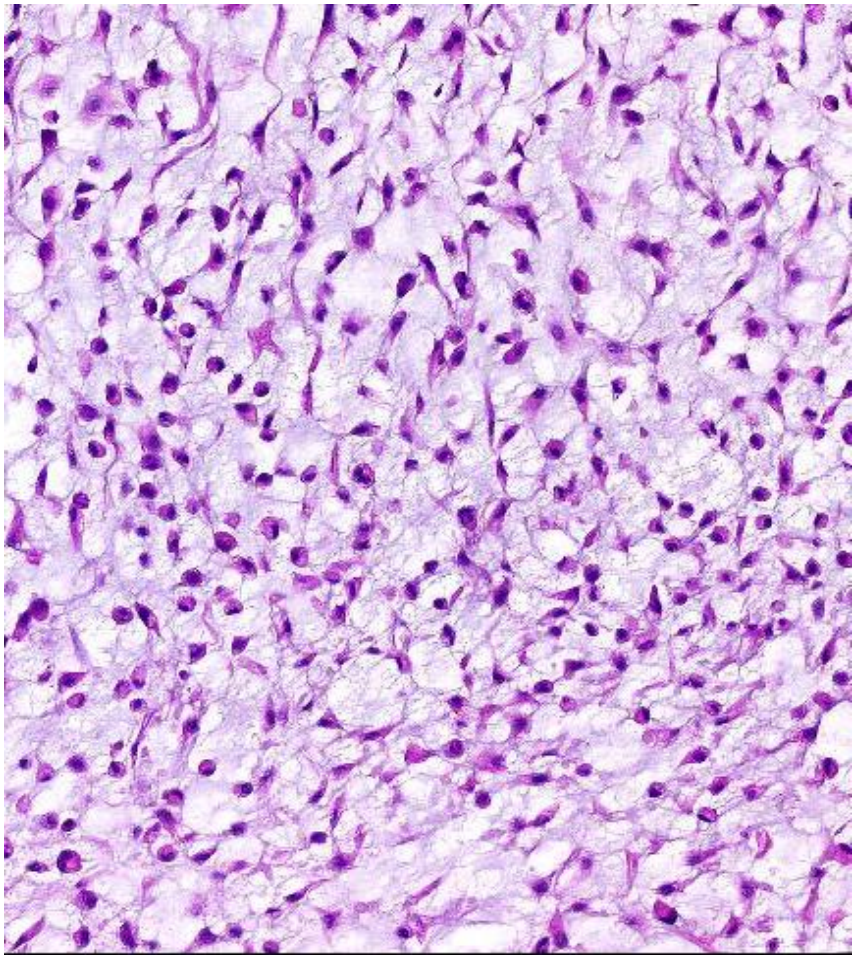


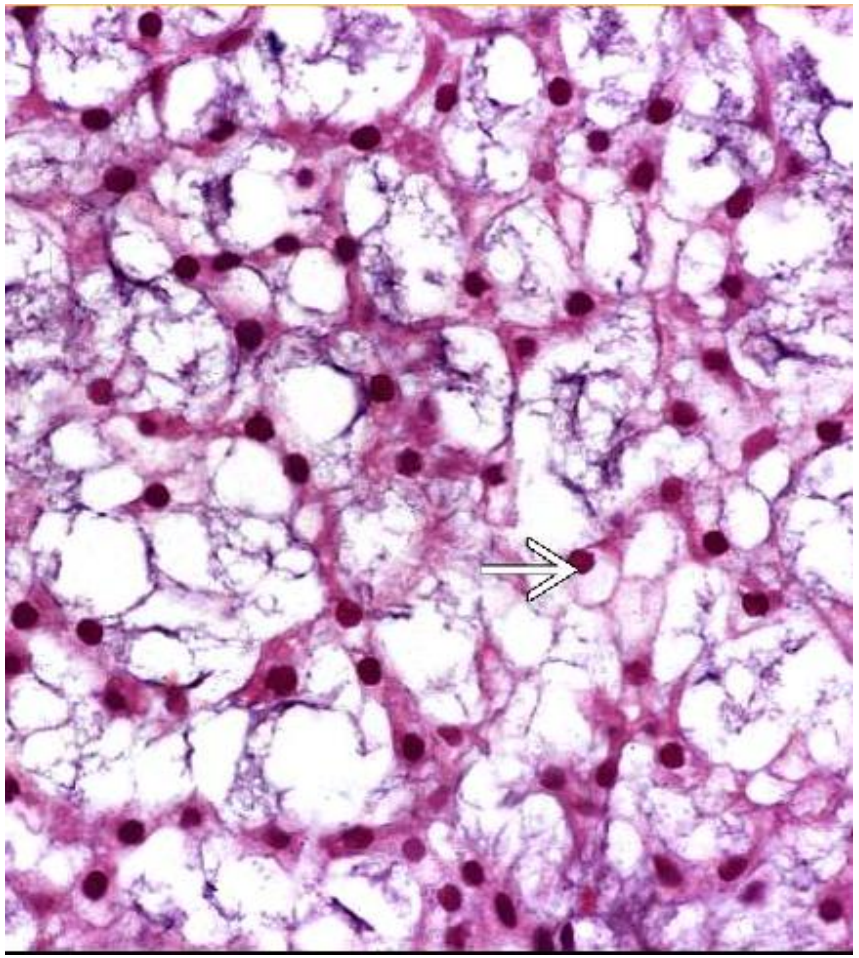


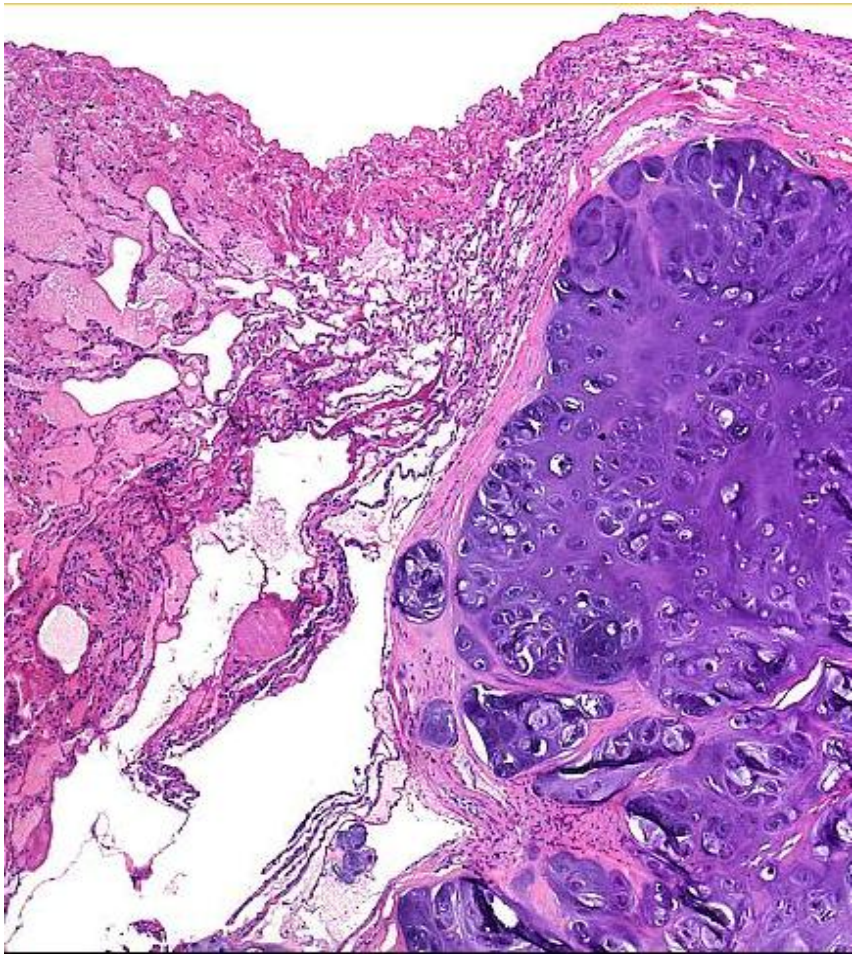


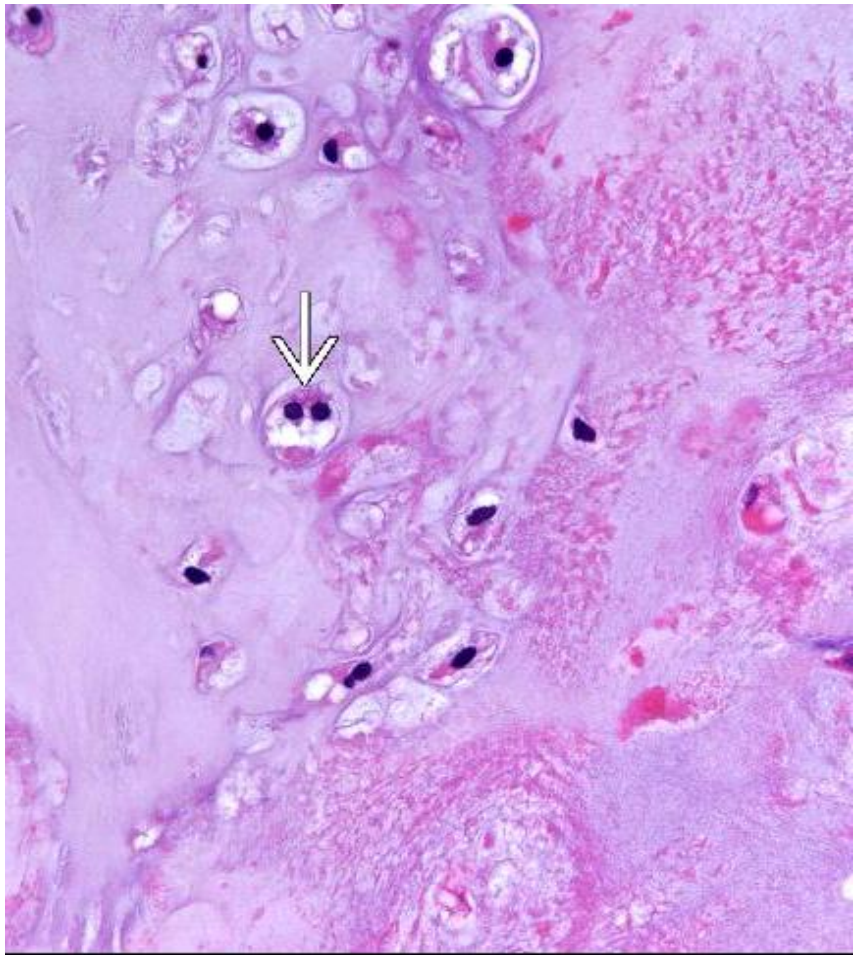


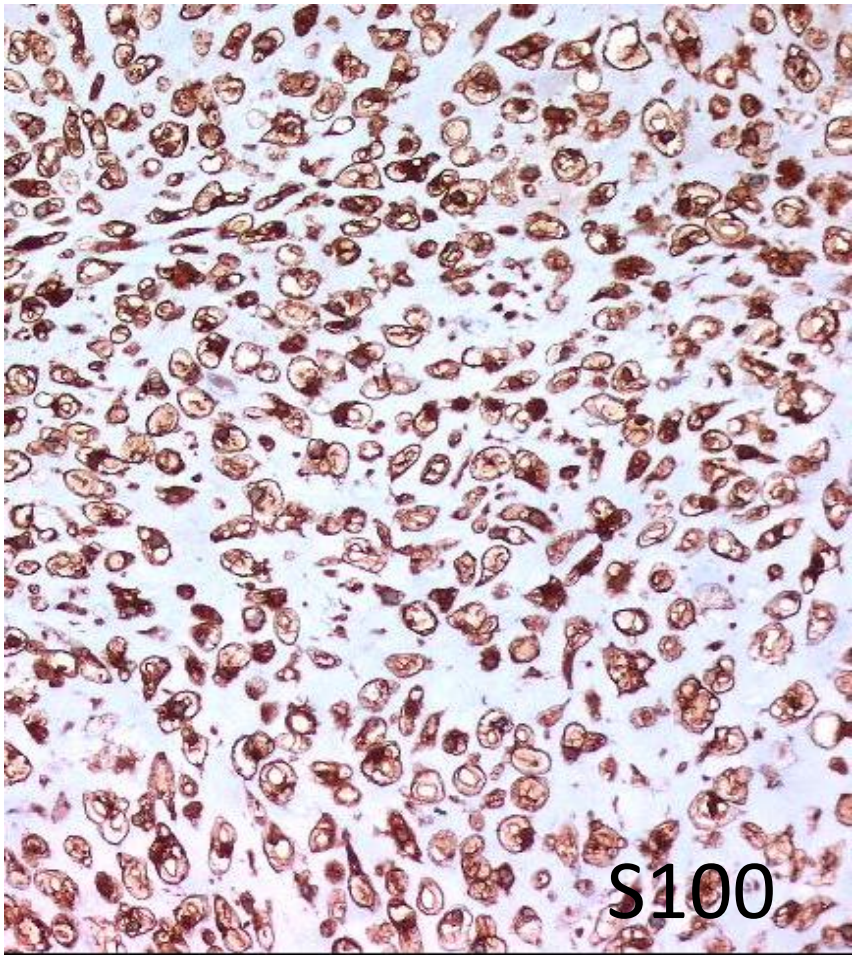








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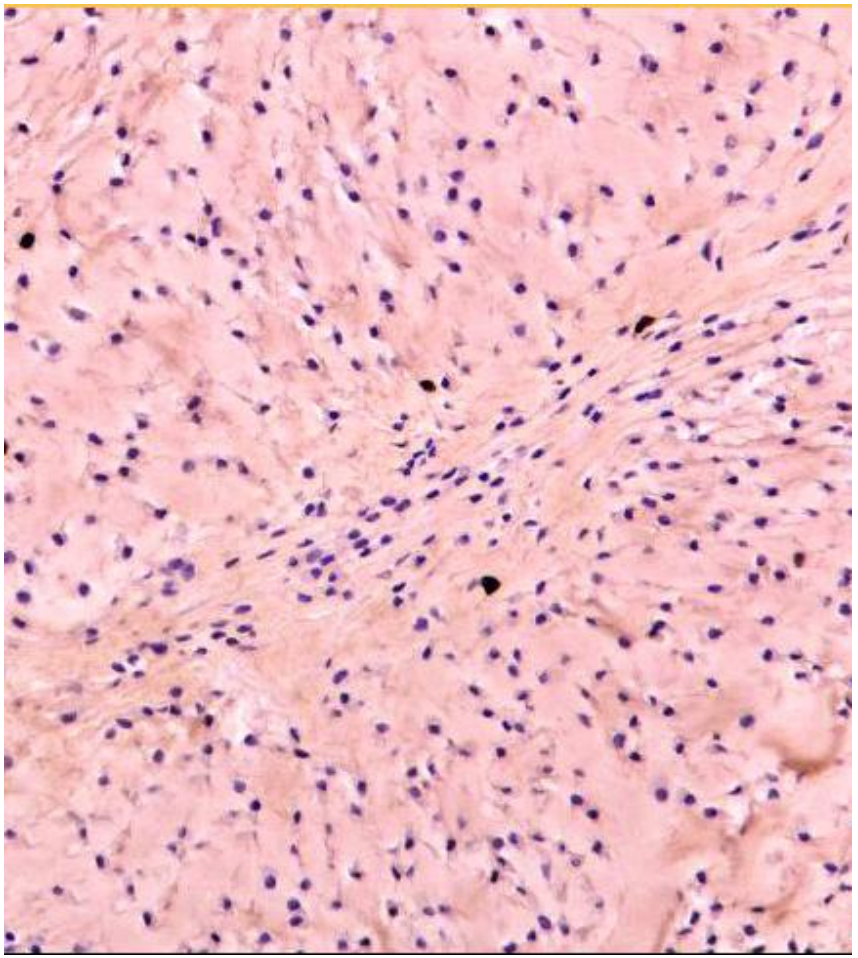


Tables

Grading of Chondrosarcoma

Grade	Cellularity	Cytologic Features
1	Hypocellular	Nuclei are small and dark, or slightly enlarged with fine chromatin
2	More cellular	Nuclei are larger, irregular, and have coarse chromatin; mitoses infrequent
3	Hypercellular	Severe pleomorphism and mitoses

[No Title]

Enchondroma vs. Low-Grade Chondrosarcoma

Enchondroma	Low-Grade Chondrosarcoma
Pain not attributed directly to neoplastic cartilage	Pain attributed to neoplastic cartilage
Lack increased cellularity, double nucleated chondrocytes, myxoid change, and chondrocyte necrosis	Increased cellularity, double nucleated chondrocytes, myxoid change, and chondrocyte necrosis
Absence of mitotic activity	Mitotic activity
Lack infiltrative growth pattern	Infiltrative growth pattern

Ancillary tests

- IDH1 and IDH2 are mutated in many chondrosarcomas
  - Primary chondrosarcomas: 38-70%
  - Secondary: 86%
  - Periosteal chondrosarcoma: 100%
- Mutation analysis can be used in difficult cases to distinguish chondrosarcoma from chondroblastic osteosarcoma in biopsy sample

Differential diagnosis

- Enchondroma
  - Does not grow with infiltrative pattern
  - Relatively less cellular and lack significant atypia
- Clear cell chondrosarcoma
- Chondromyxoid fibroma
- Chordoma
  - Chondroid chordomas difficult to differentiate
  - Both tumors are s100 protein positive
- Fracture callus

Diagnostic checklist

- On core biopsy, it can be impossible to differentiate between enchondroma and low-grade chondrosarcoma
  - Radiographic features should be correlated with histology
- In difficult cases open biopsy should target interface of tumor and normal bone
- In tubular bones this distinction is not critical as both enchondroma and low-grade chondrosarcoma can be treated with thorough curettage

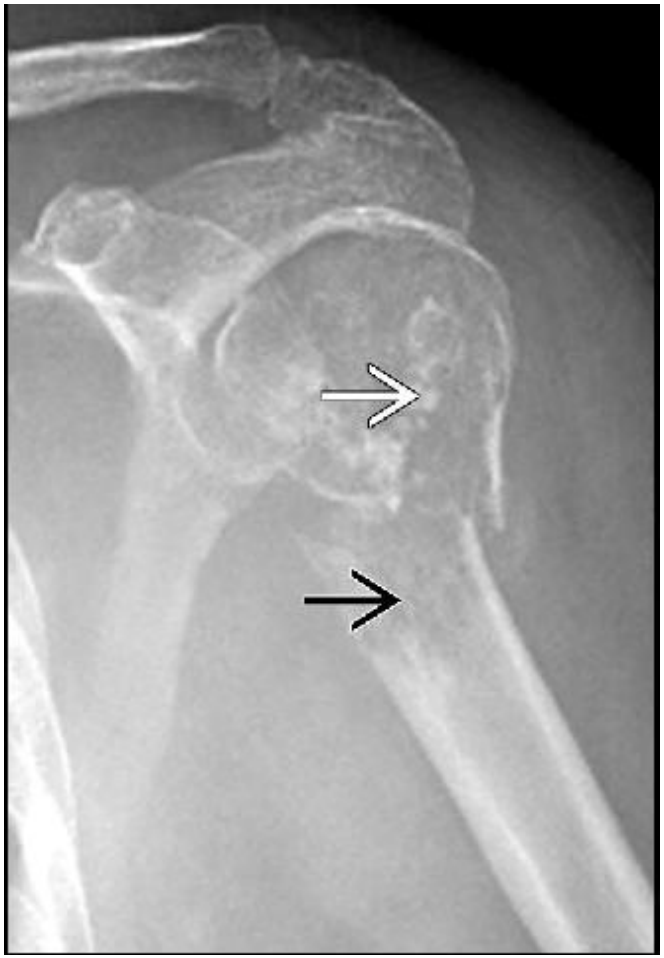
Dedifferentiated Chondrosarcoma

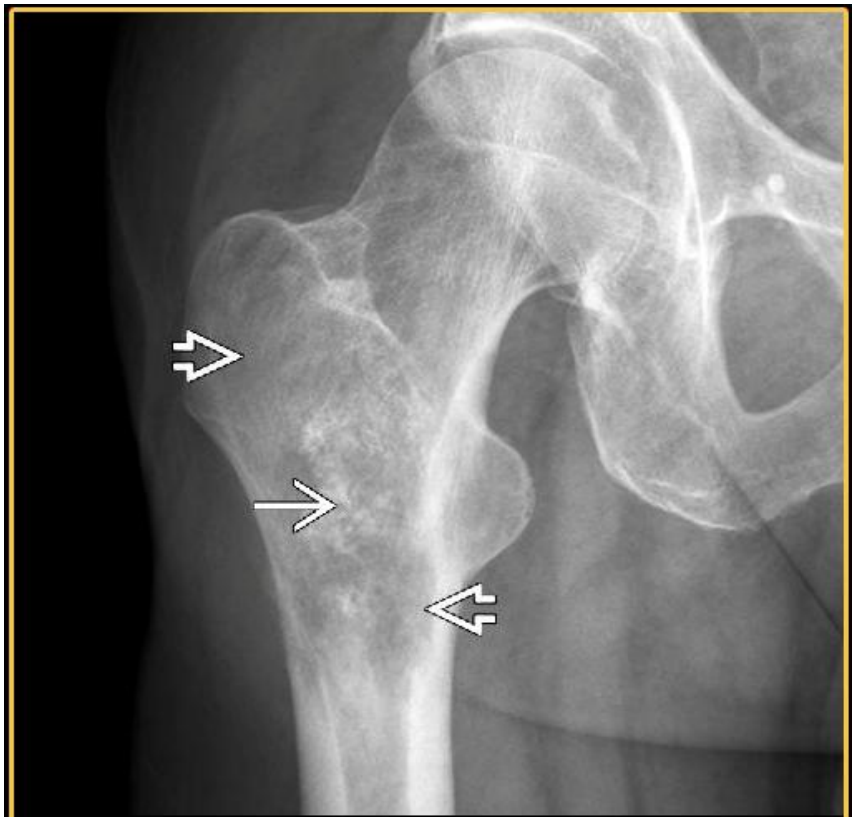
- Definition
  - High- Grade sarcoma arising in association with low-grade cartilaginous neoplasm with abrupt transition between the two components
    - Cartilaginous component usually low grade
    - Less frequently cartilaginous component is an enchondroma or osteochondroma
- Etiology/pathogenesis
  - IDH1 and 2 genetic mutations have been identified in majority of chondrosarcomas

Clinical issues

- Epidemiology
  - Incidence: 10% of conventional chondrosarcomas
  - Age: Usually adults, 50-70 years old
  - Gender: Males>females
- Site
  - Pelvis, femur, humerus
- Treatment
  - Wide excision and systemic therapy
  - The latter relatively ineffective
- Prognosis
  - Very poor

Imaging findings





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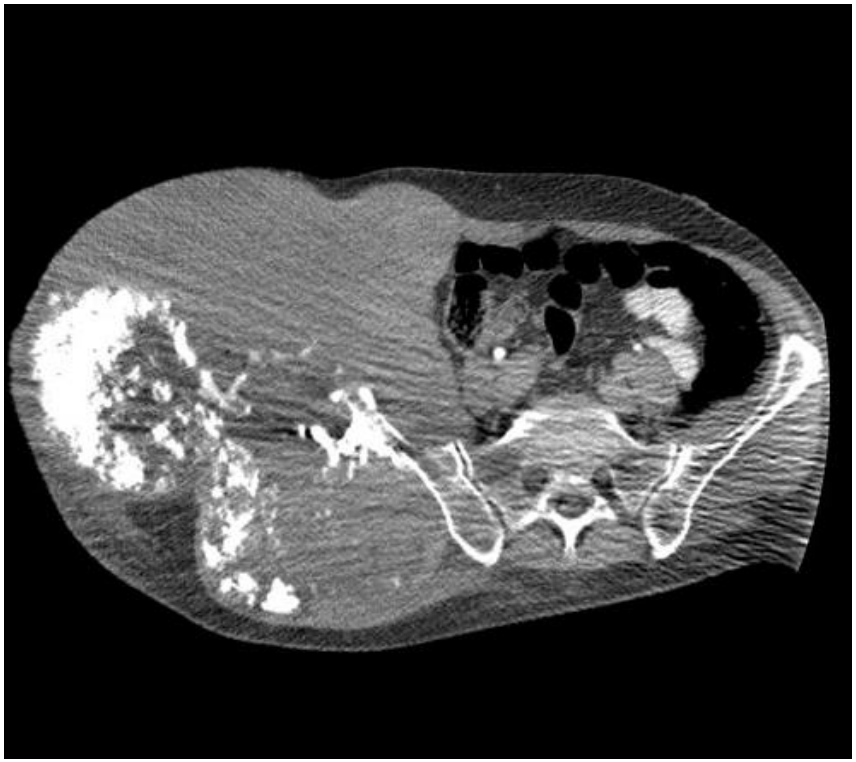

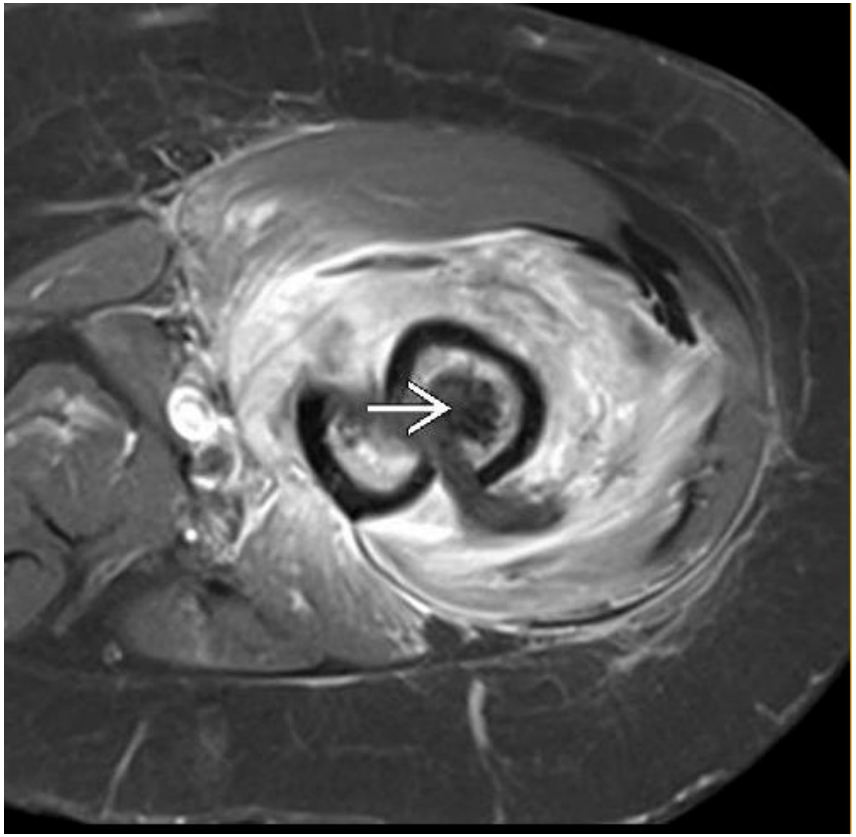

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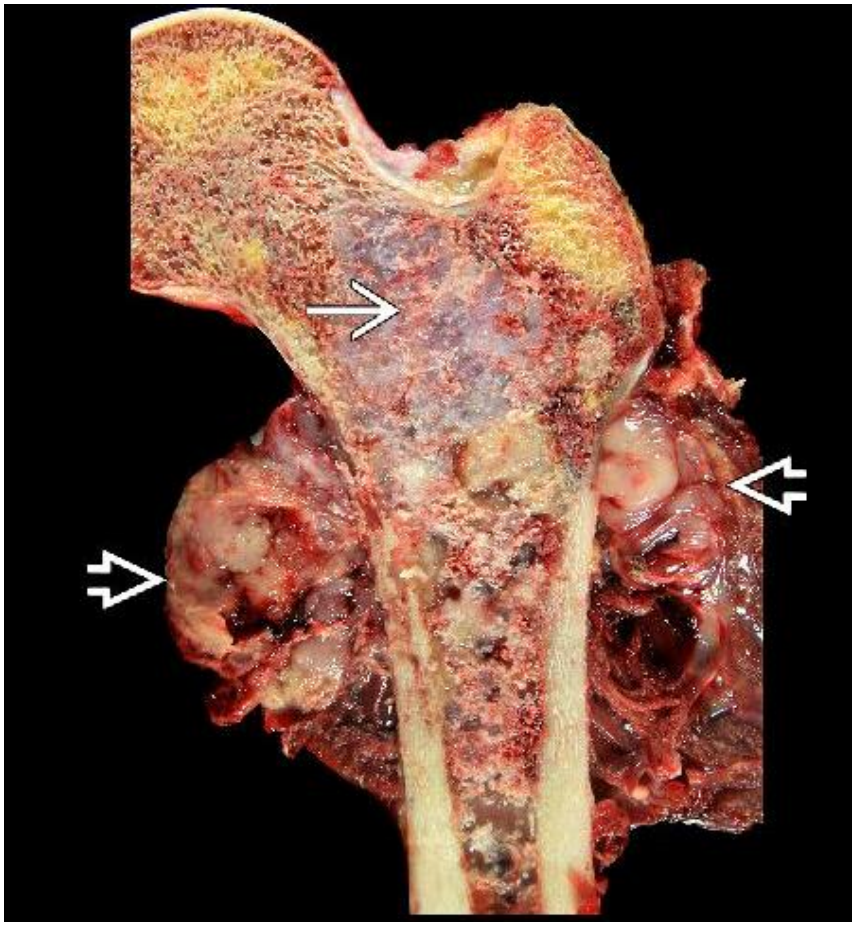

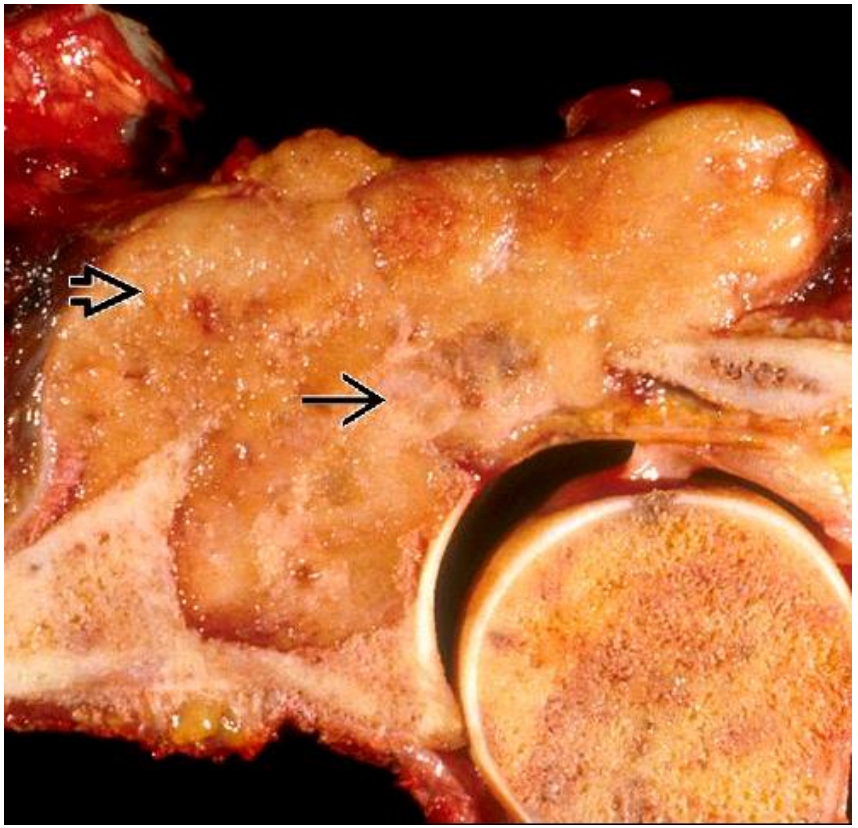

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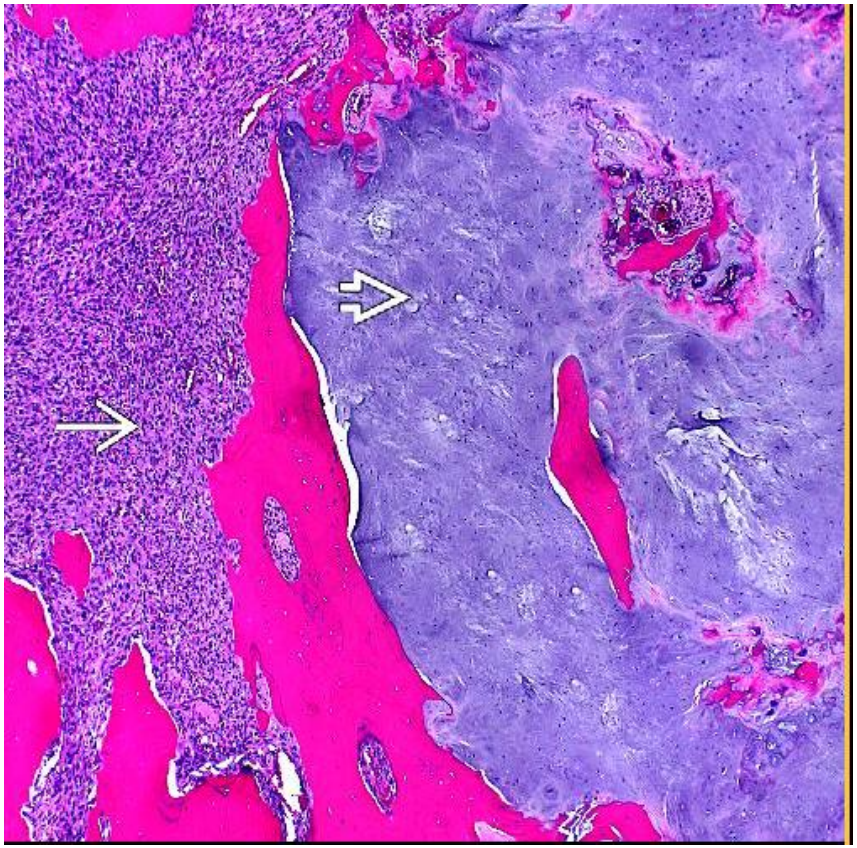

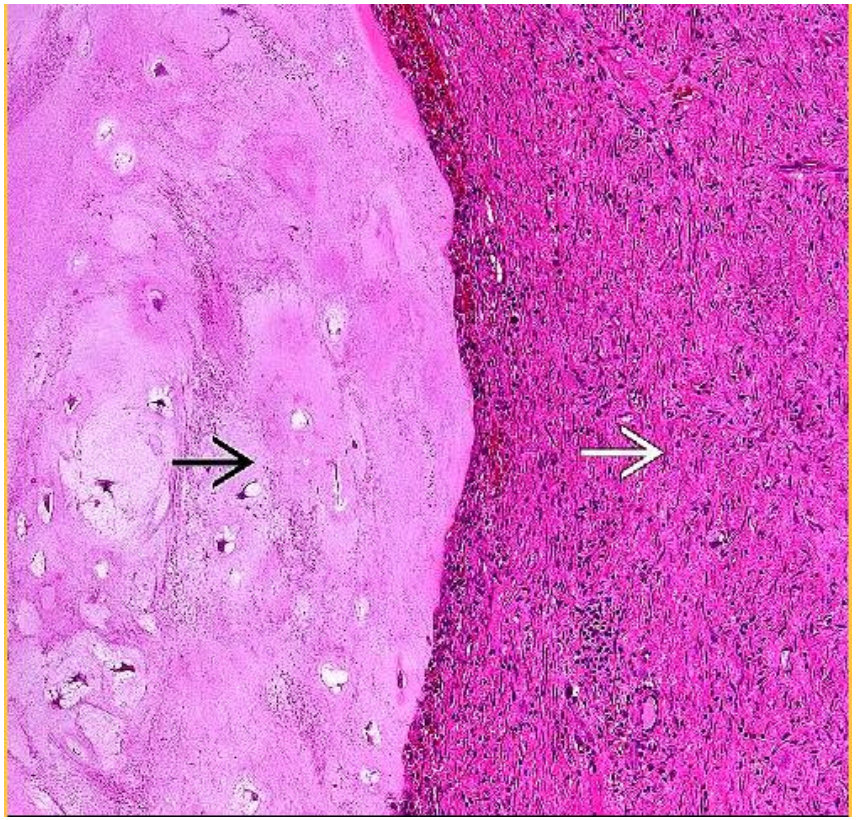

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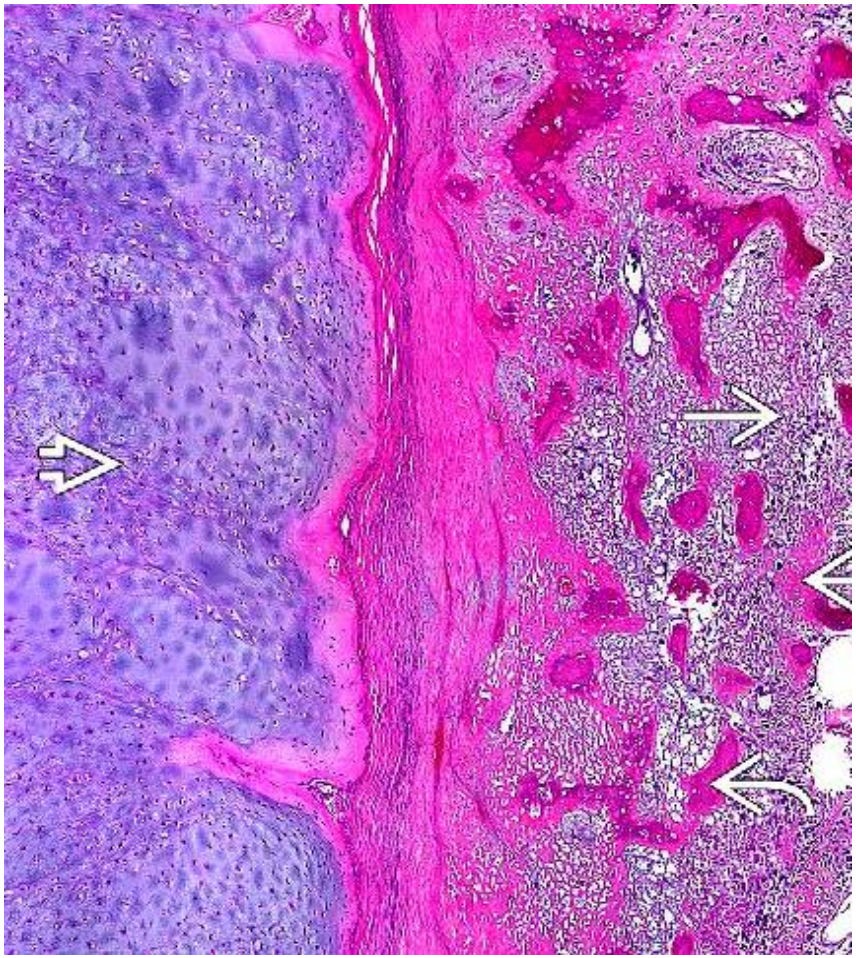

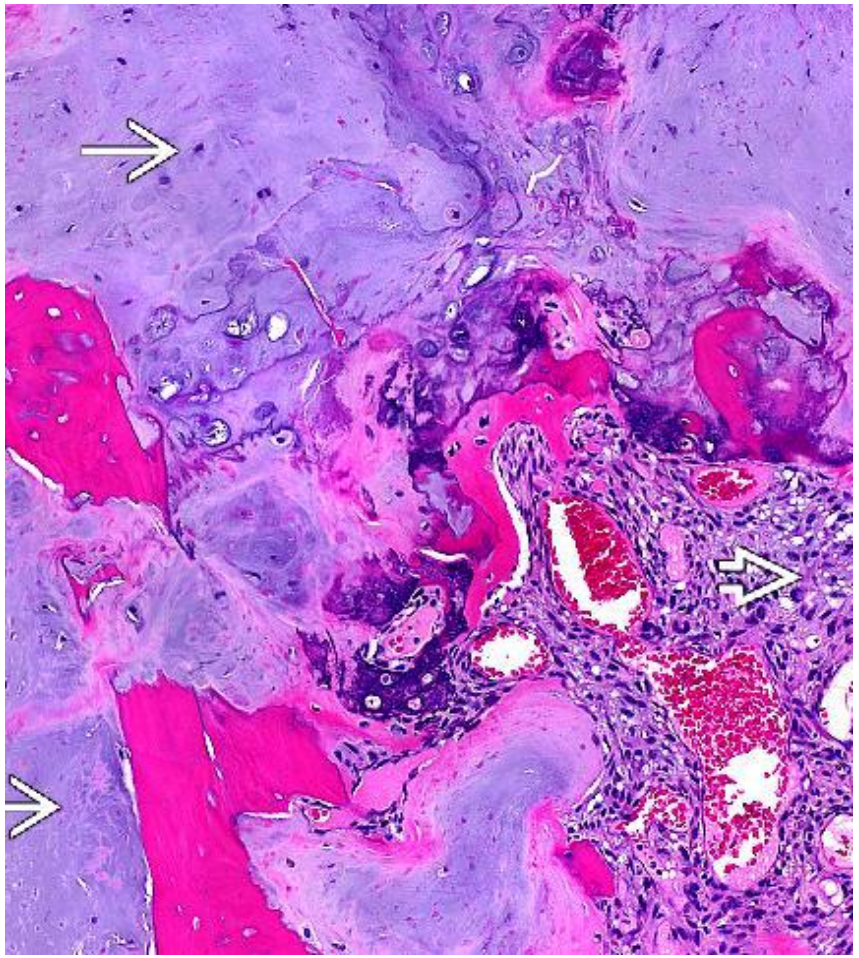

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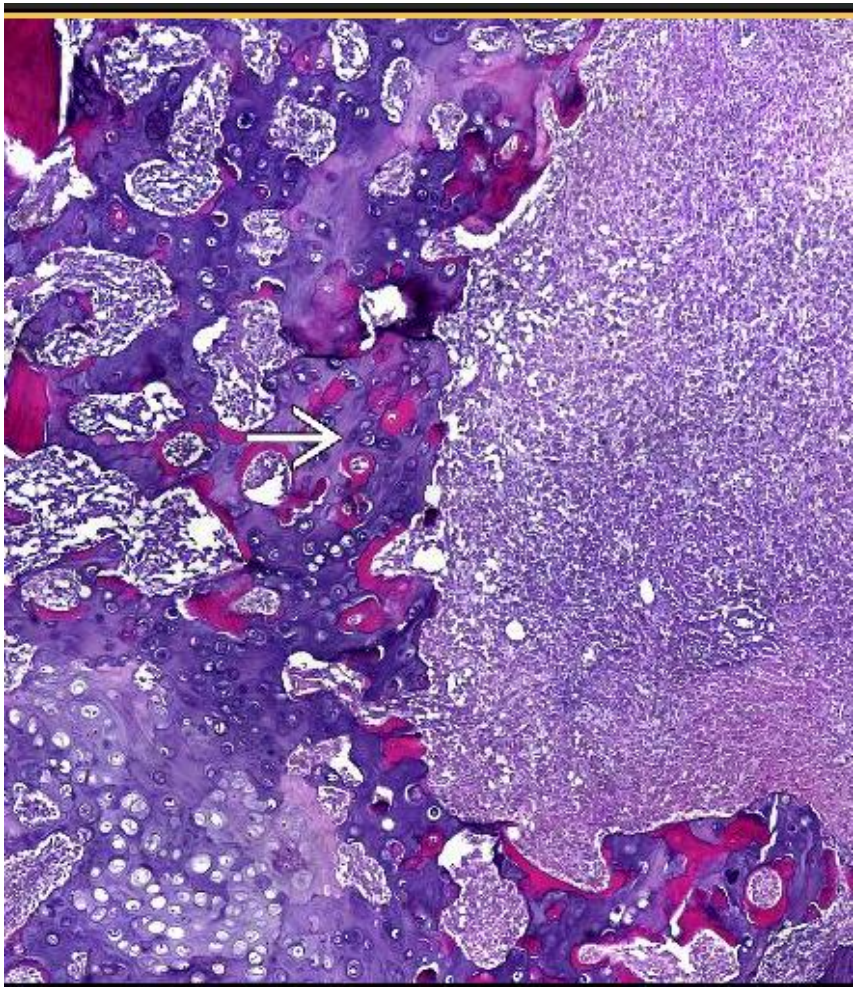

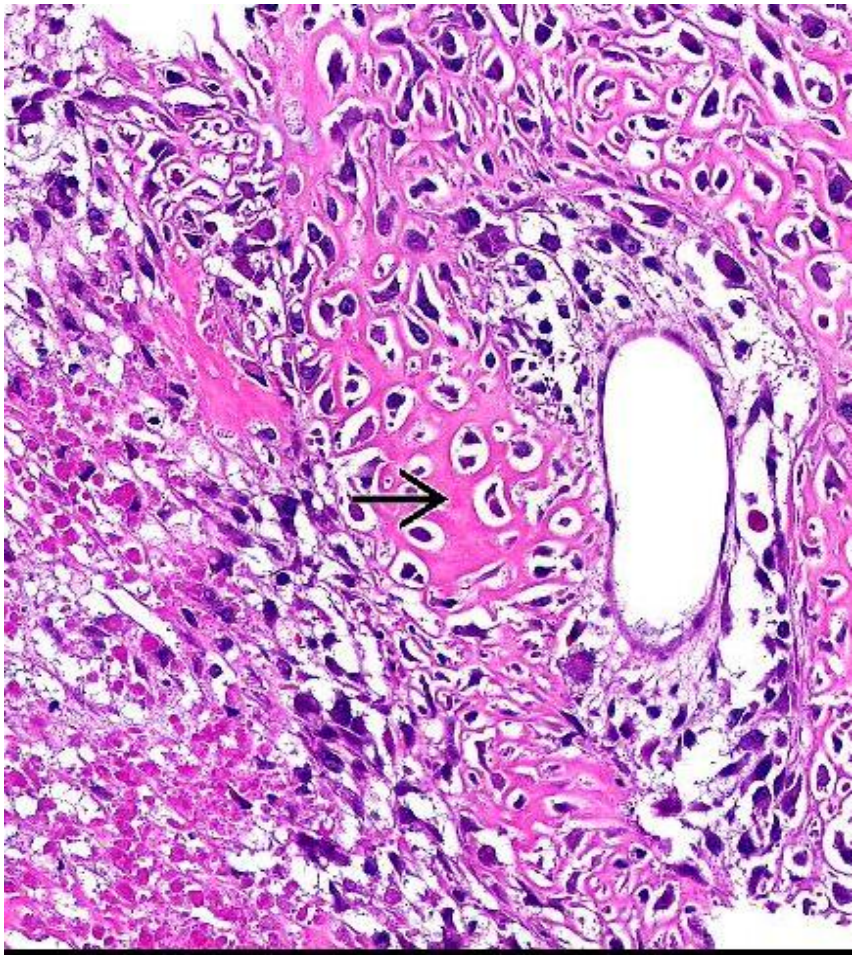

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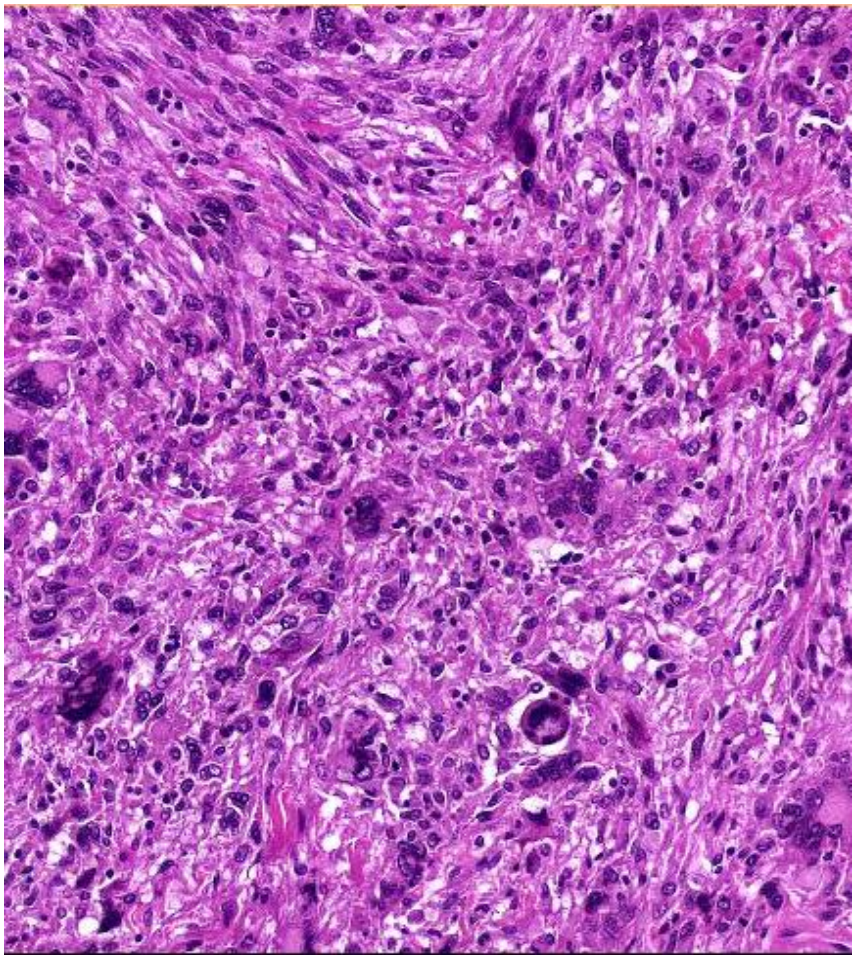

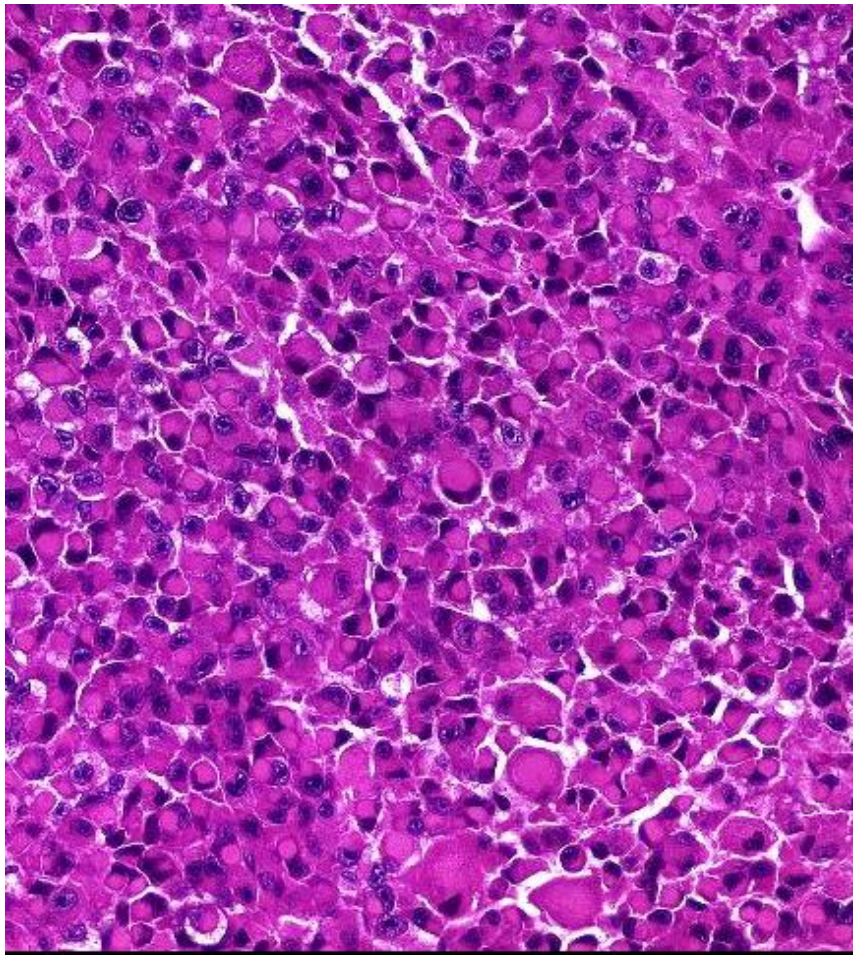

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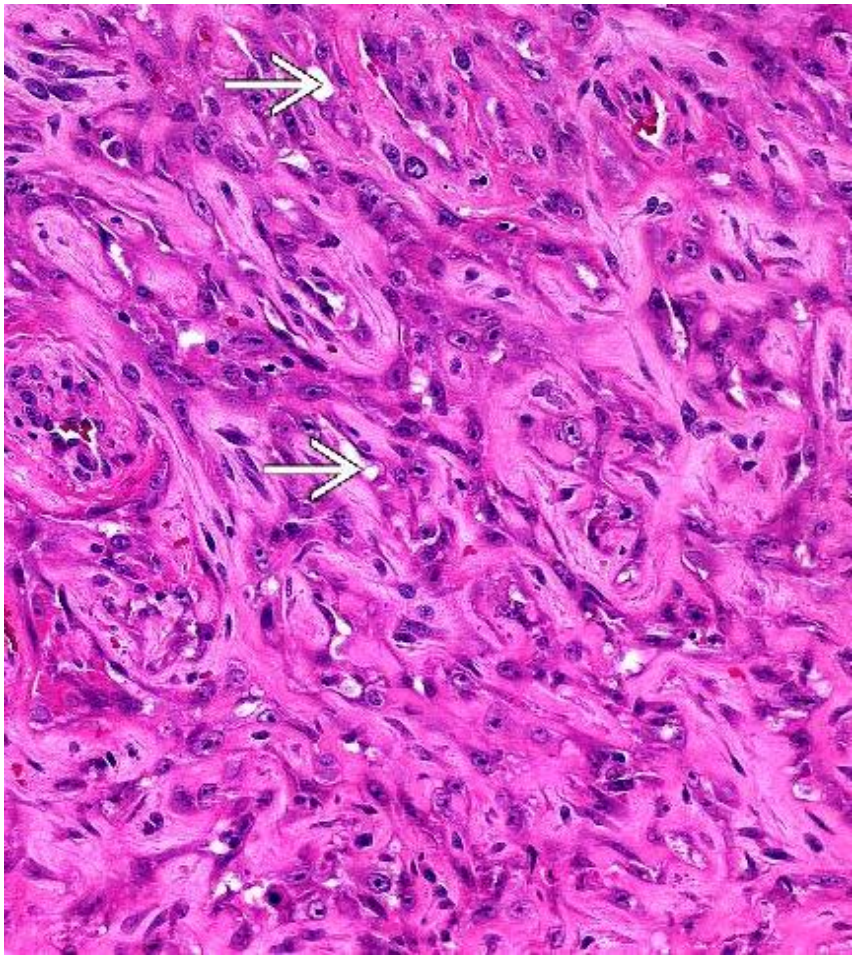
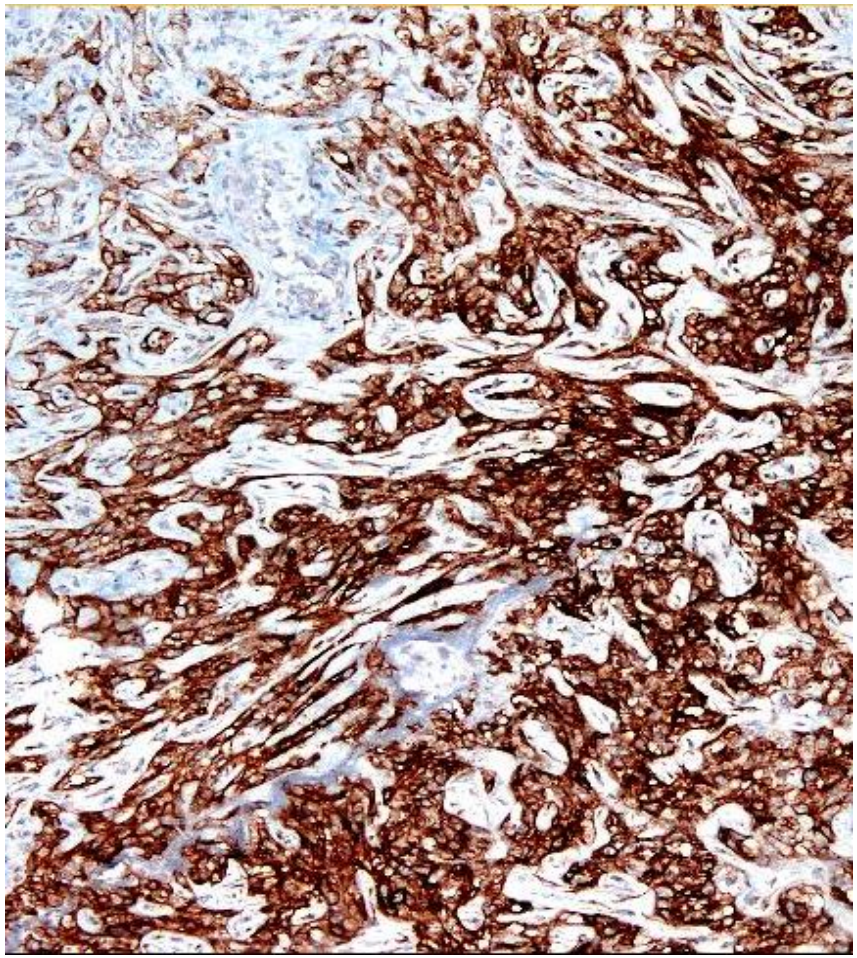




Differential Diagnosis

- Chondroblastic osteosarcoma
  - Especially difficult when the dediff component is osteosarcoma
  - Usually younger patients
  - Cartilaginous component is high grade
- High grade spindle cell sarcoma
  - Impossible to make the diagnosis in small sample
  - Any high grade spindle cell sarcoma in older individuals should be thoroughly sampled
- Metastatic sarcomatoid carcinoma
  - High grade sarcomatoid component in dediff chondro can be strongly keratin positive
  - Sampling and radiologic correlation

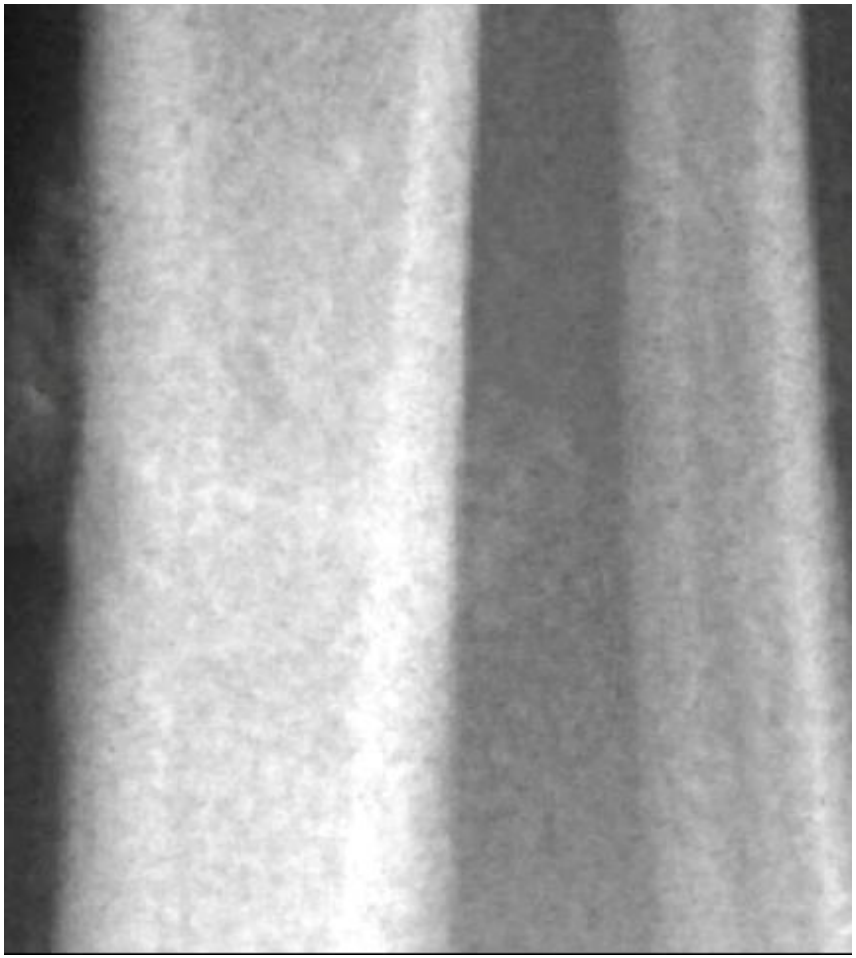
Mesenchymal Chondrosarcoma

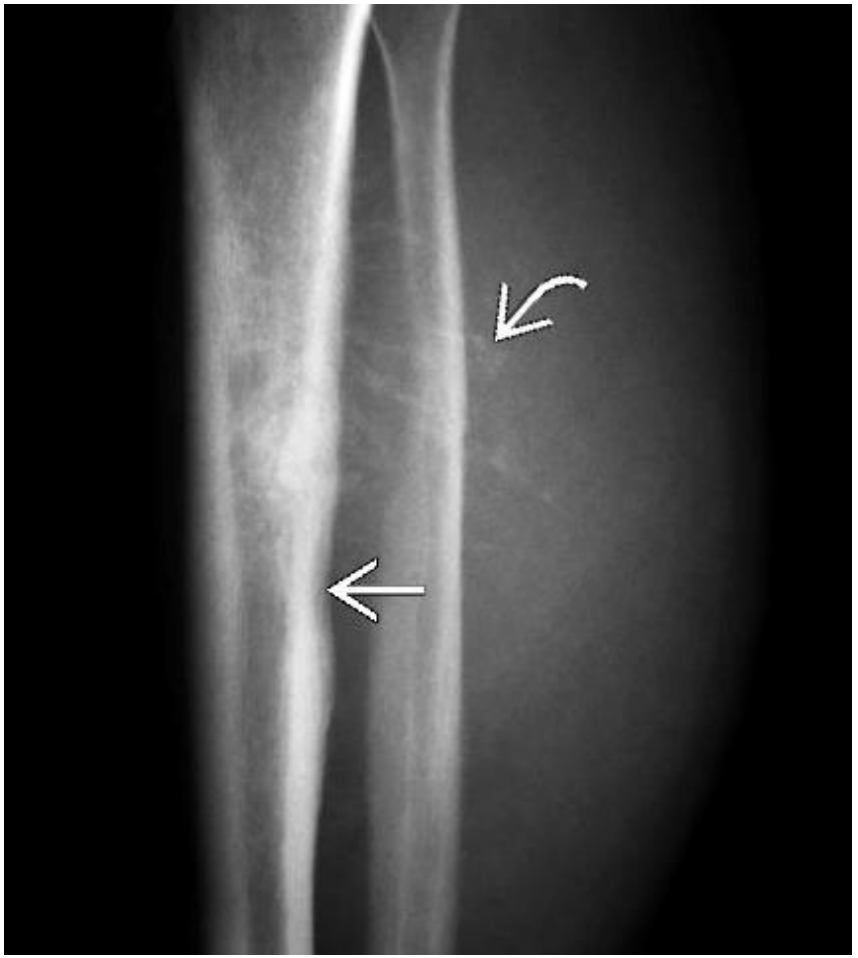
- Rare variant of chondrosarcoma arising in bone and less commonly in soft tissue
- Mutation in mesenchymal stem cell producing neoplasm
- Accounts for approximately 2% of skeletal chondrosarcoma
- Typical occurs during 2-3rd decade

Clinical issues

- Site
  - Most commonly in bones of **craniofacial skeleton especially the jaw**
  - Vertebrae, ribs, pelvis, and long bones frequently involved
- Treatment
  - En bloc excision with negative margins
  - Adjuvant radiation for incomplete excised tumor
  - Chemotherapy debatable but often utilized
- Prognosis
  - 5 and 10-year survival 55 and 26% respectively
  - Prognosis better for tumor arising in jaws
  - Lung most common site of metastasis
  - Clinical course may be prolonged

Imaging findings





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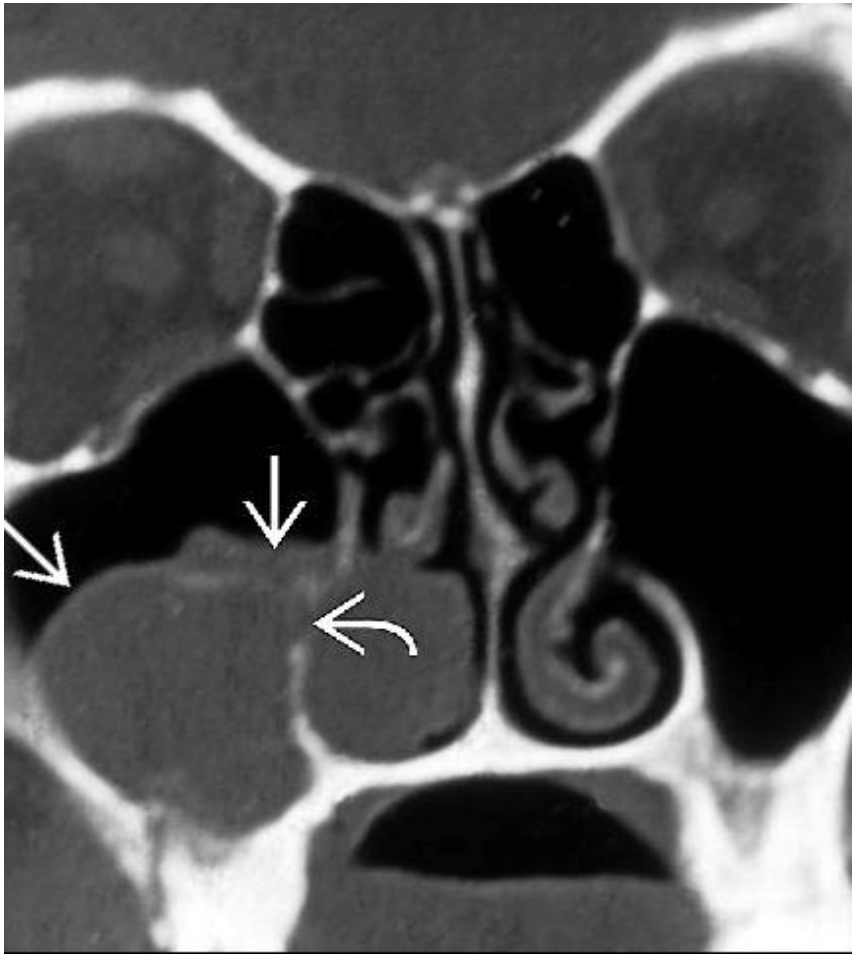

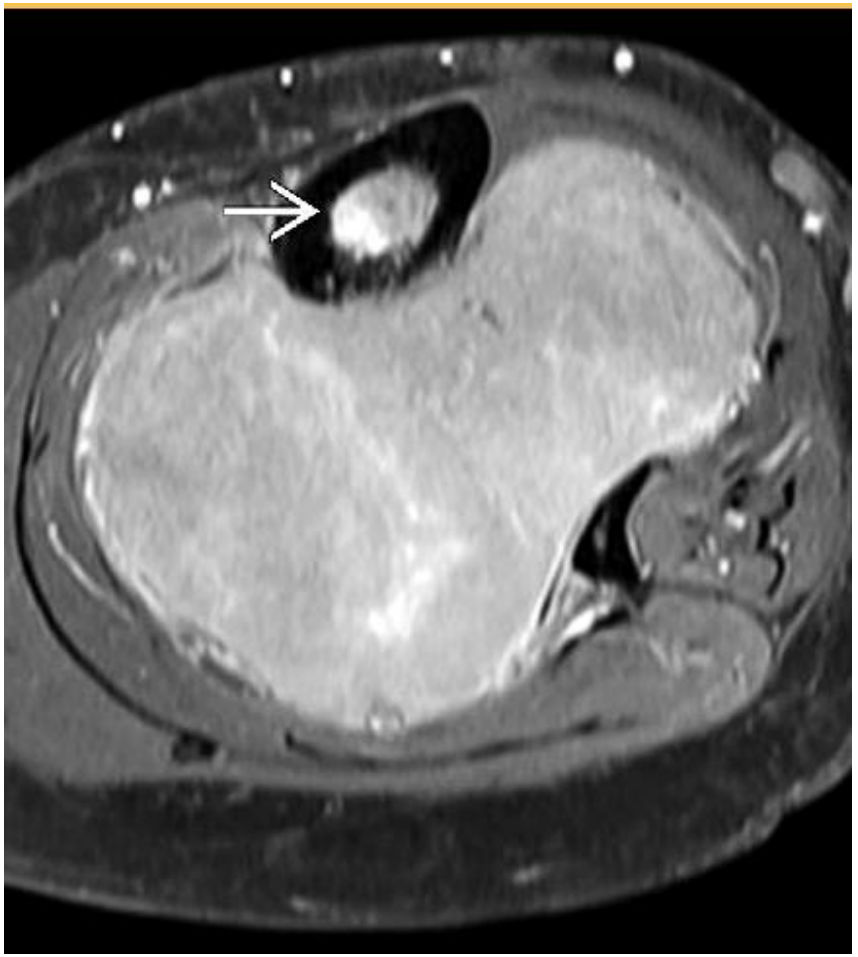

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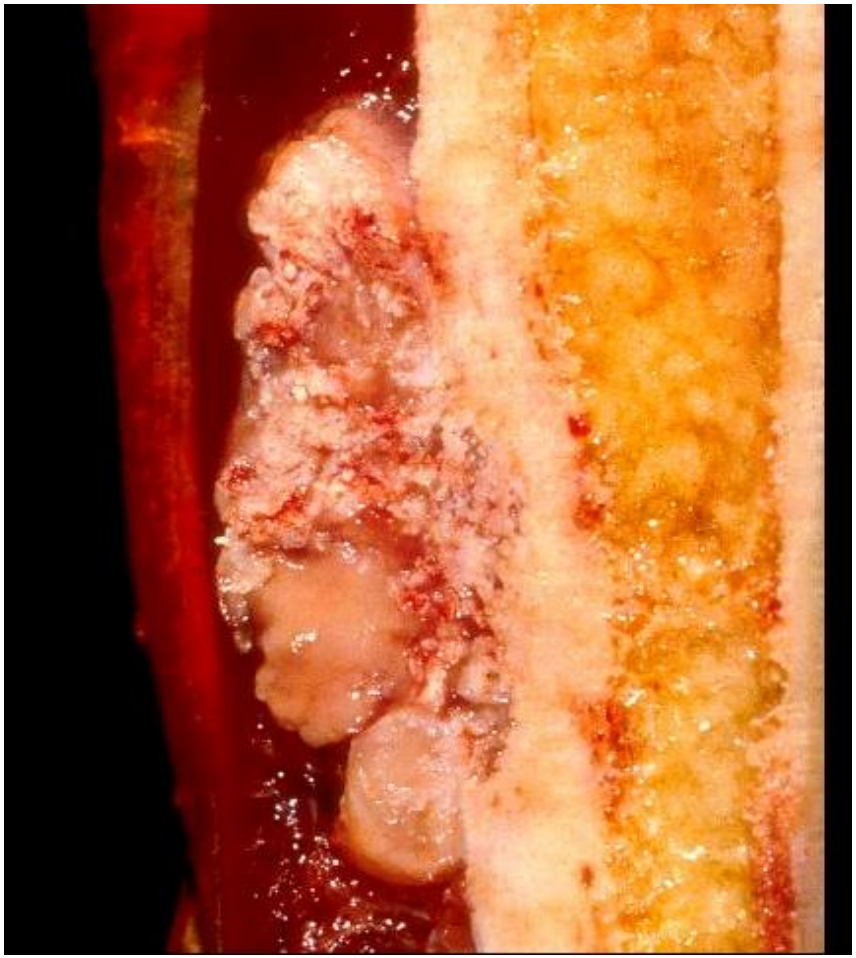

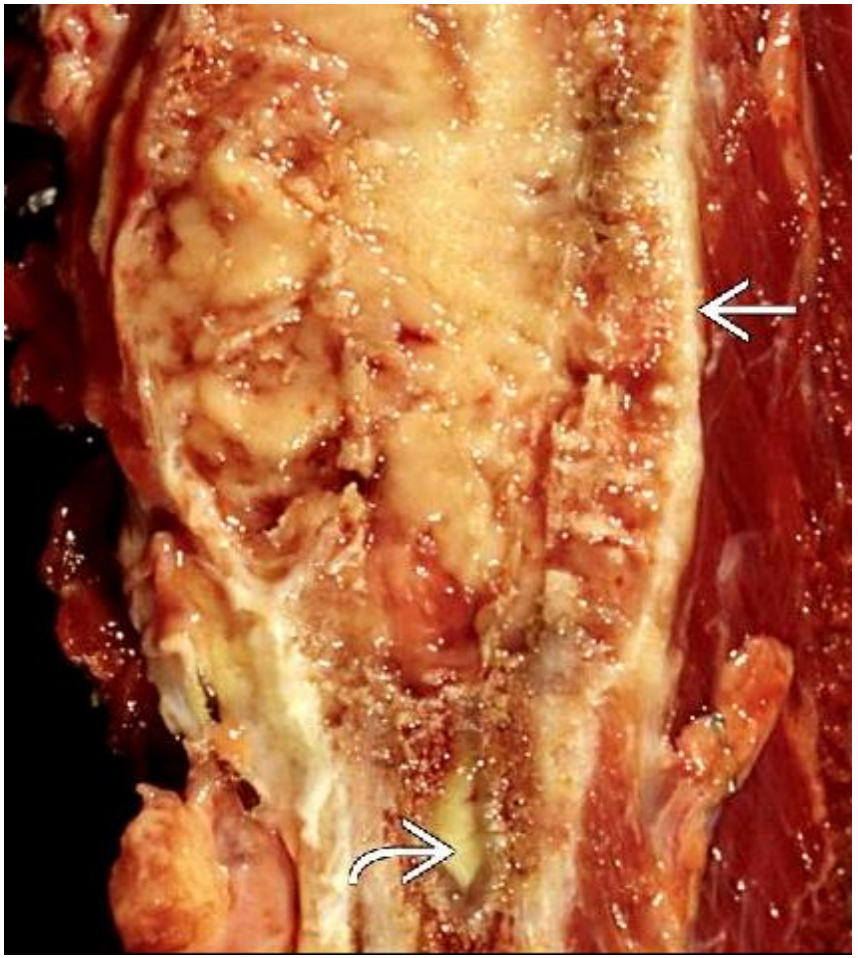

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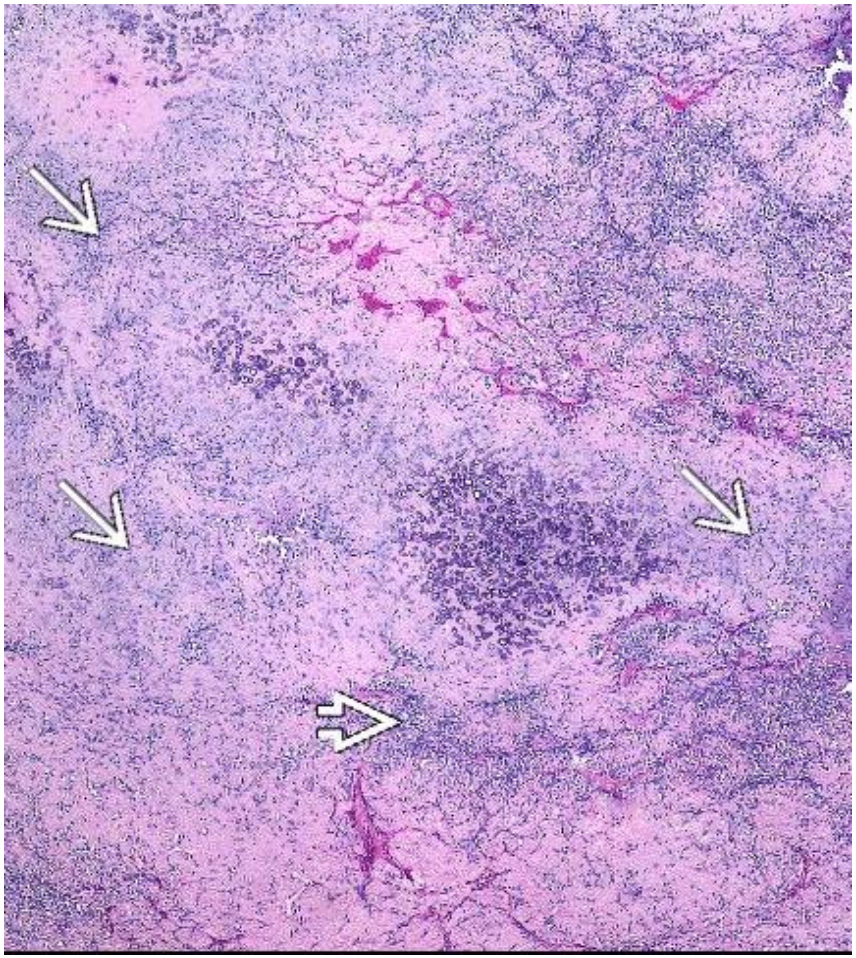

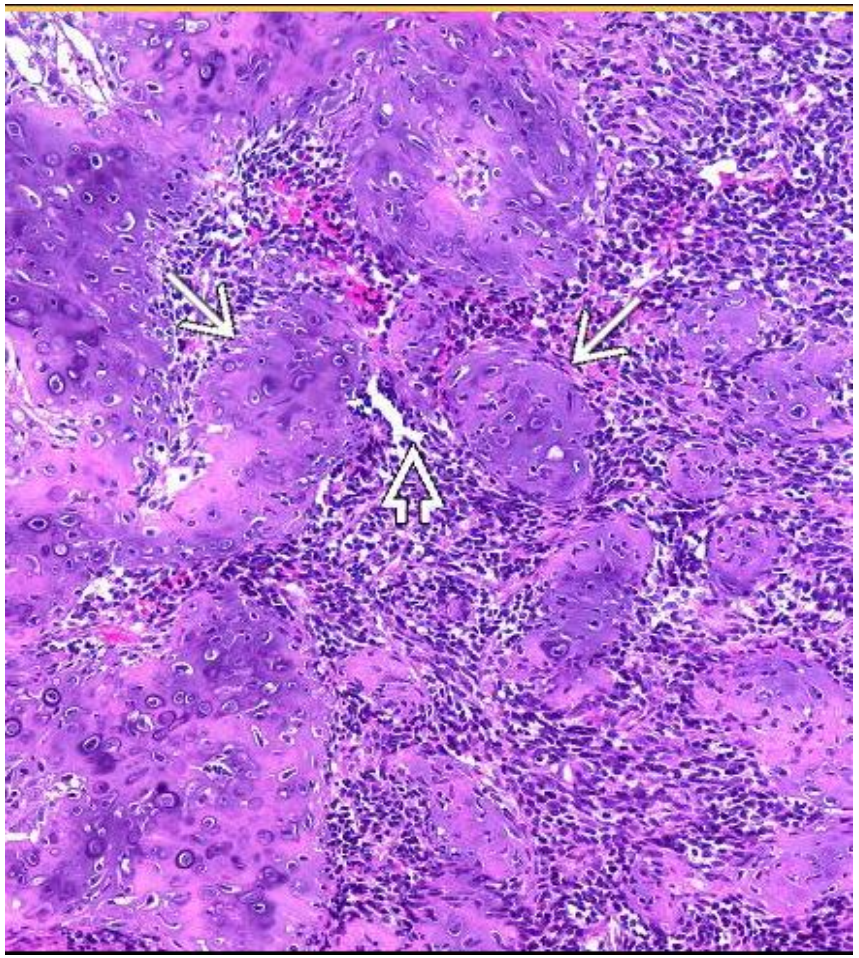

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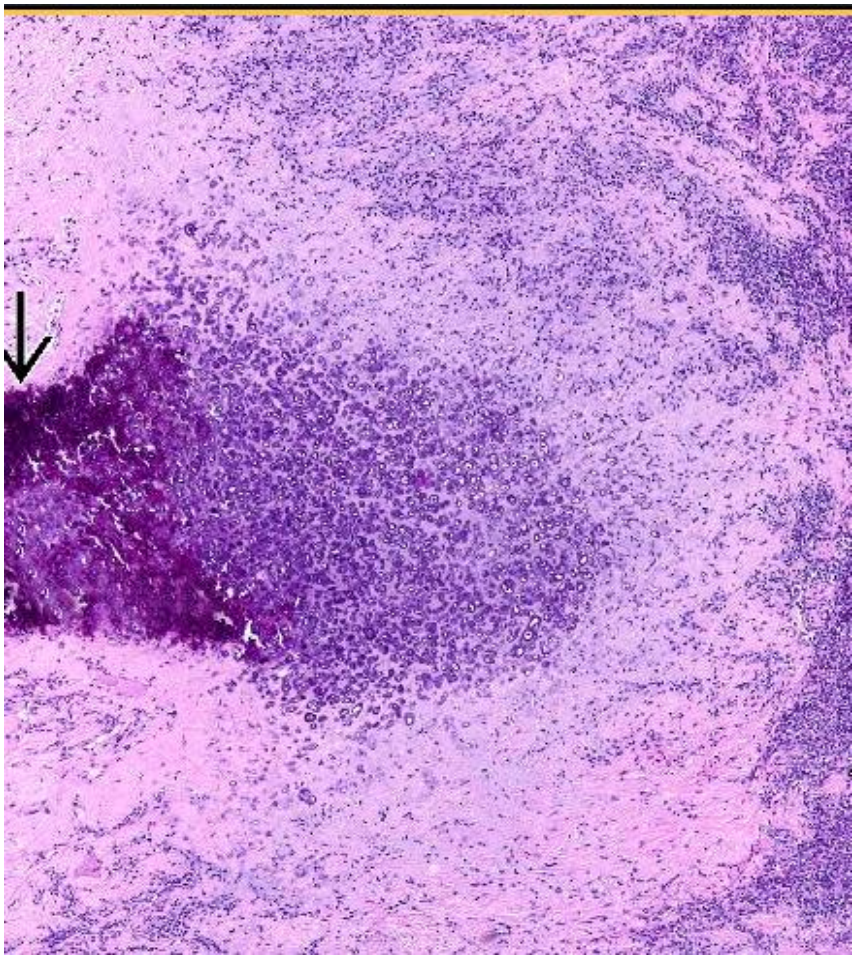

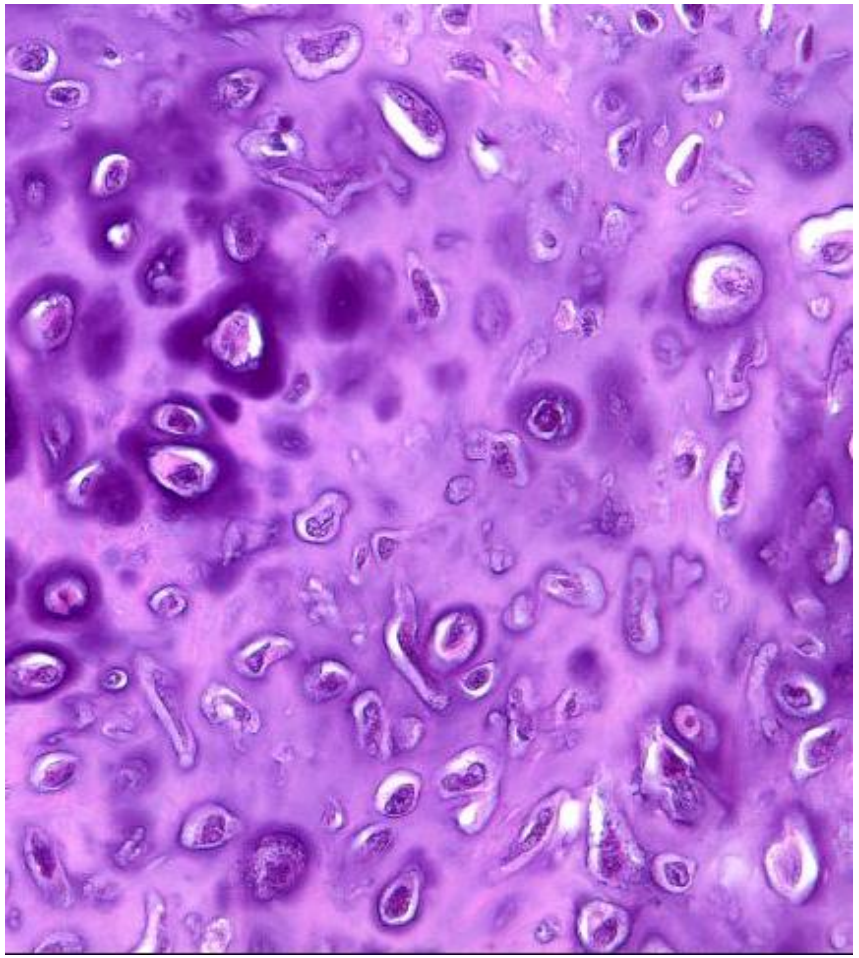

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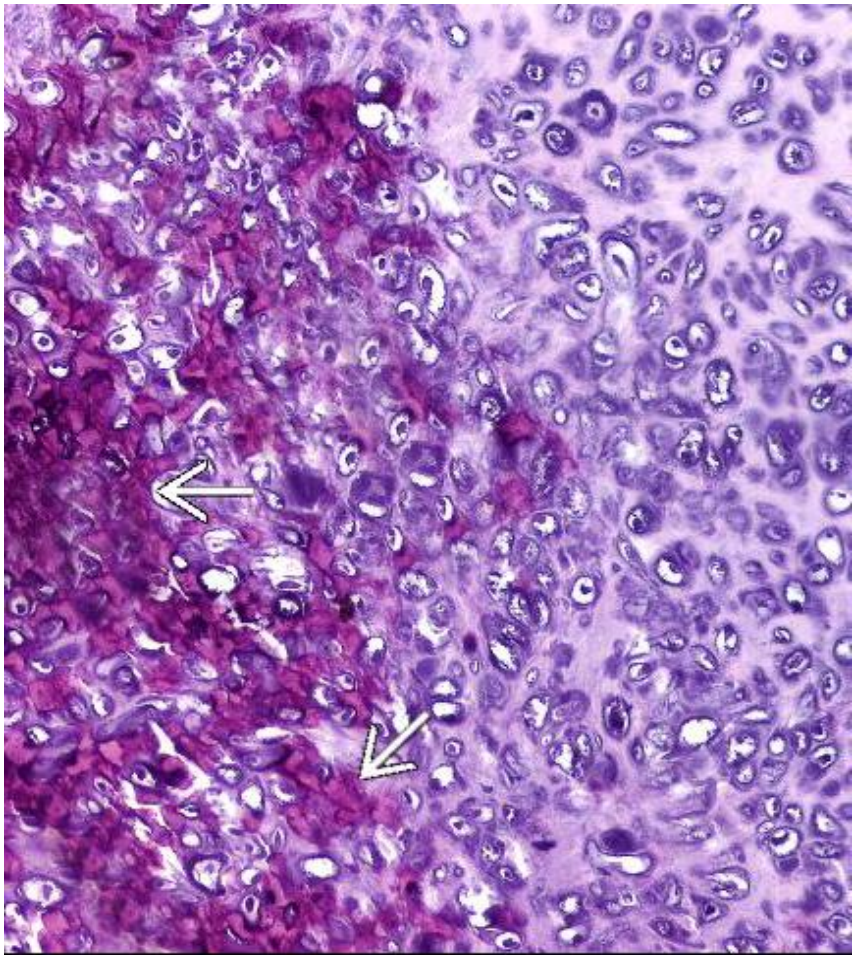

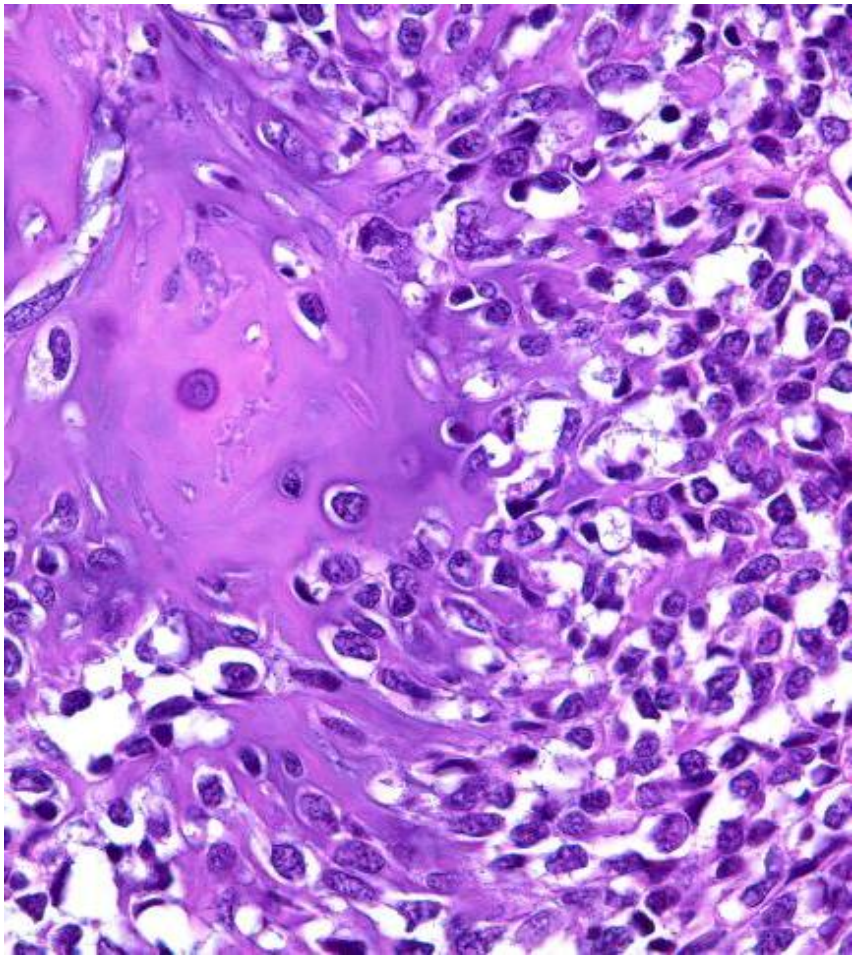

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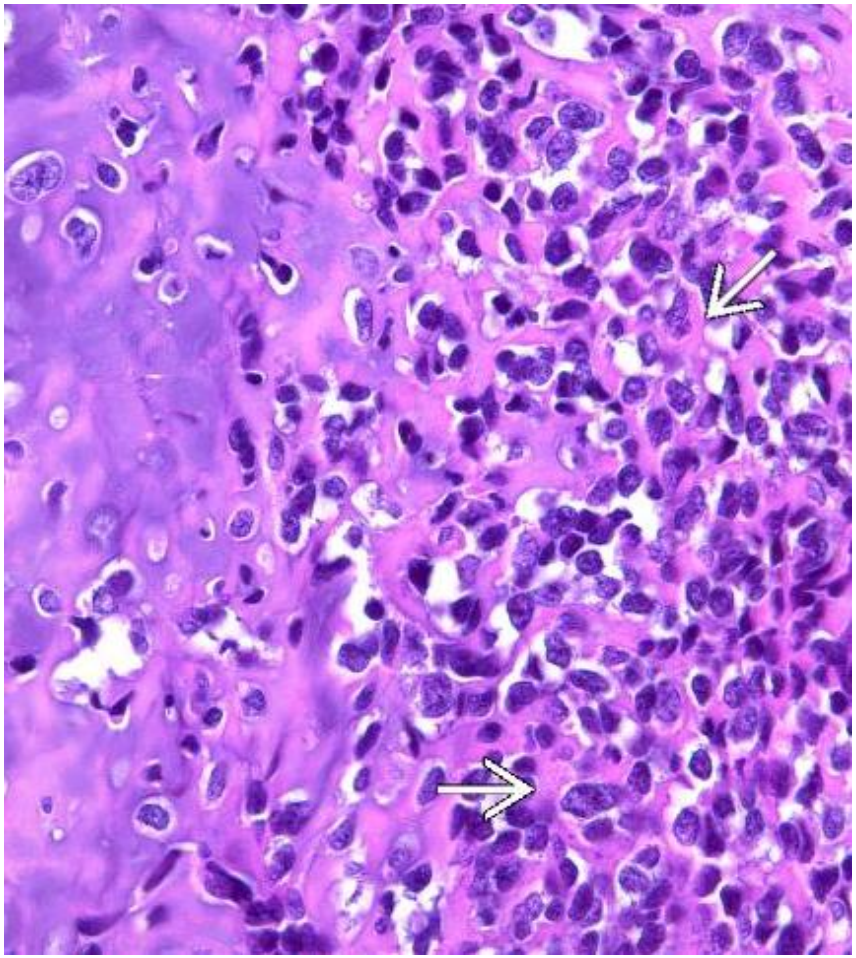

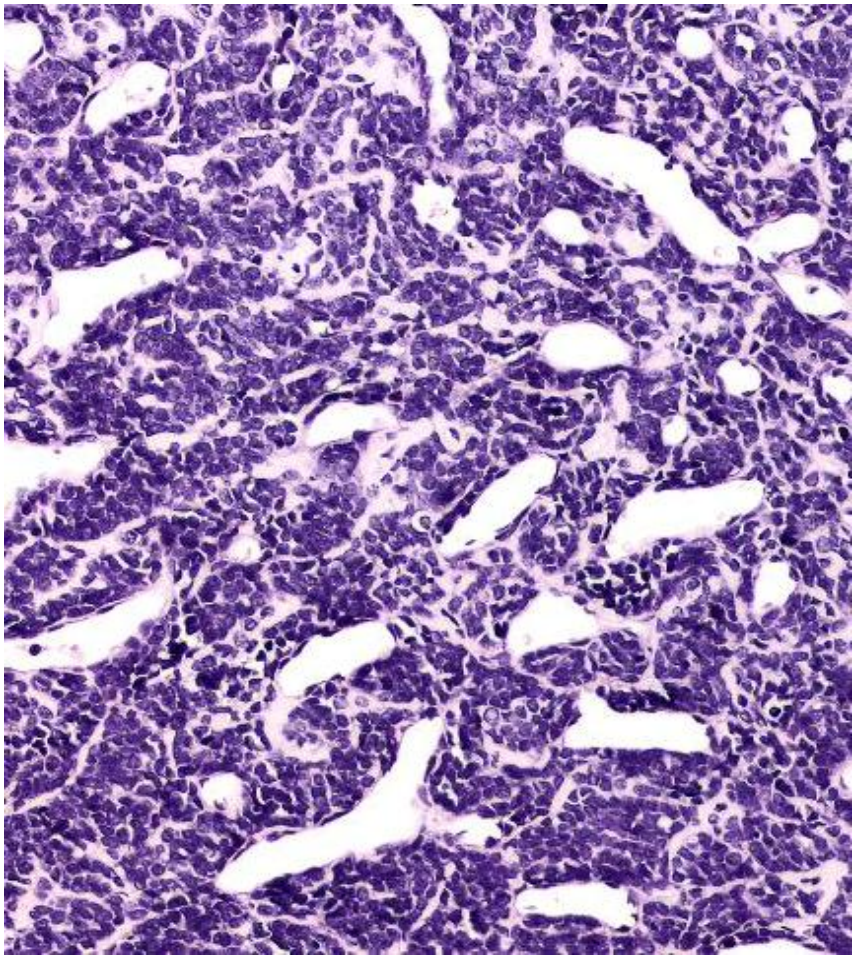

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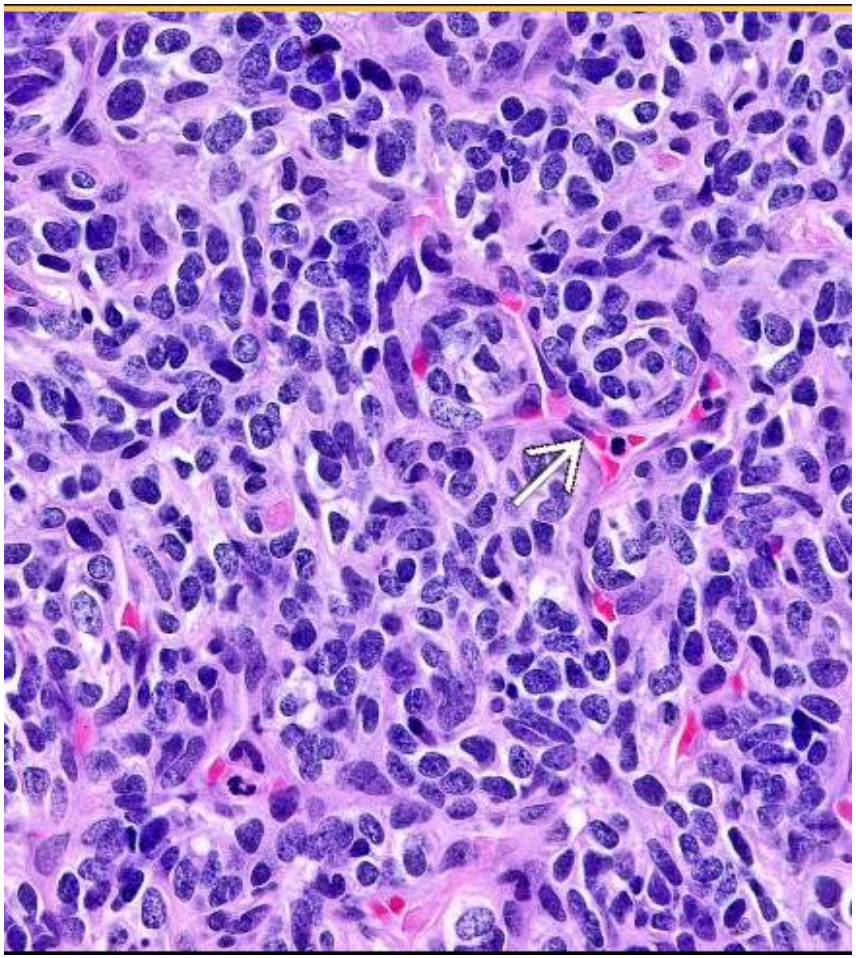

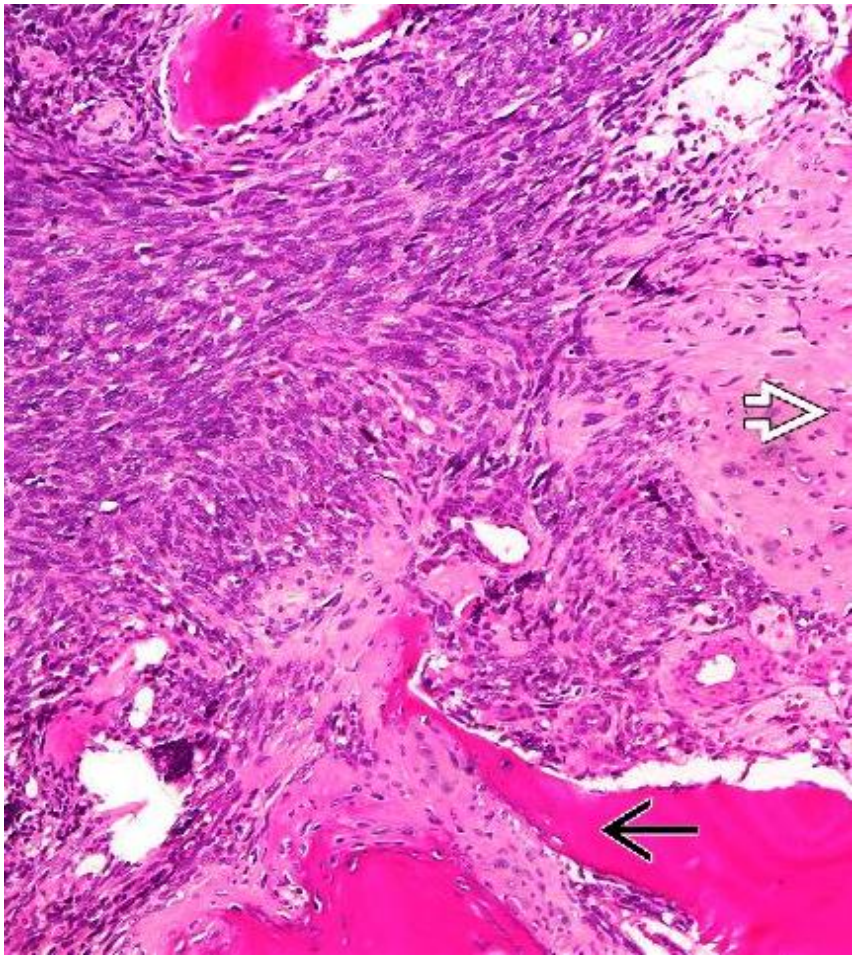

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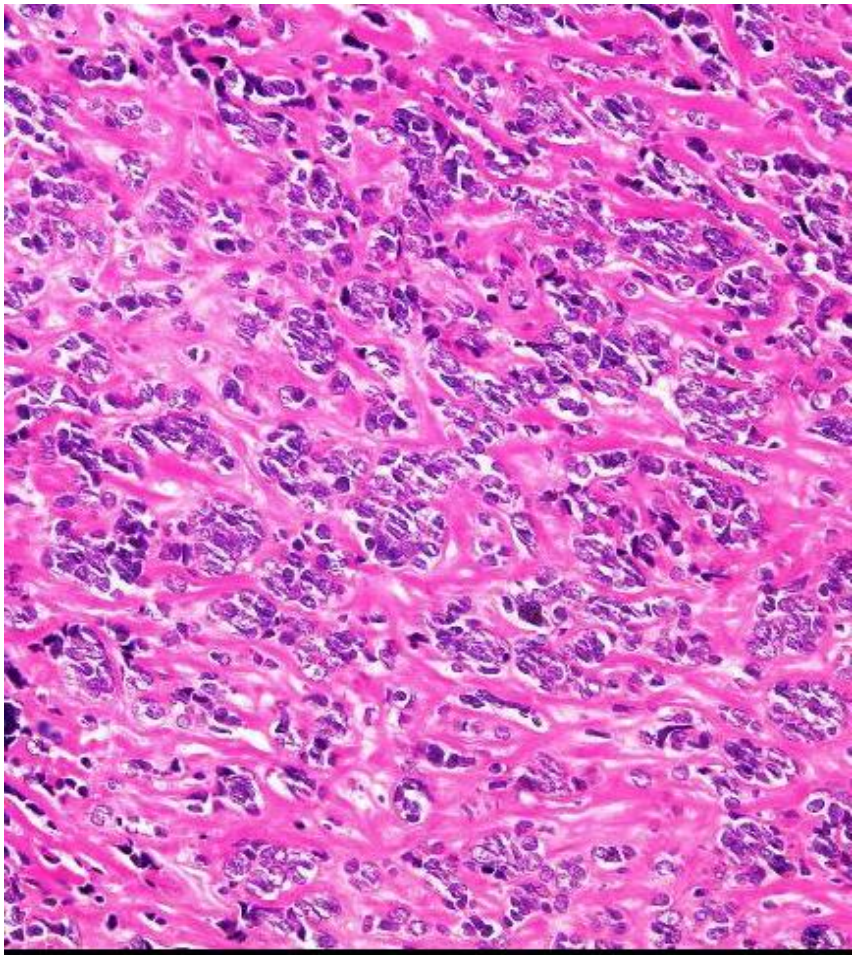

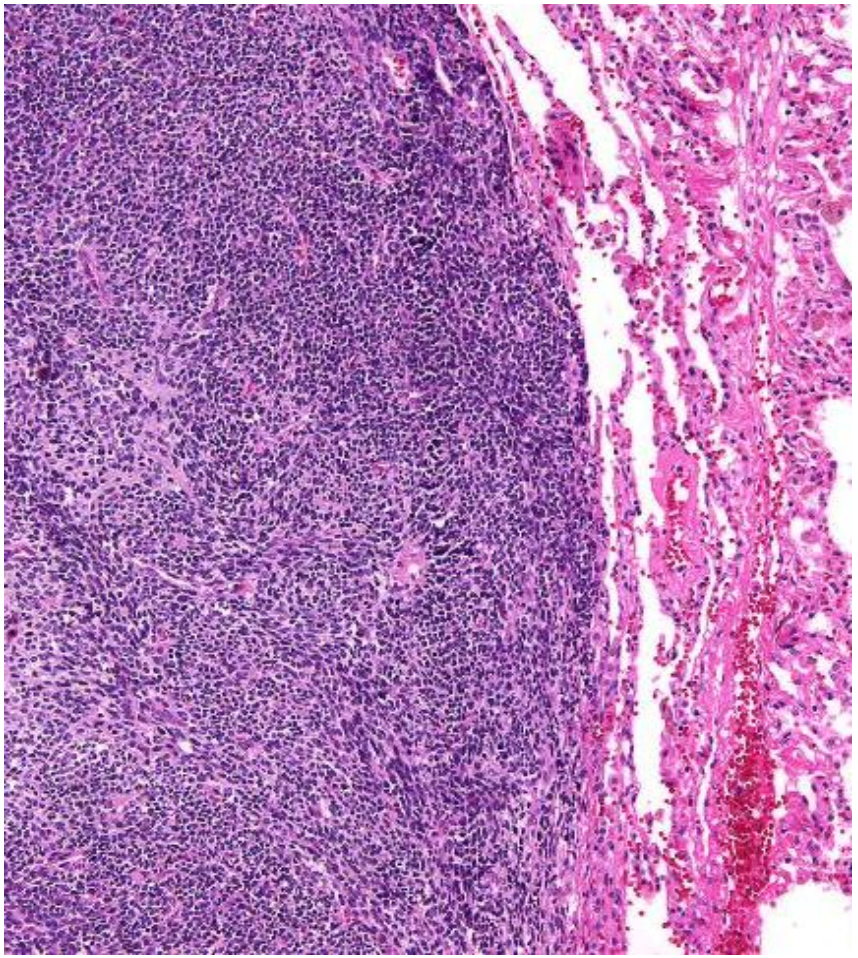

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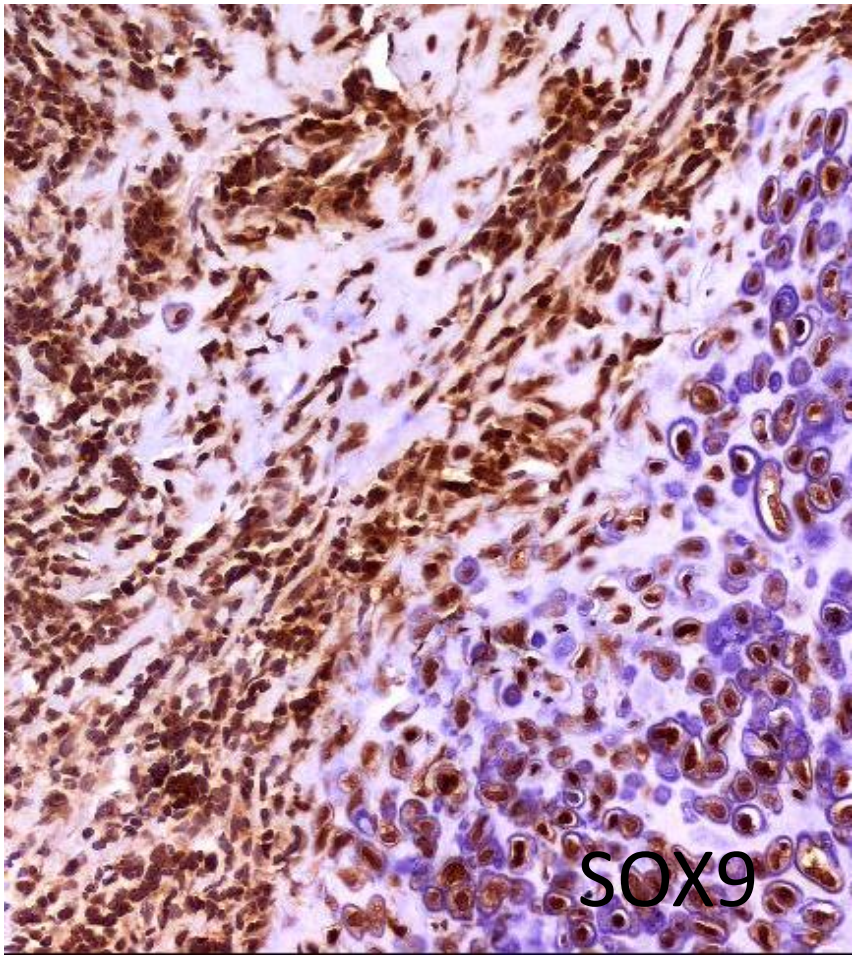
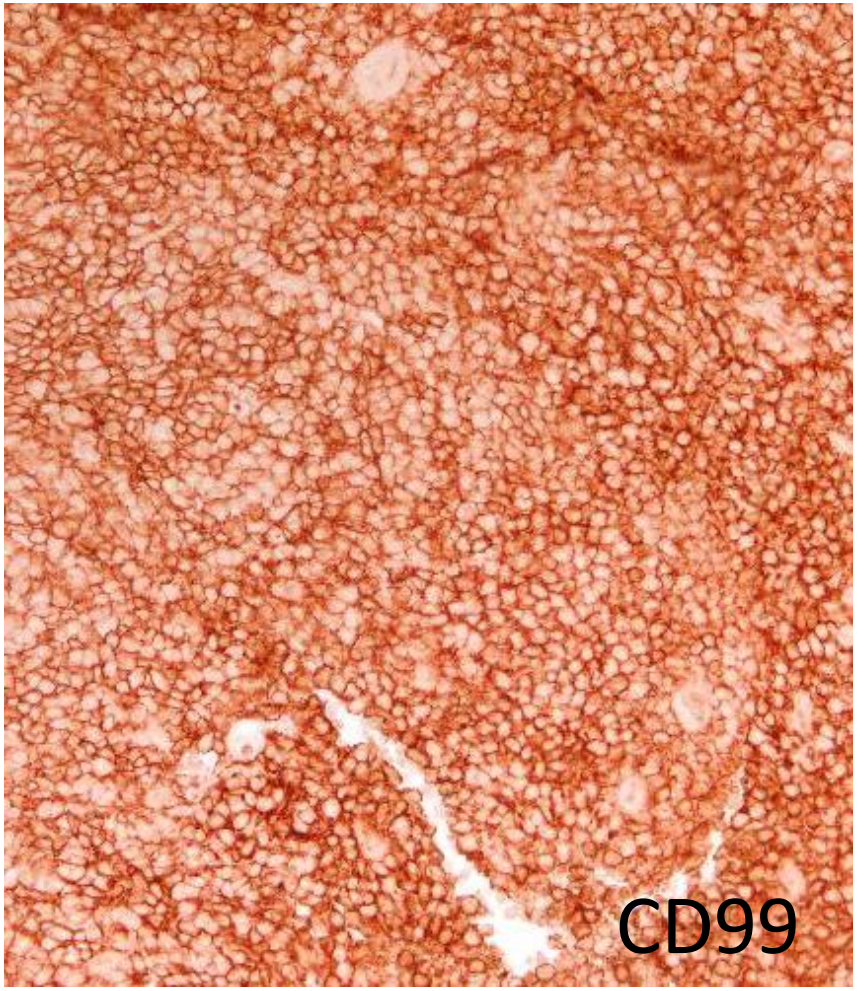




Ancillary testing

- Cartilage expresses S100
- Small round blue cells express CD99 and SOX9
  - SOX9 is also expressed in Ewing sarcoma and osteosarcoma
  - Desmin and EMA has been reported
- Recently a recurrent translocation has been described
  - HEY1-NCOA2

Differential diagnosis

- Ewing sarcoma
  - Does not contain neoplastic cartilage
  - Fli1 positive; mesenchymal chondrosarcoma negative
- Small cell osteosarcoma
- Malignant lymphoma
- Rhabdomyosarcoma
  - Express muscle markers

Fibroosseous tumors

Fibrous dysplasia

- Common monostotic or polyostotic benign fibroosseous neoplasm of bone

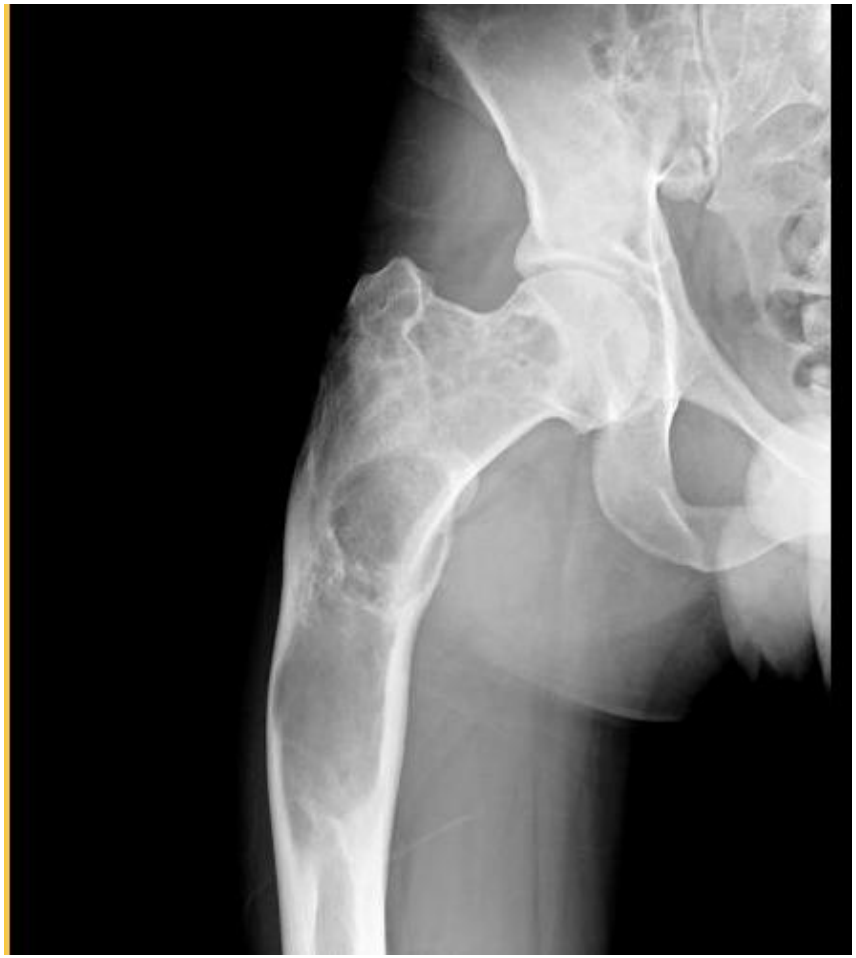
Etiology/Pathogenesis

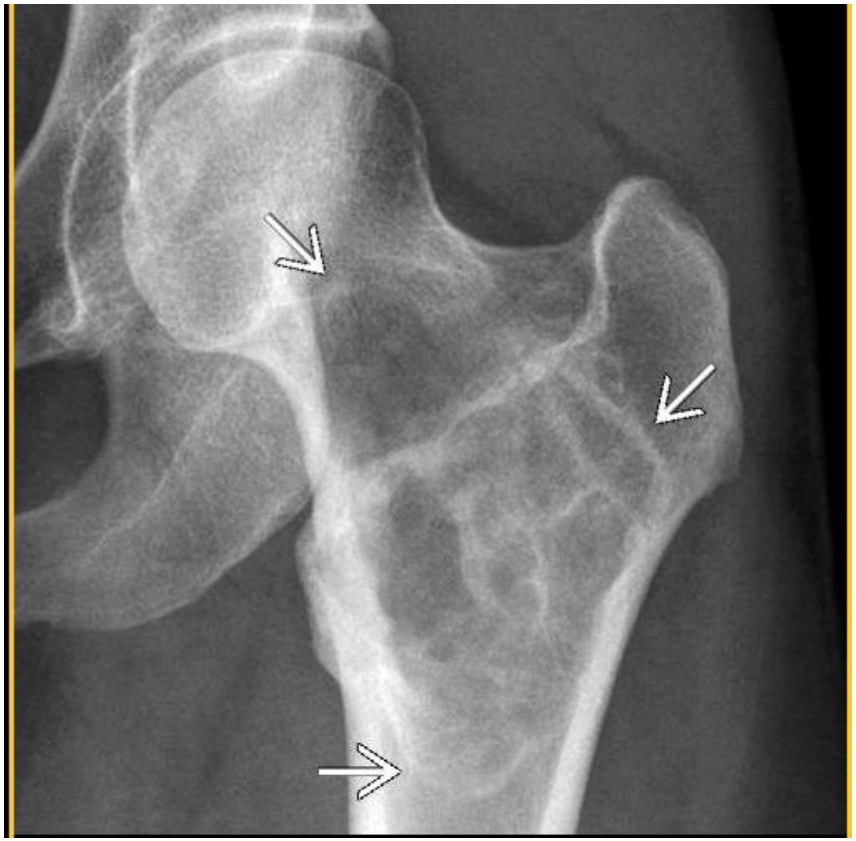
- Mutation in cell surface G-protein receptor results in constitutive activation and production of cyclic AMP and hyperactivity of affected cells

Clinical issues

- Accounts for 7% of benign bone tumors
- Monostotic form 8-10x more common than polyostotic
- Bone lesions are often asymptomatic and discovered as incidental finding
- Bone pain most common symptom
- Polystotic disease is associated with McCune-Albright and Mazabraud syndrome

Image findings





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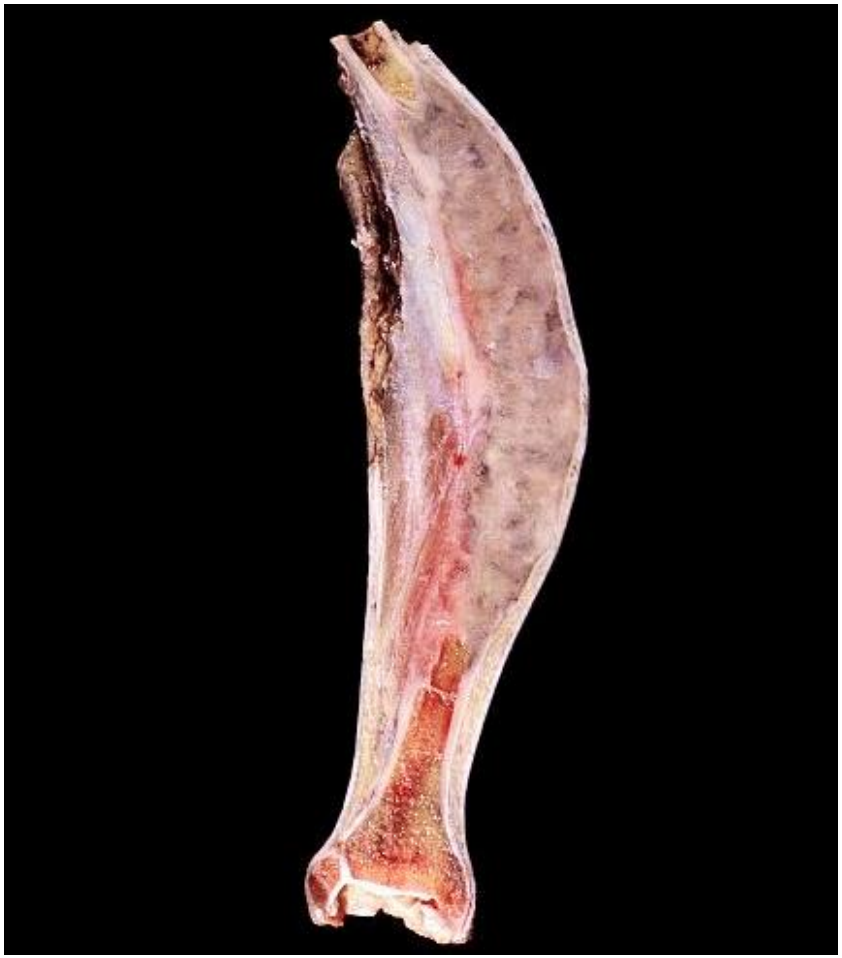

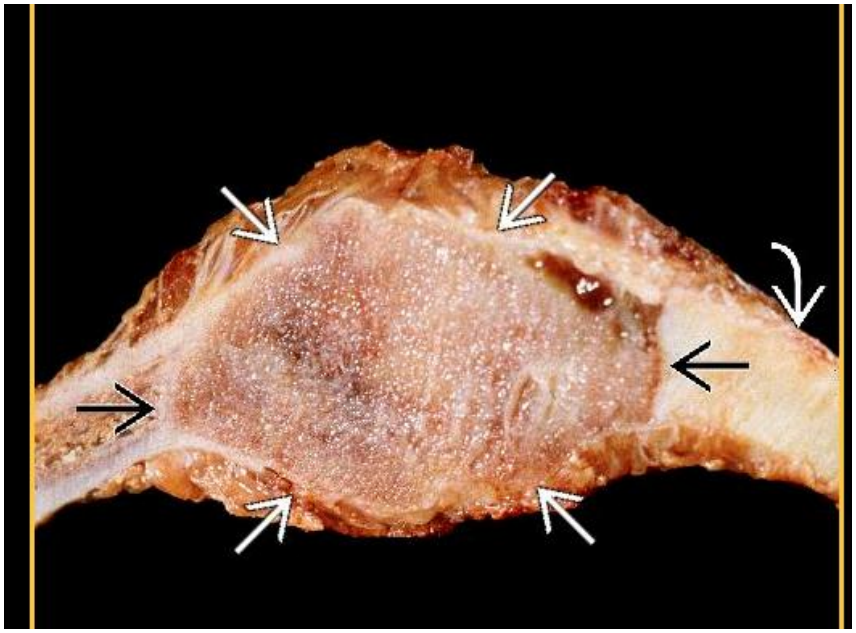

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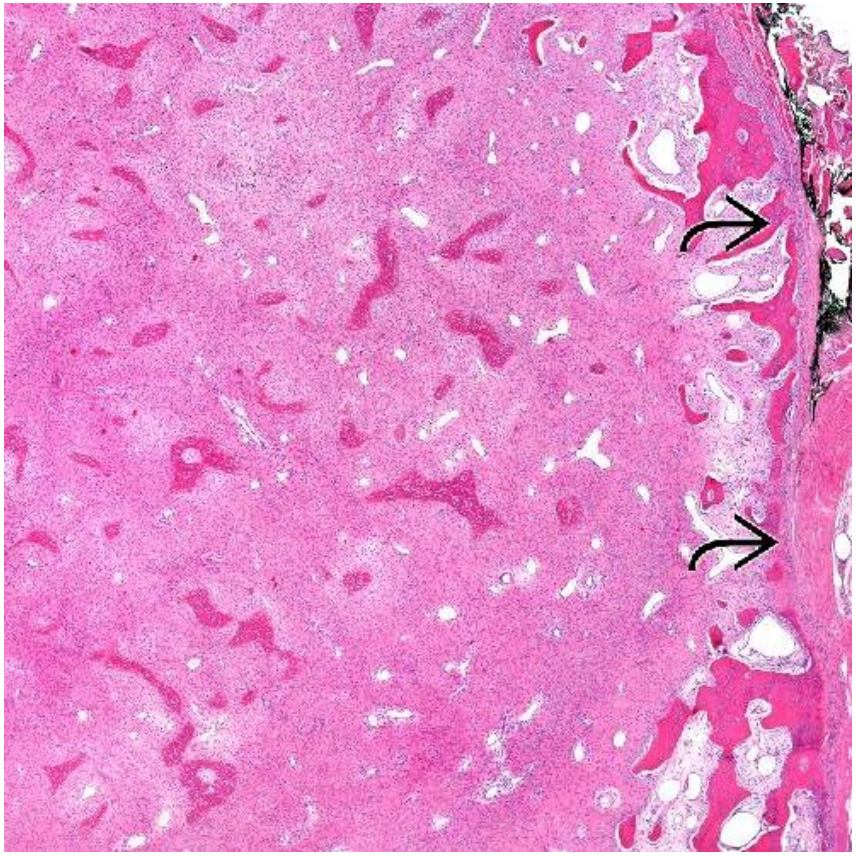

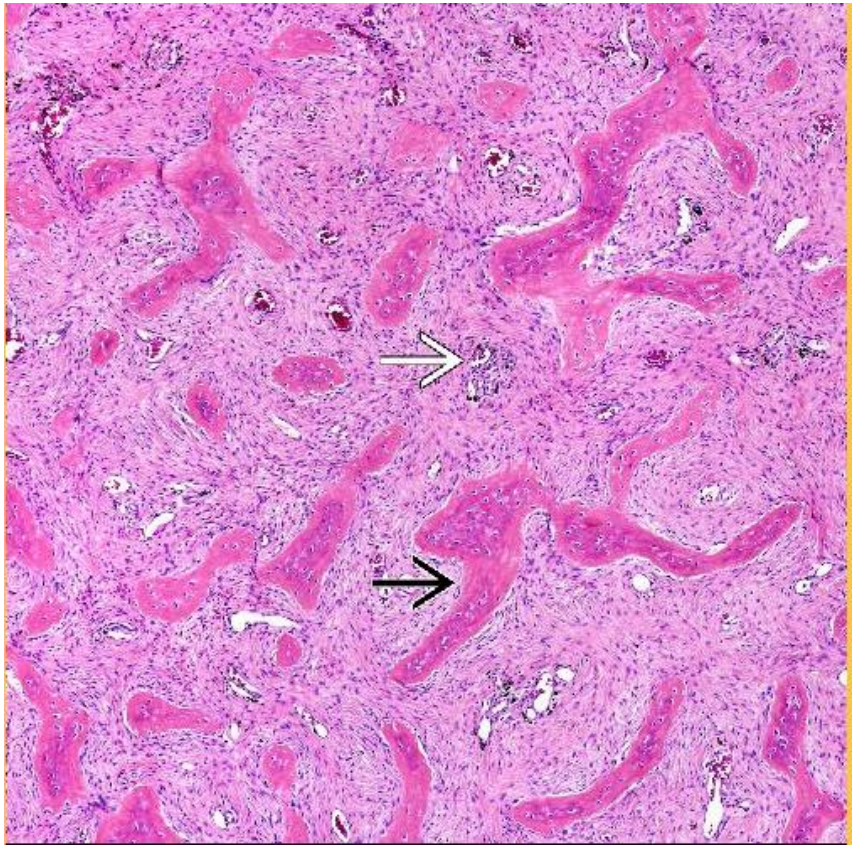

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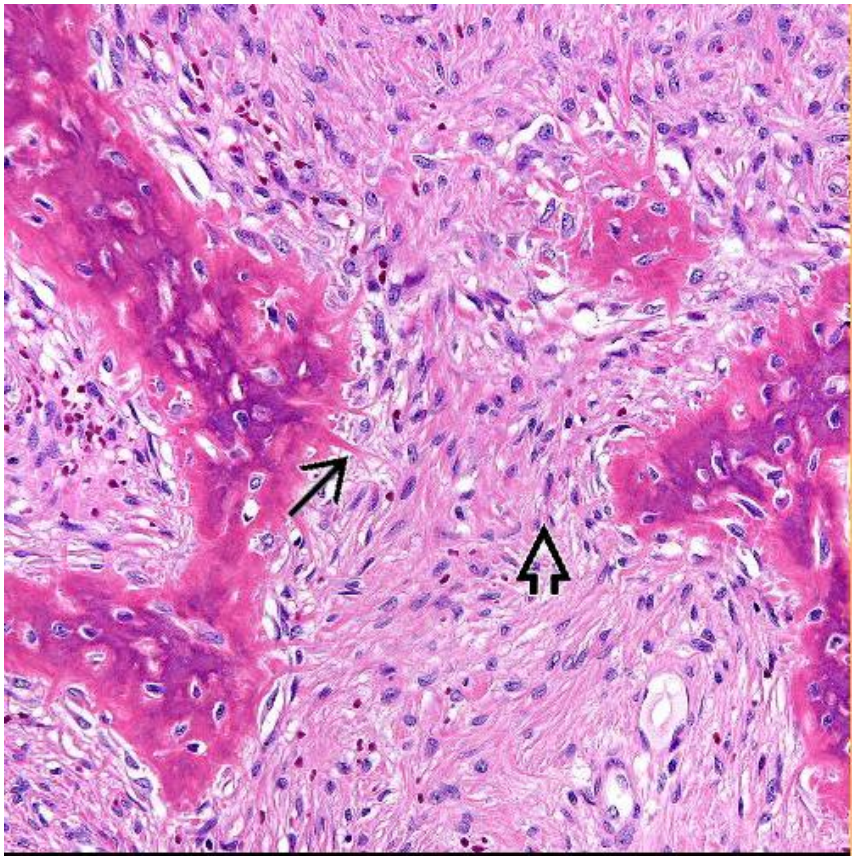
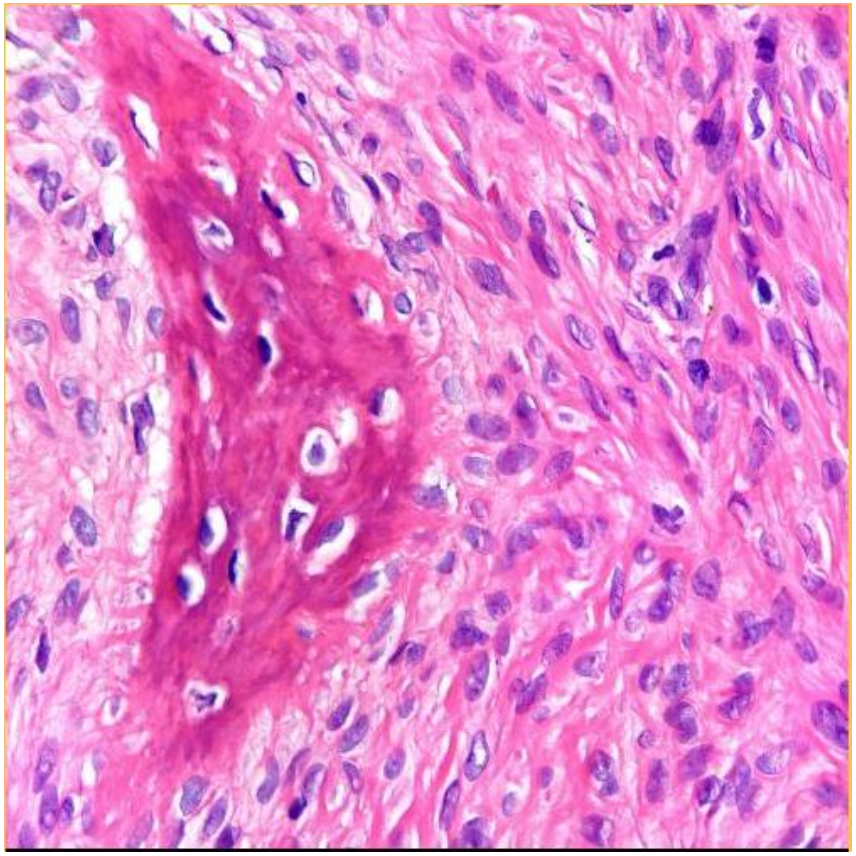




Tips

- Benign well circumscribed fibroosseous tumor
- Neoplastic bone is woven and lacks conspicuous osteoblastic rimming
- moderately cellular tumor composed of spindle cells arranged in storiform pattern

Cystic lesions of bone

Aneurysmal bone cyst

- Destructive, expansile benign neoplasm of bobe characterized by multiloculated blood-filled cystic spaces
- Classified into primary and secondary variants

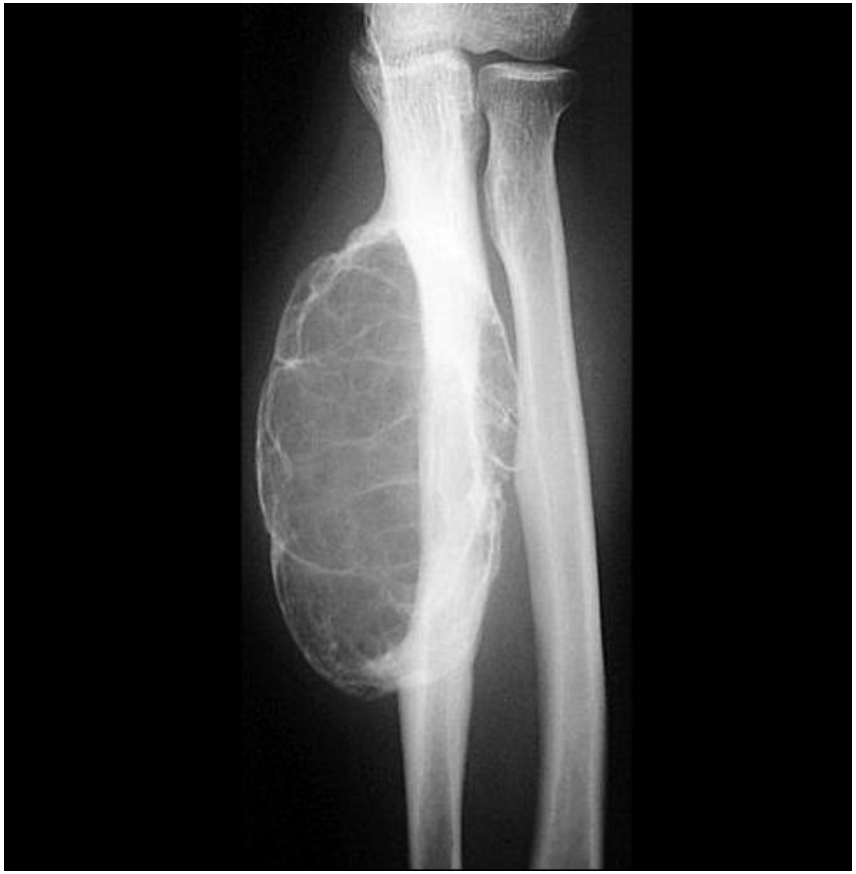
Etiology/Pathogenesis

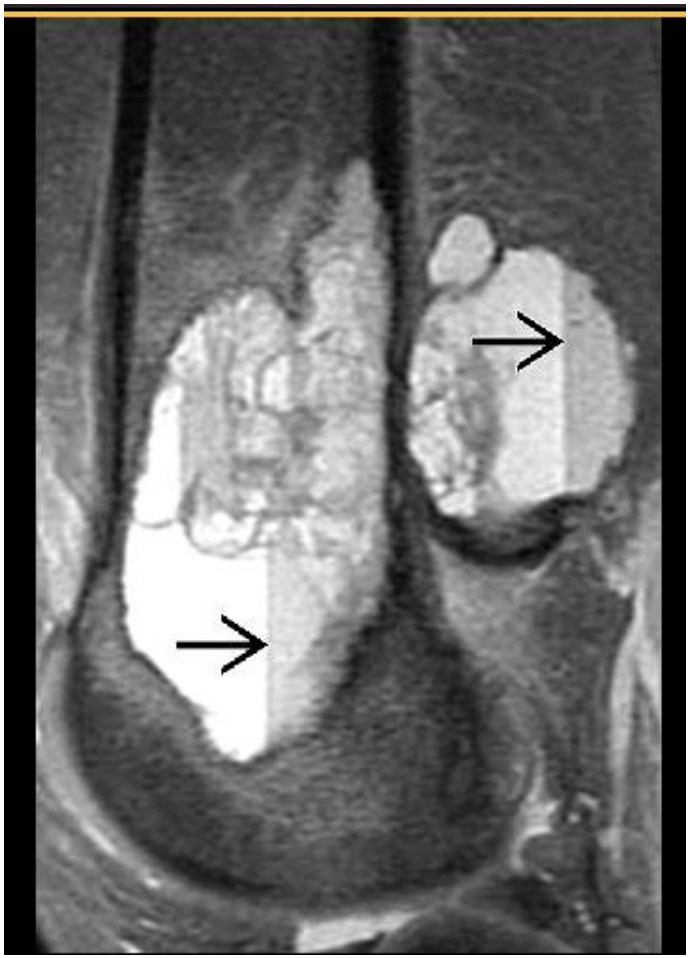
- Recent cytogenetic and molecular studies demonstrating t(16;17) strongly suggest that primary ABC is neoplastic
- This translocation results in CDH11-USP6 gene fusion transcript

Clinical issues

- 80% develop in 1st and 2nd decade of life
- Common sites of involvement; metaphysis of long bones of upper and lower extremities, posterior elements of vertebra, small bones of hands and feet
- Present with pain and swelling
- Treated with curettage or en bloc resection
- low recurrence rate

Image findings





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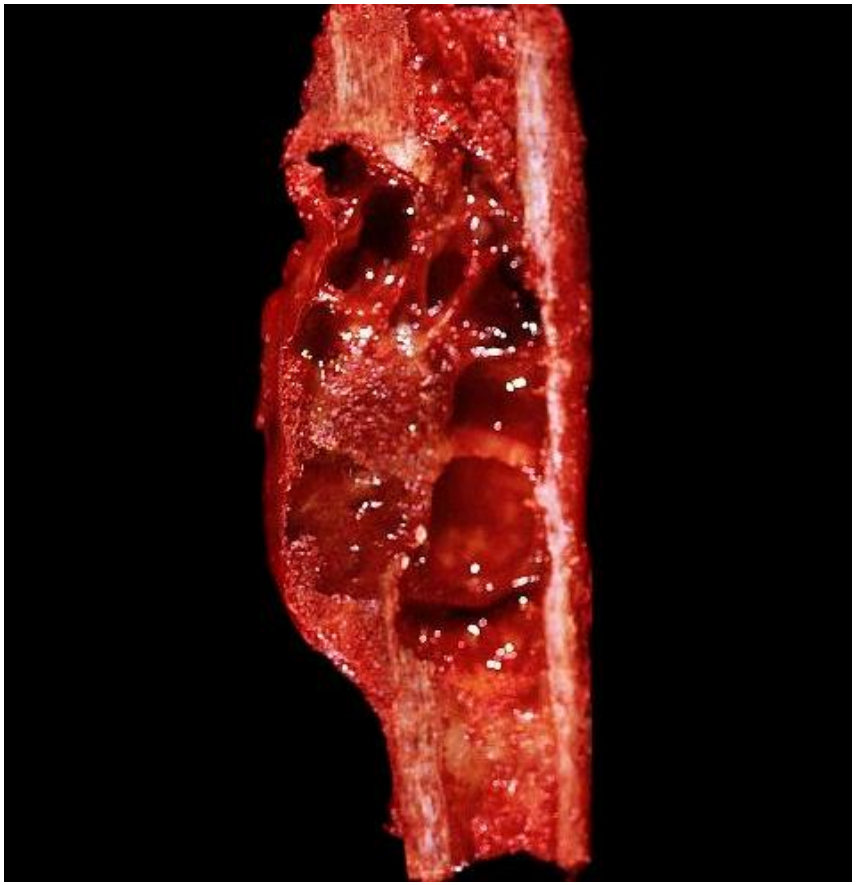
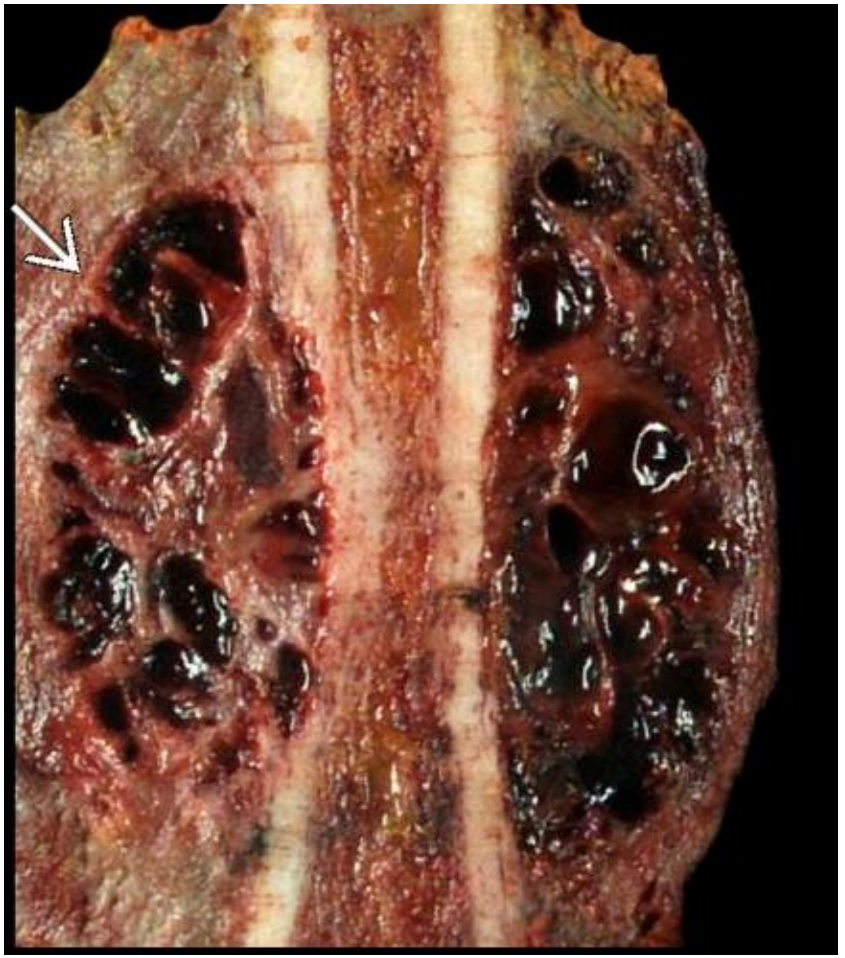
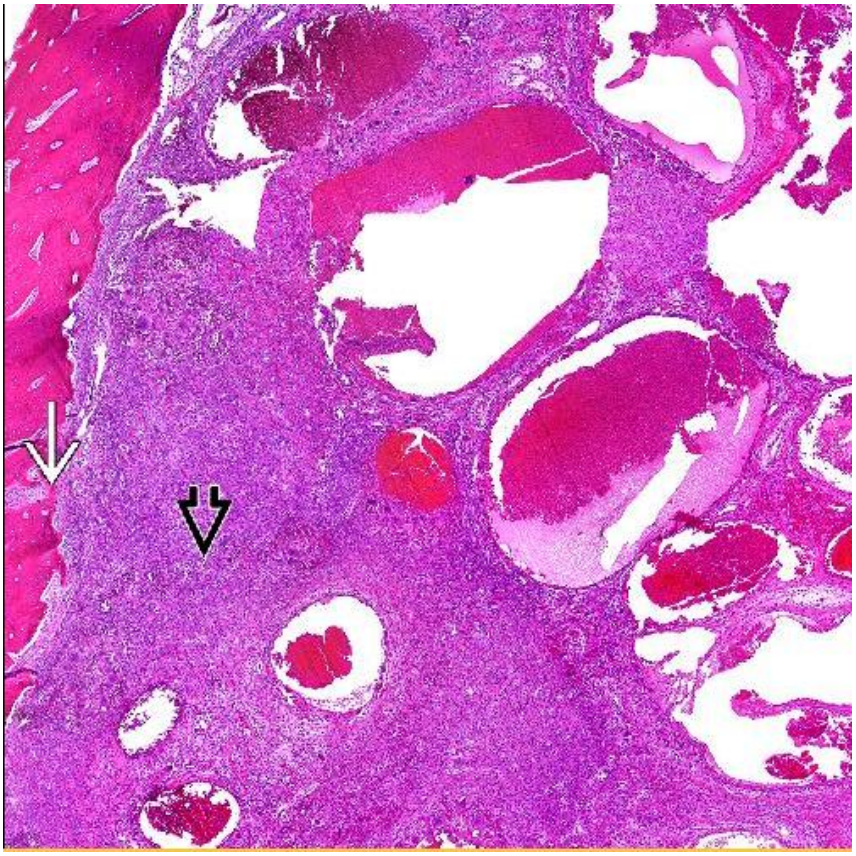
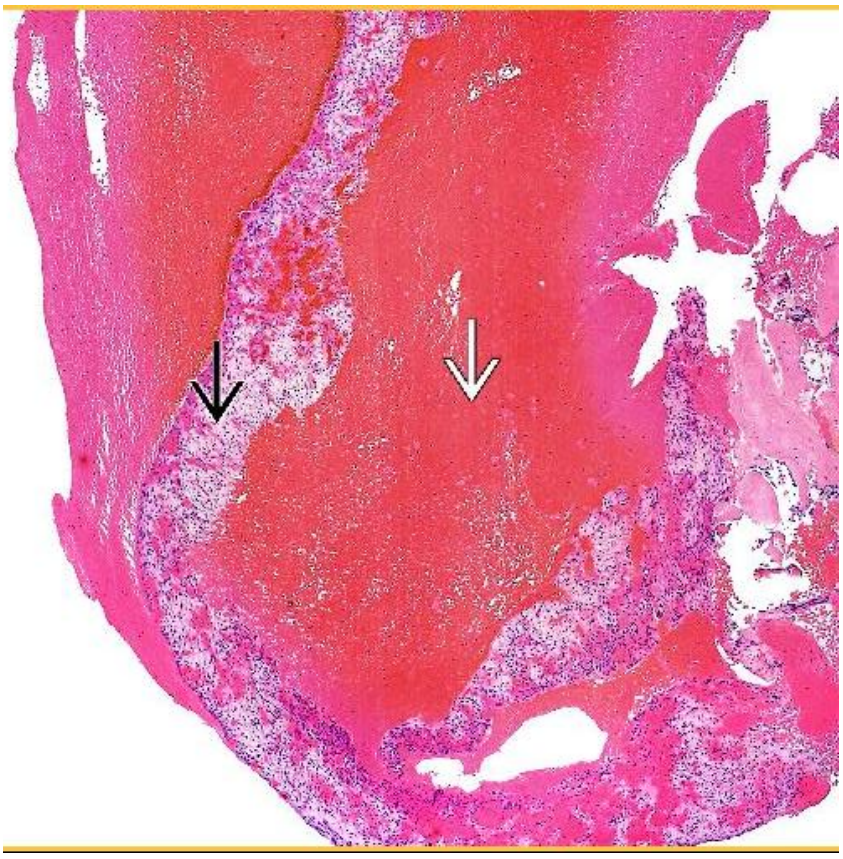
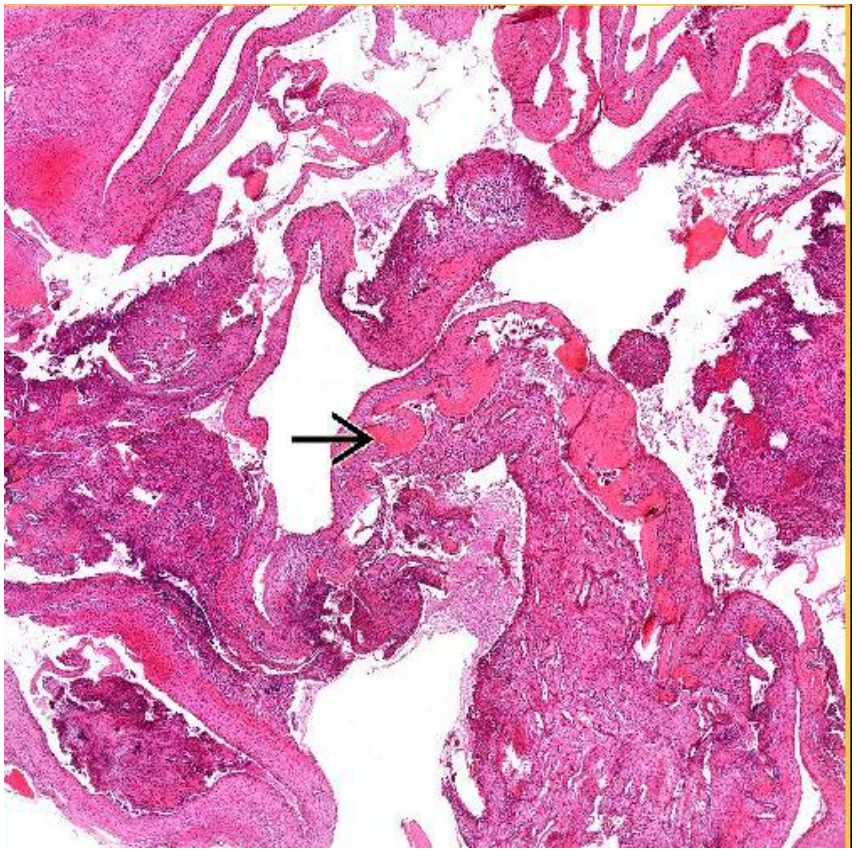
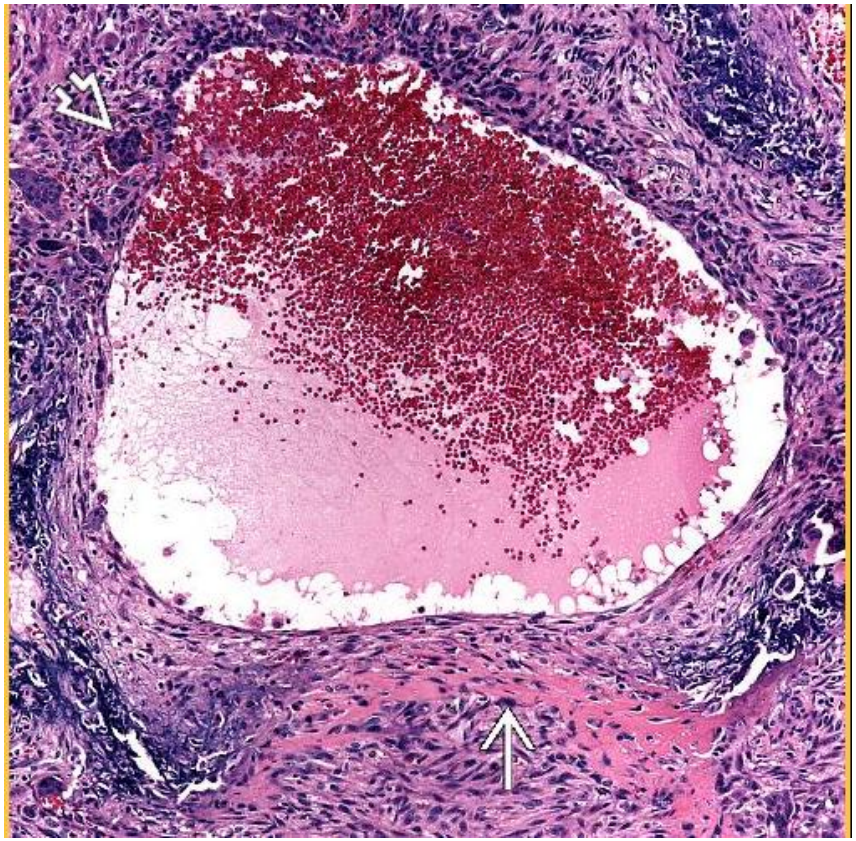


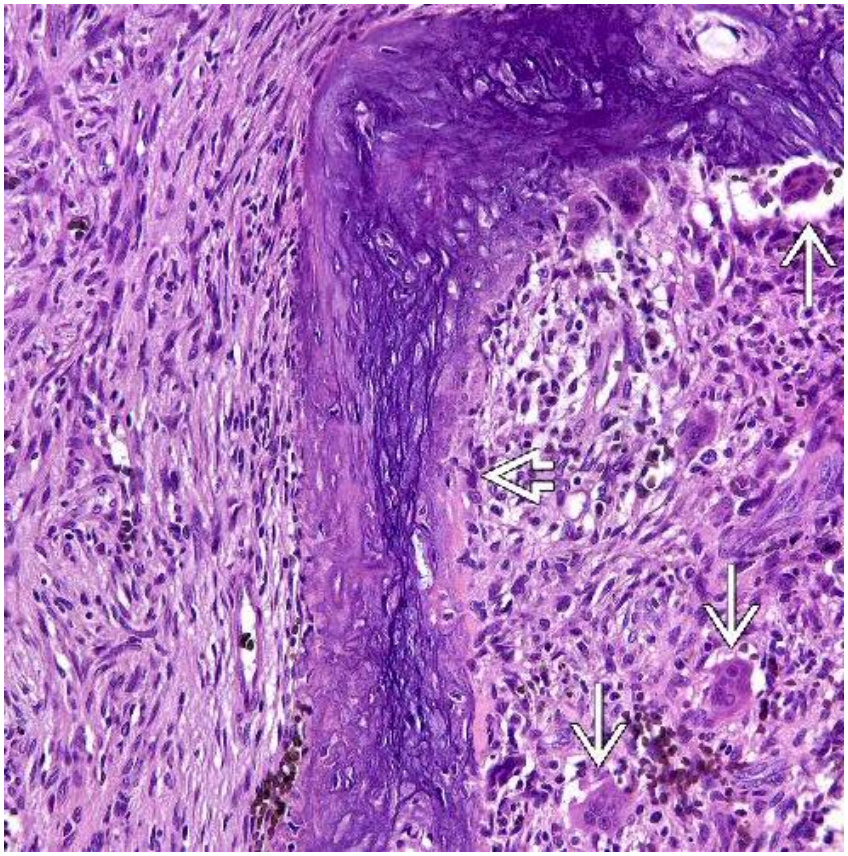


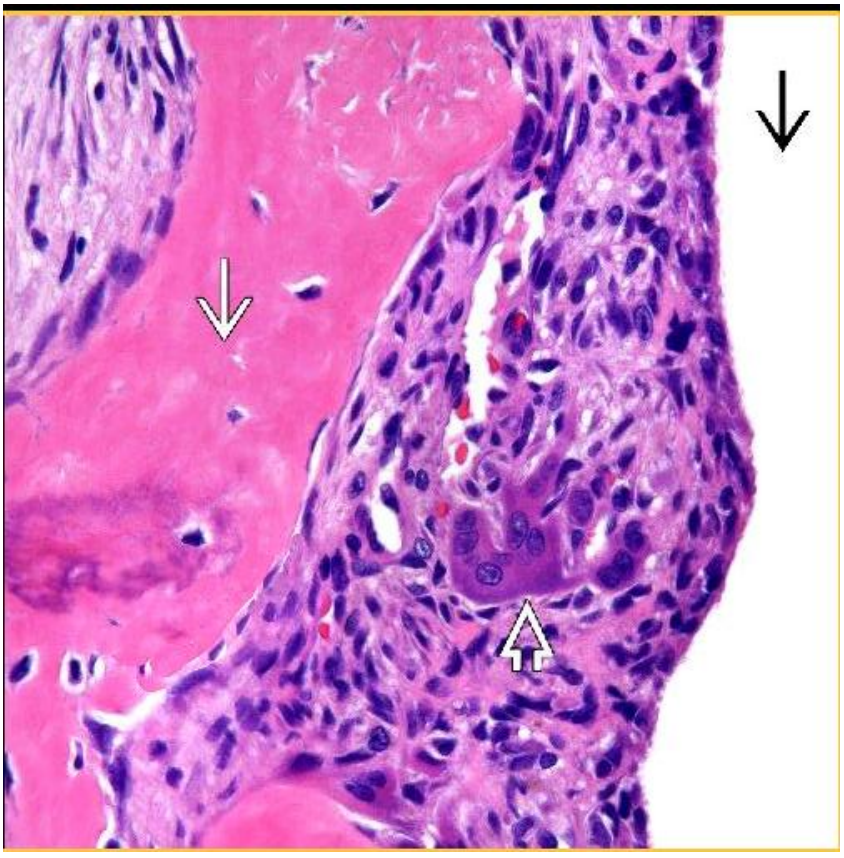












Giant cell rich tumors

Giant cell tumor of bone

- Neoplasm composed of cytologically benign, oval pr polyhedral mononuclear cells that are admixed with numerous, evenly distributed, osteoclast-like giant cells

Clinical issues

- Represents approximately 5% of primary bone tumors
- Vast majority arise in epiphyseal-metaphyseal region of long tubular bones; in skeletally mature individuals
- Pain and swelling
- Usually treated by curettage
- Local recurrence rate approximately 25% for patients treated with curettage
- 1-2% of GCTs eventually metastasize, primarily to lungs

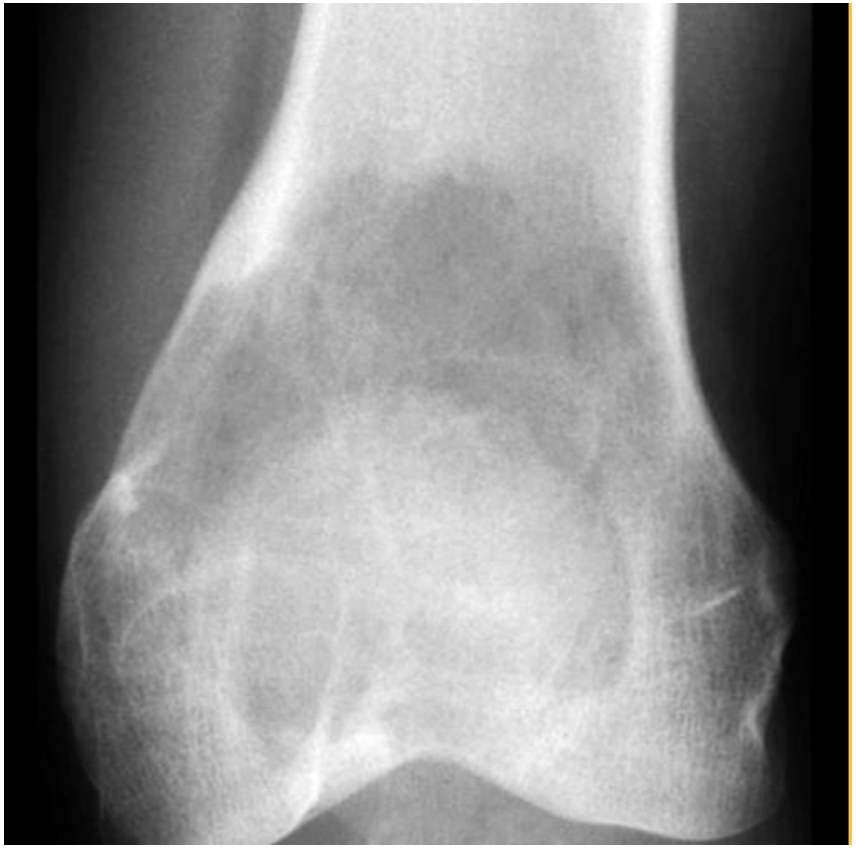
Etiology pathogenesis

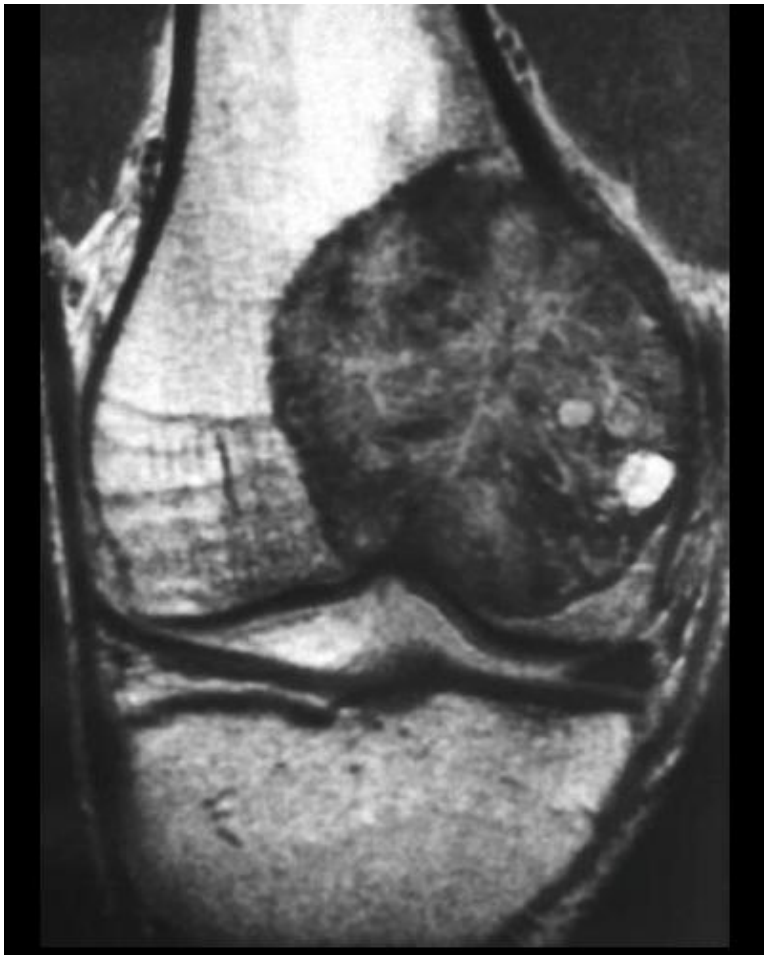
- Mononuclear cells are neoplastic of possible osteoblast phenotype that induce formation of osteoclast-type giant cells by expressing receptor activator of NF-kB (RANK) ligand
- Osteoclast-type giant cells express receptor RANK, which binds to RANK ligand on surfaces of mononuclear cells

Drugs

- Preliminary studies with RANK ligand inhibitors such as denosumab seem to be effective and may possibly supplement radiation treatment and surgery in difficult cases

Image findings





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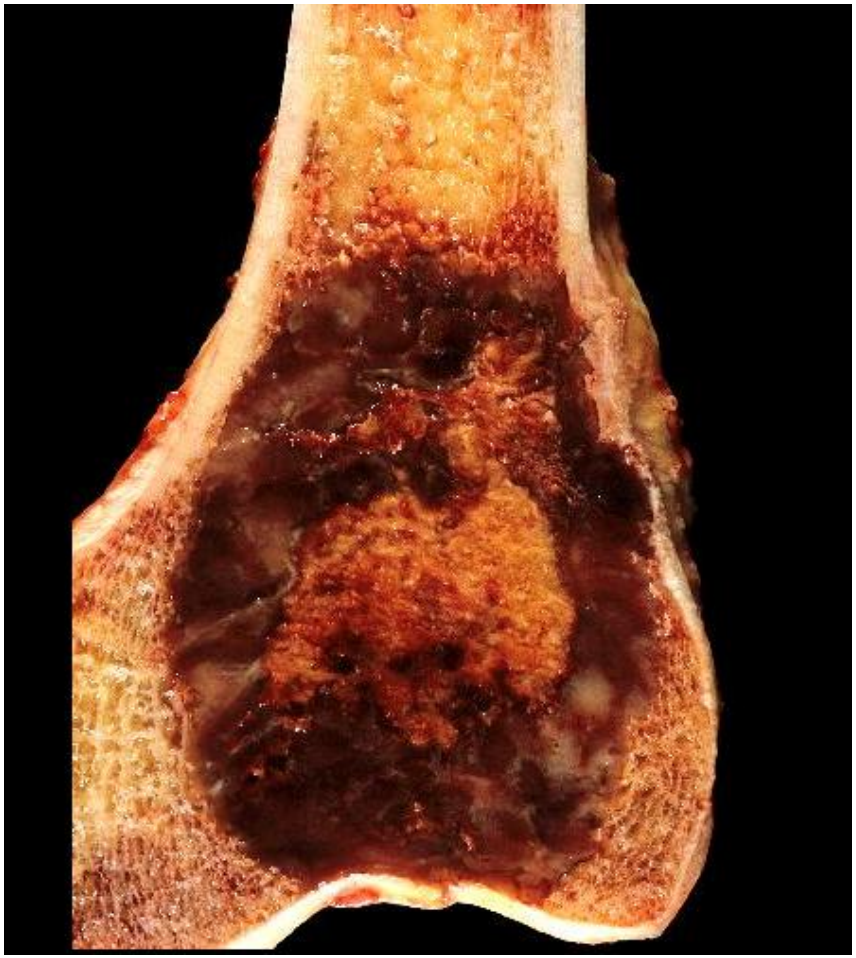

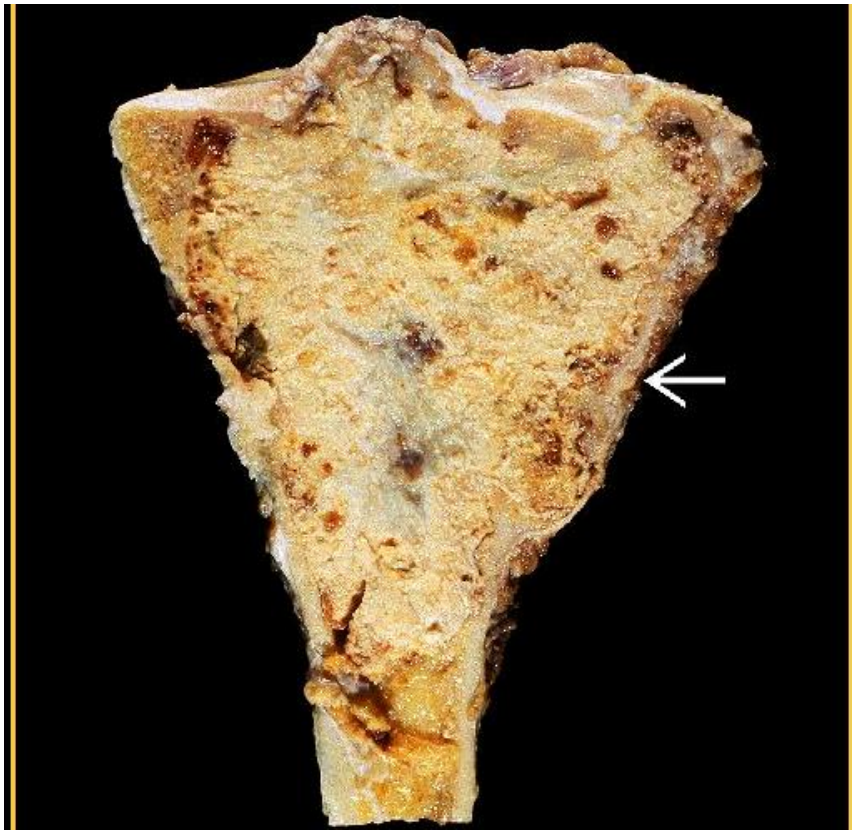

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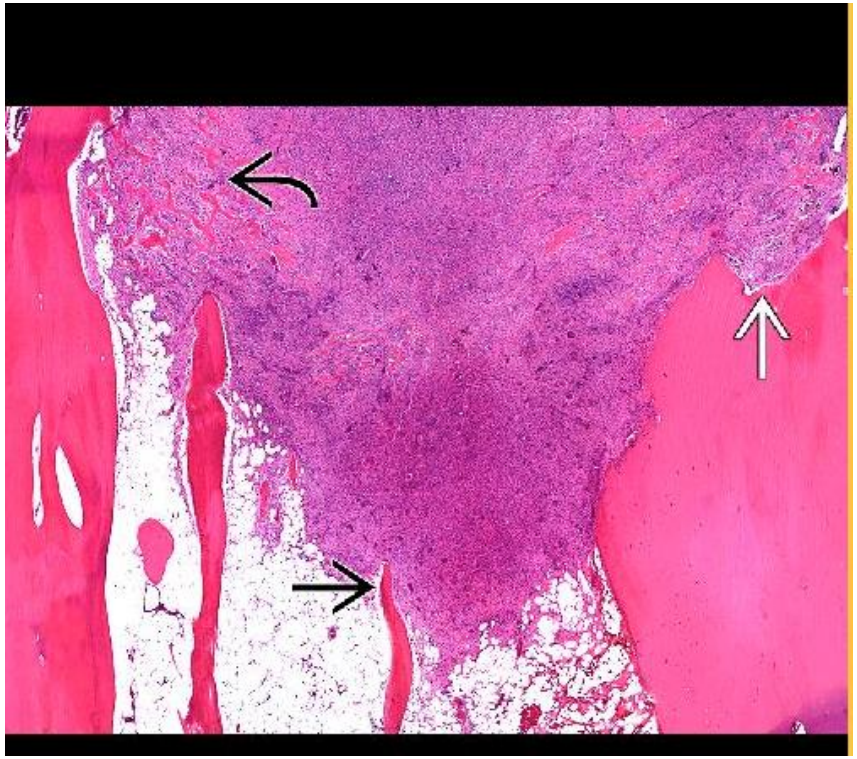
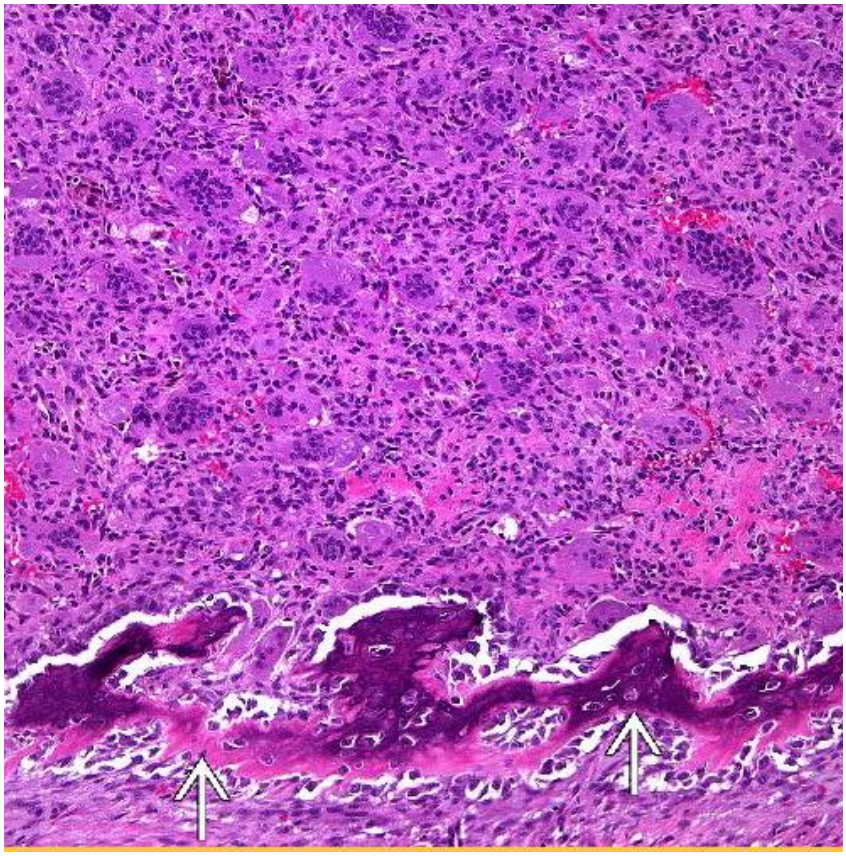
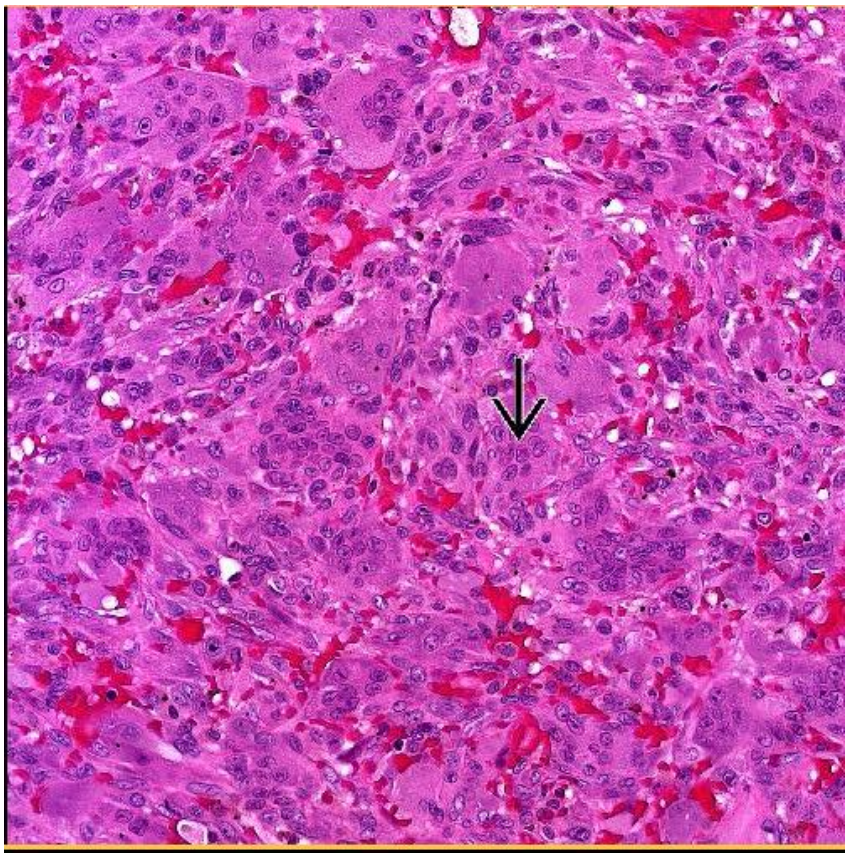
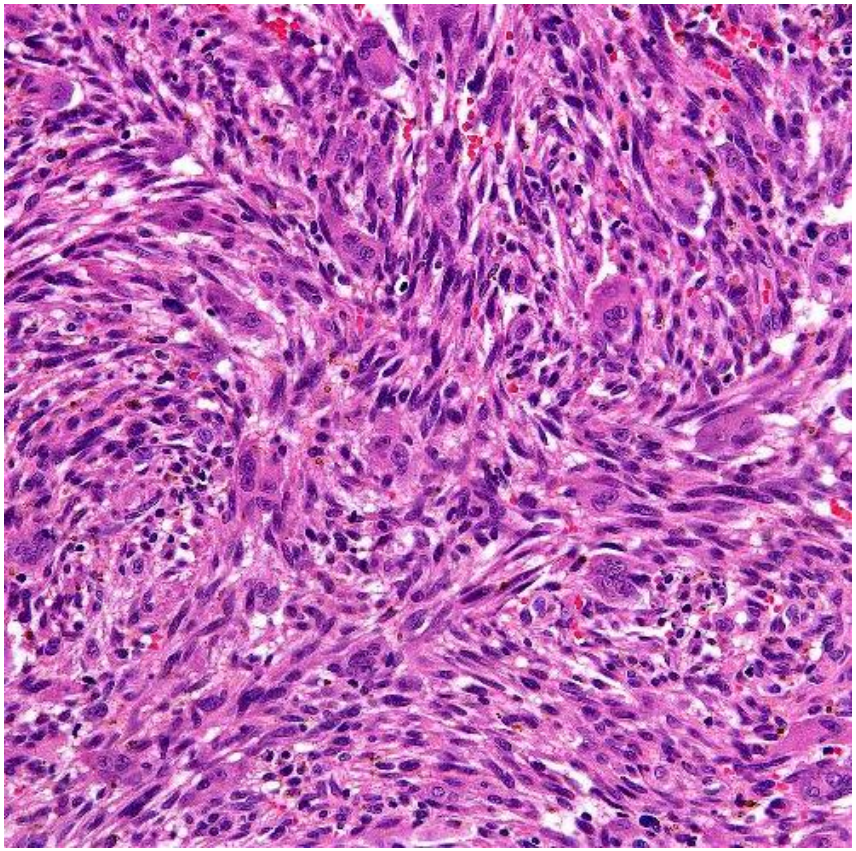
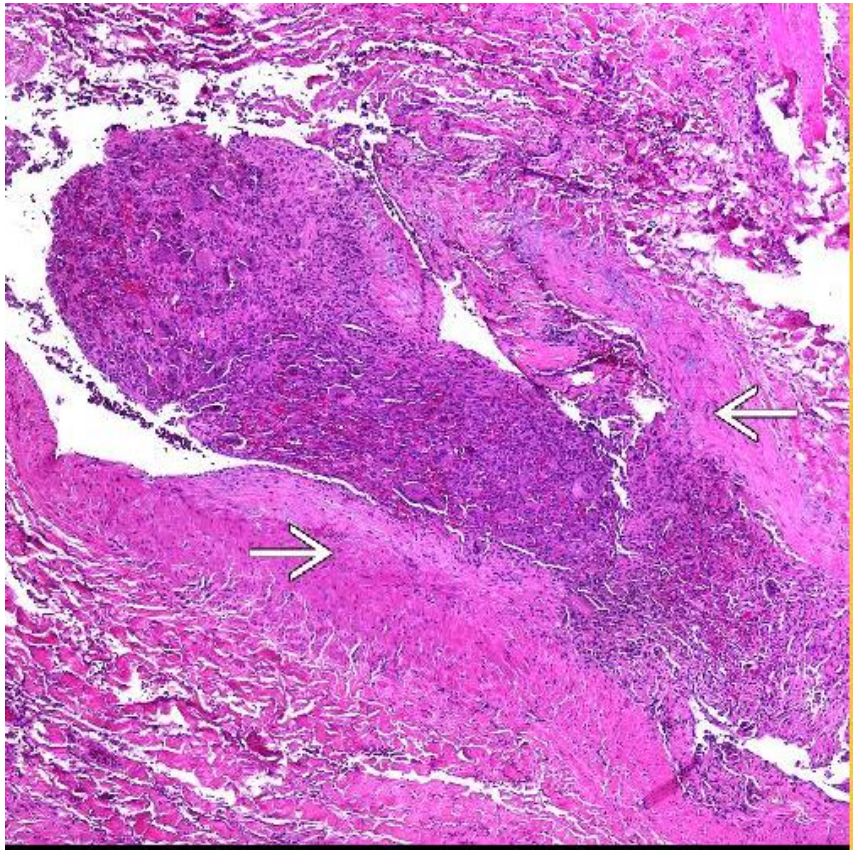










Tips

- Lytic lesion in distal long bone extending to subchondral area in a adult is characteristic
- Proliferation of mononuclear cells and evenly distributed osteoclast-type giant cells
- Nuclei of mononuclear cells identical to those of osteoclast-type giant cells
- If a needle biopsy looks like BFH think possible GCT

Vascular tumors

Epithelioid hemangioendothelioma

- Uncommon epithelioid endothelial neoplasm with metastatic potential that usually arises in soft tissues,liver, lung and bones

Clinical issues

- Rare vascular tumor
- Peak frequency: 2nd- 3rd decades of life
- Multifocal in 1/3 to 1/2 patients
- morphologic f

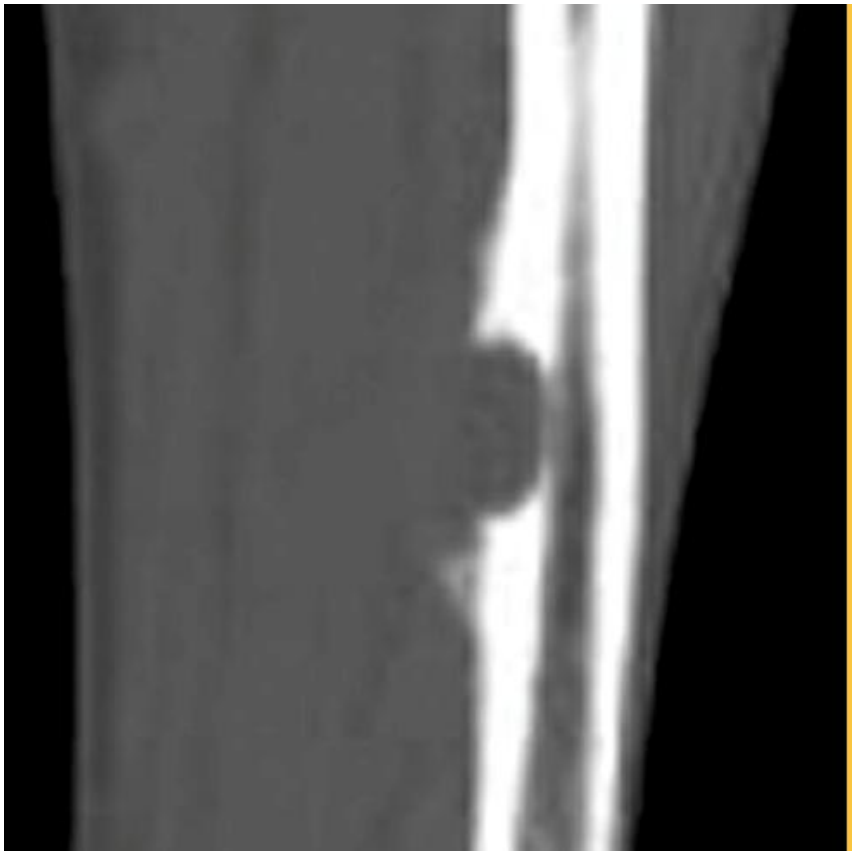
Clinical issues

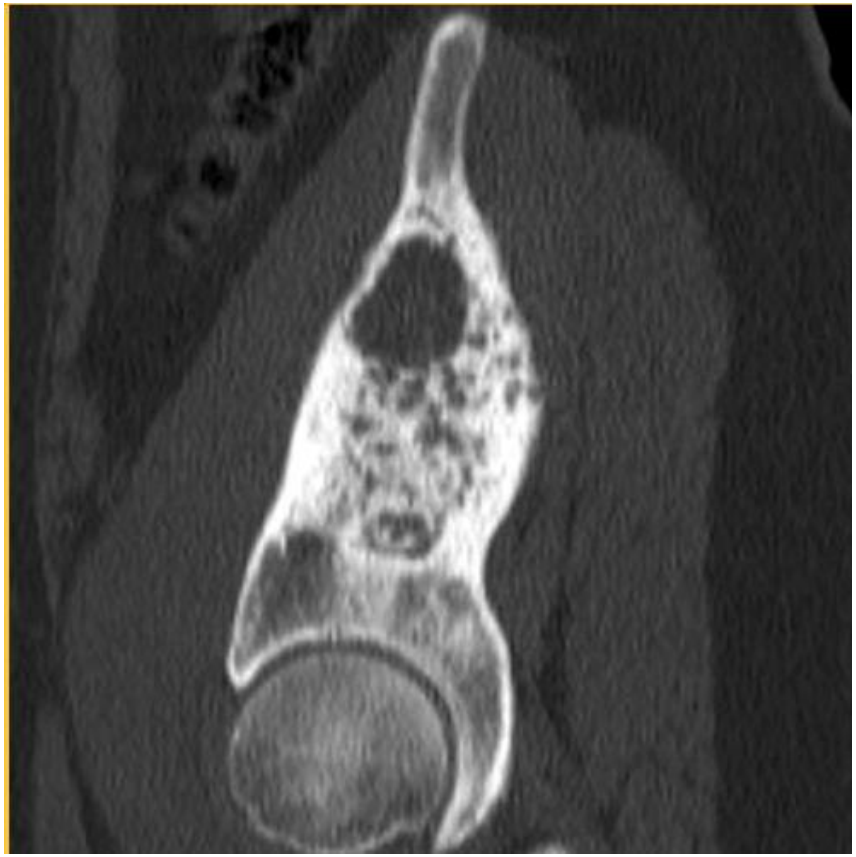
- May involve multiple sites in single bone or multiple bones simultaneously
- localized pain
- swelling
- clinical behavior cannot always be predicted by morphologic features of tumor

Cytogenetics

- EHE has been shown to contain t(1;3)
- Causes fusion of WWTR1-CAMTA1
- Can be detected by RT-PCR or FISH

Image findings





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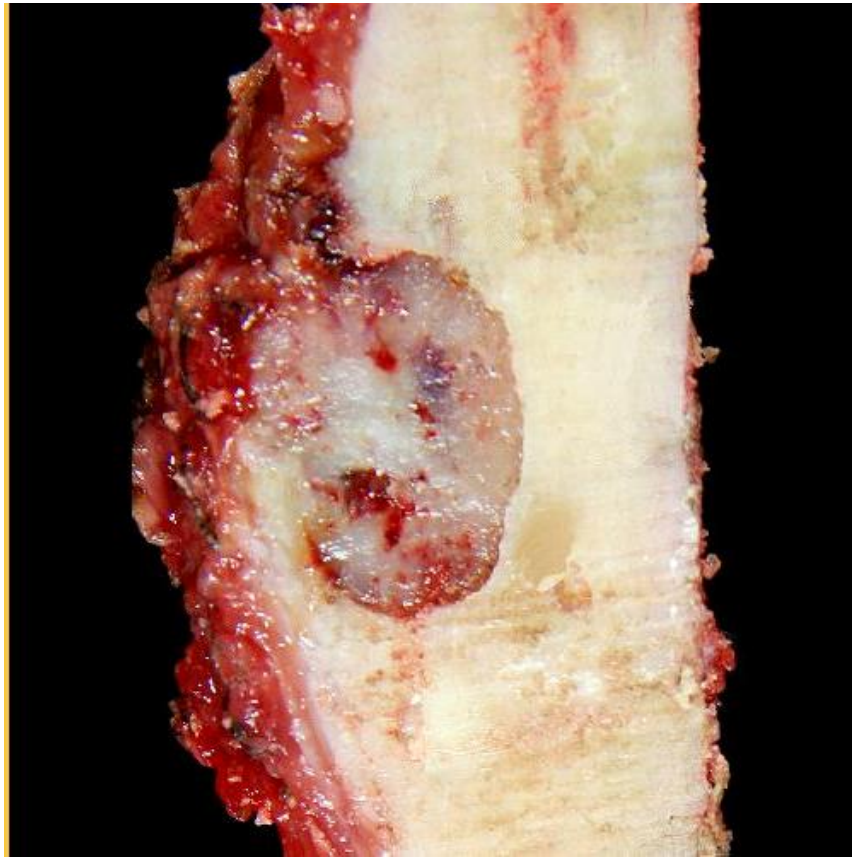
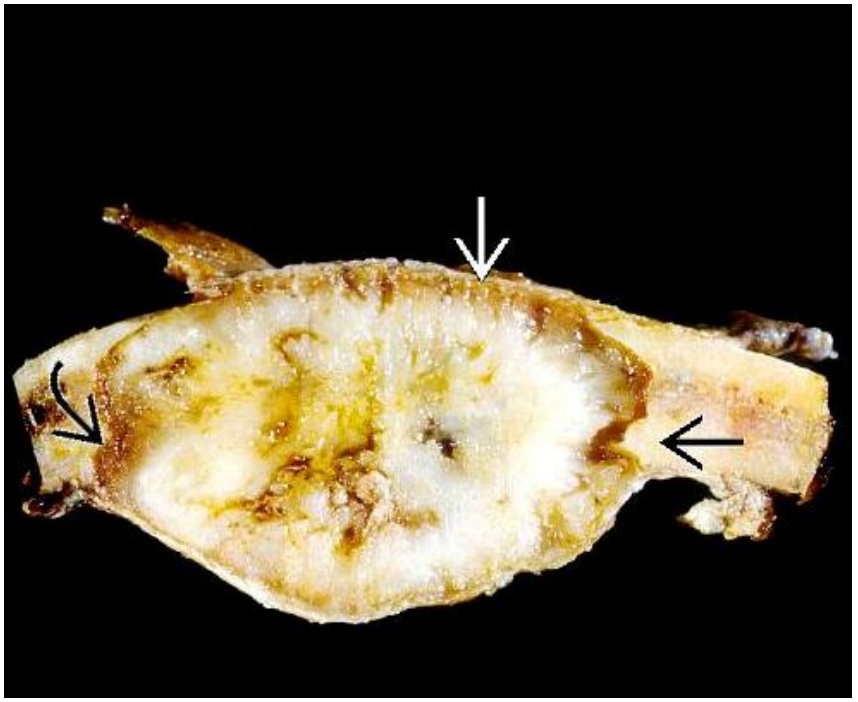
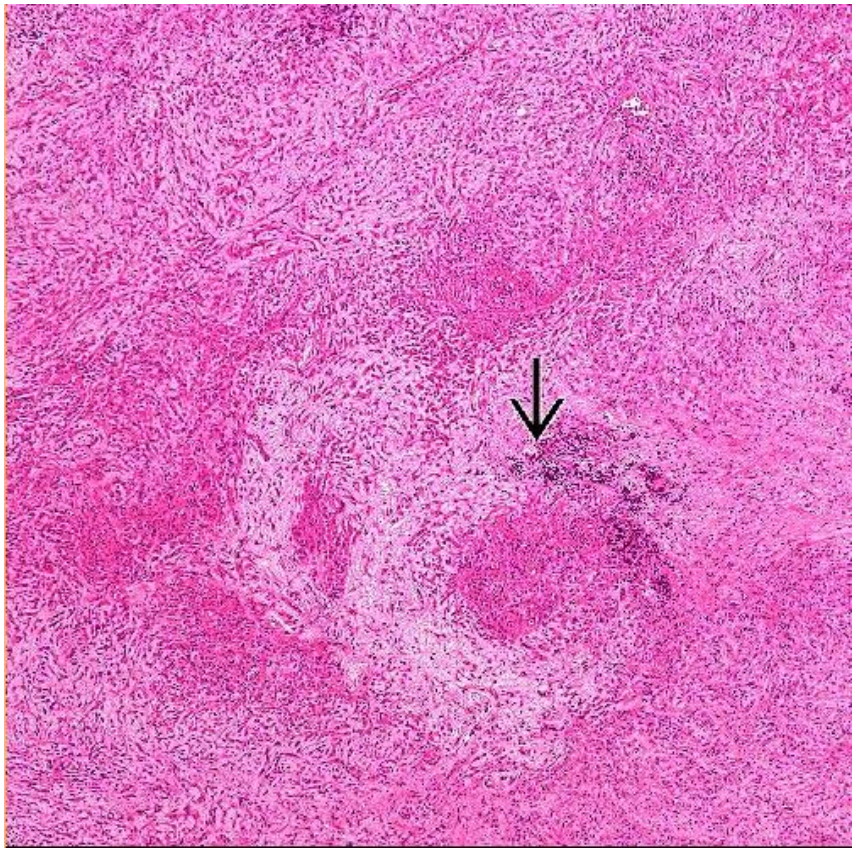
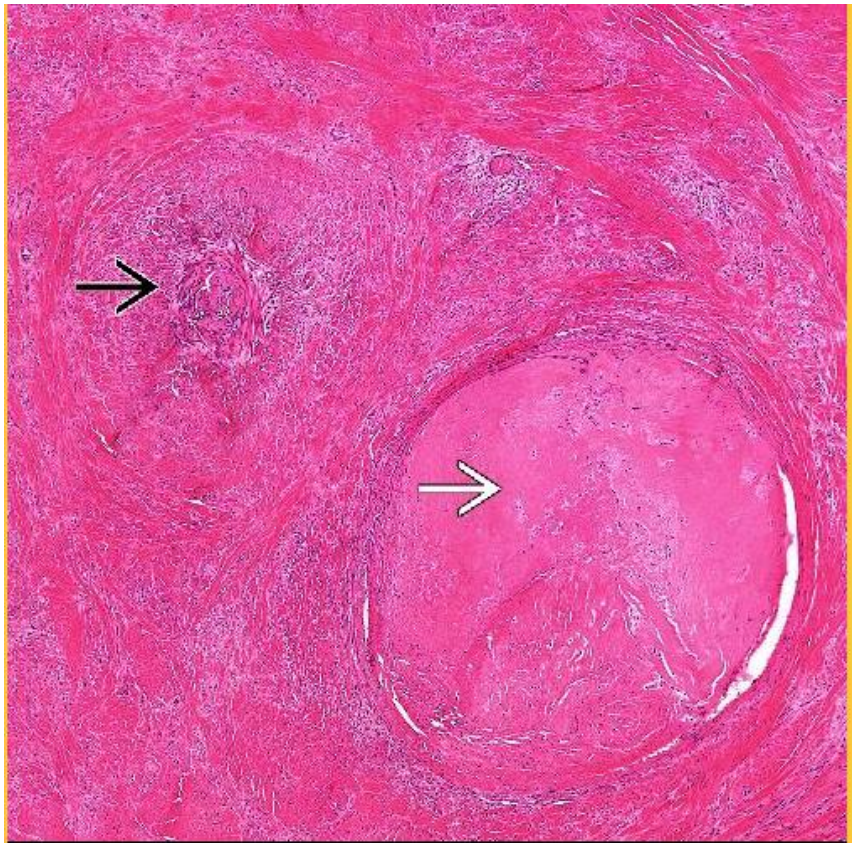
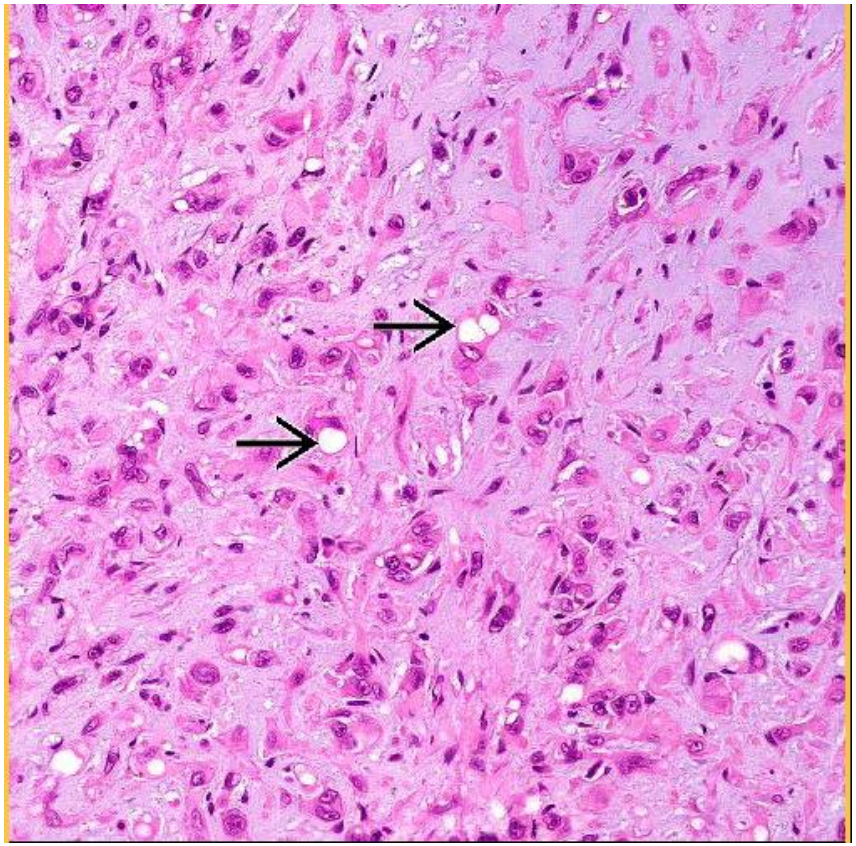
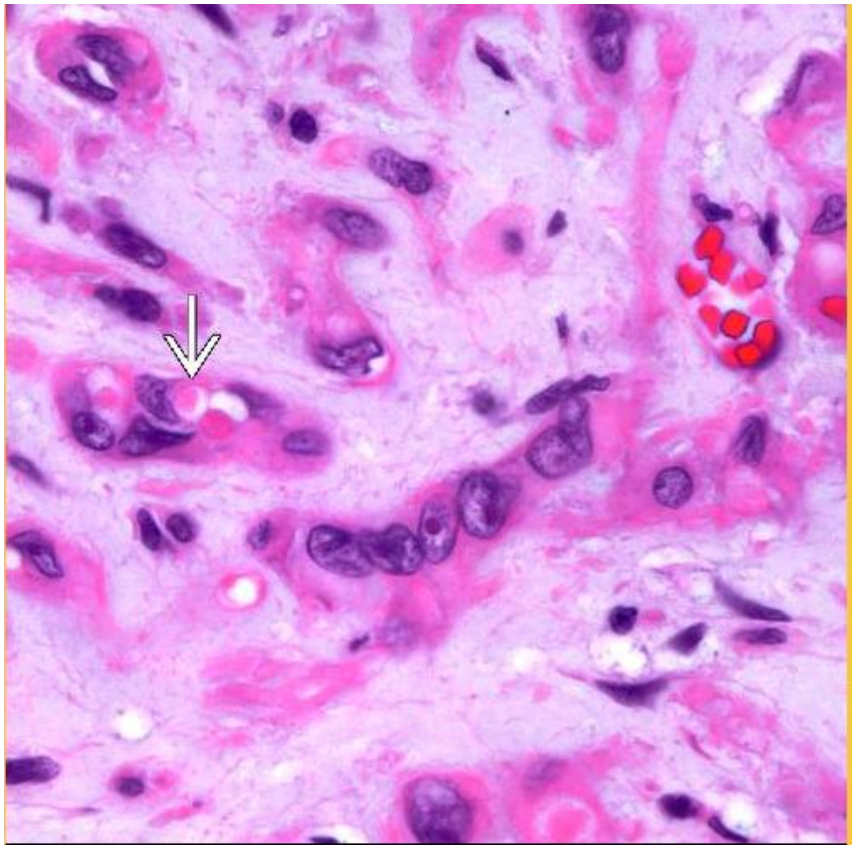












Tips

- Always consider epithelioid vascular tumor in the differential diagnosis of epithelioid tumor in bone
- Epithelioid vascular tumors can be keratin positive but stain for endothelial markers
- When multifocal can mimic metastatic carcinoma

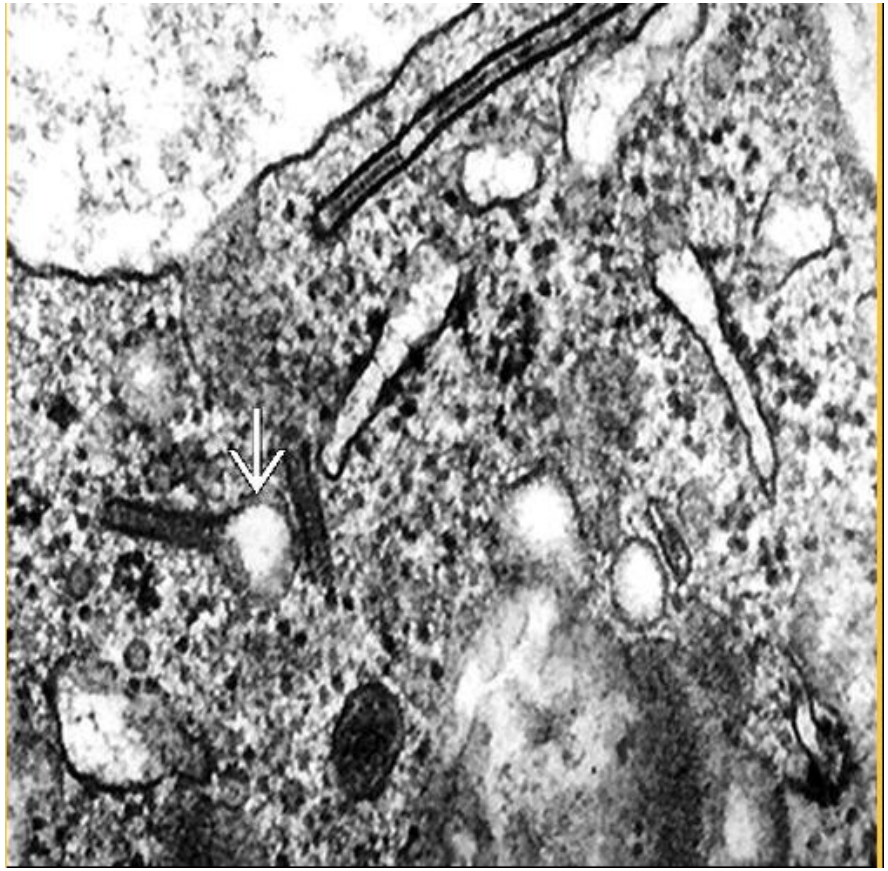
Hematopoietic tumors

Langerhans cell histiocytosis

- Eosinophilic granuloma
- Histiocytosis X
- Intraosseous neoplastic proliferation of Langerhans cells

Clinical issues

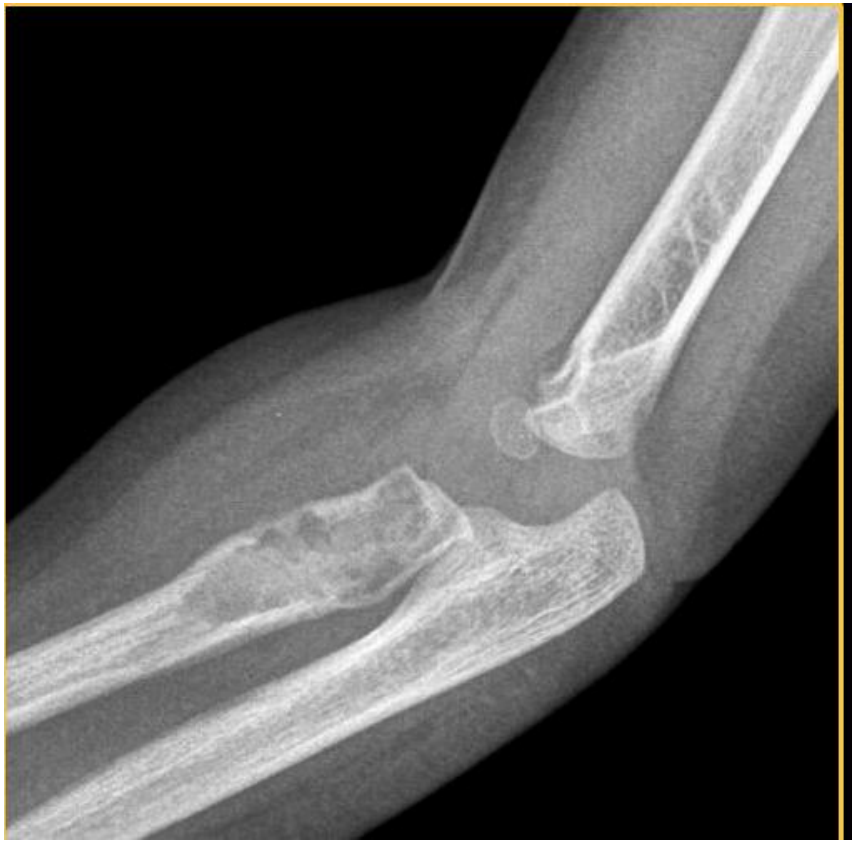
- Usually diagnosed during 1st to 3rd decades of life
- Can develop in any bone but most commonly in slull and jaw
- Monoostotic disease usually managed by curretage or by direct intralesional injection of corticosteroids
- Patients with monostotic skeletal involvement have excellent prognosis
- Multifocal systemic disease has guarded prognosis

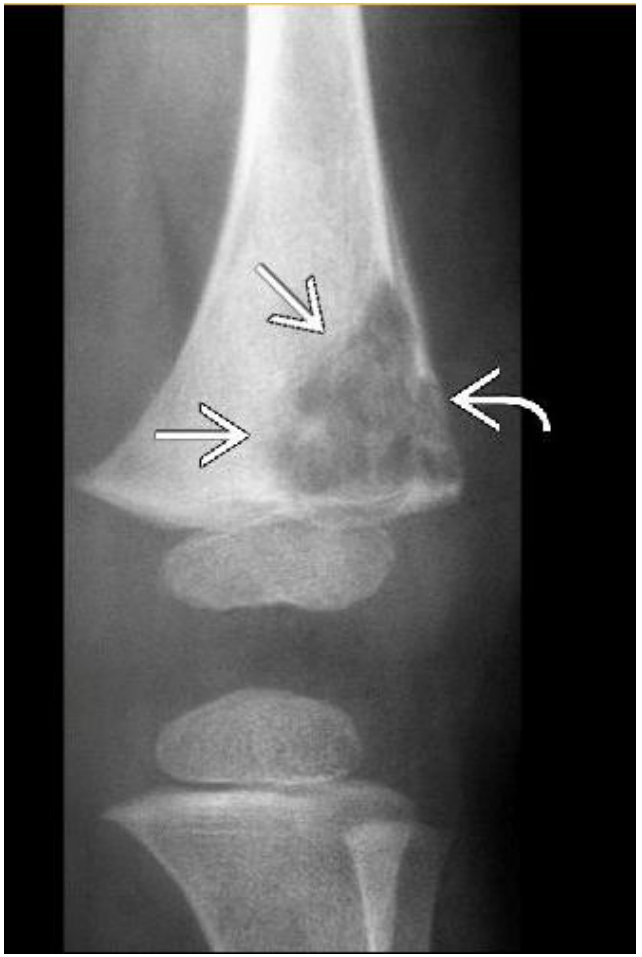


Ultrastuctural features

✳**Birbeck granules** are tubular pentalaminar membrane-bound cytoplasmic organelles;frequently have terminal oval protrusions resembling tennis racket or lollipop

Image findings





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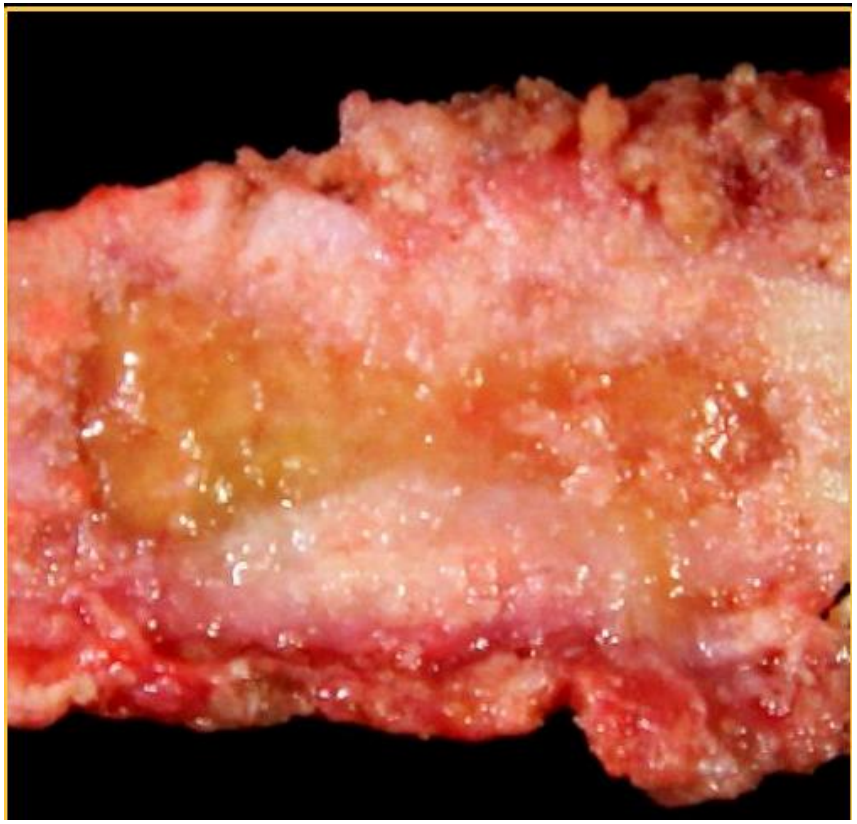

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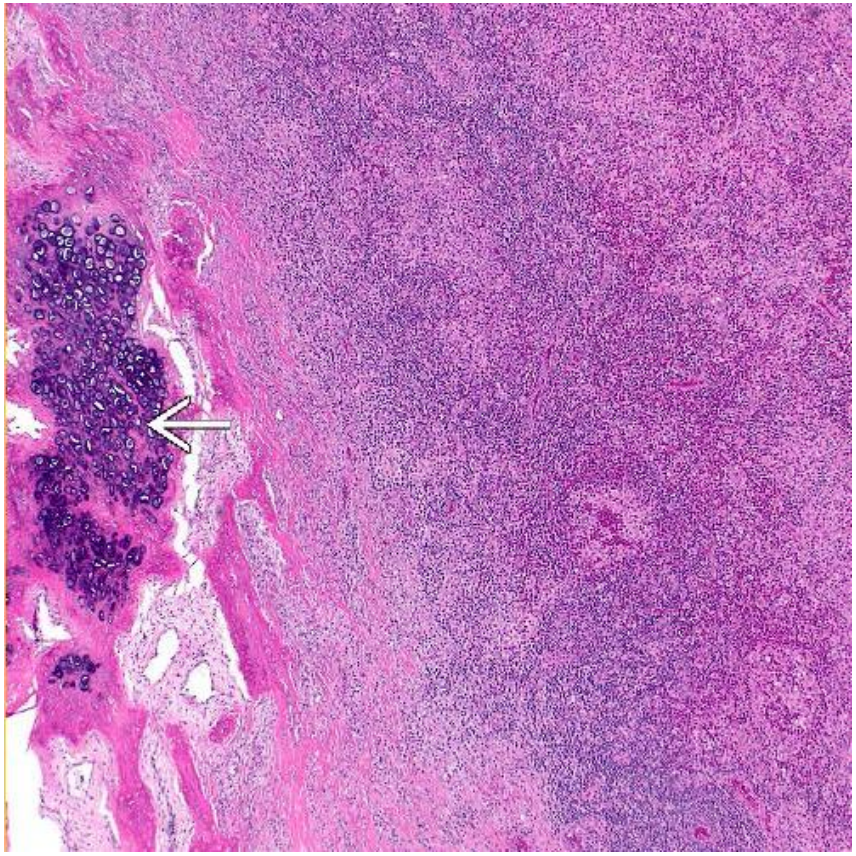

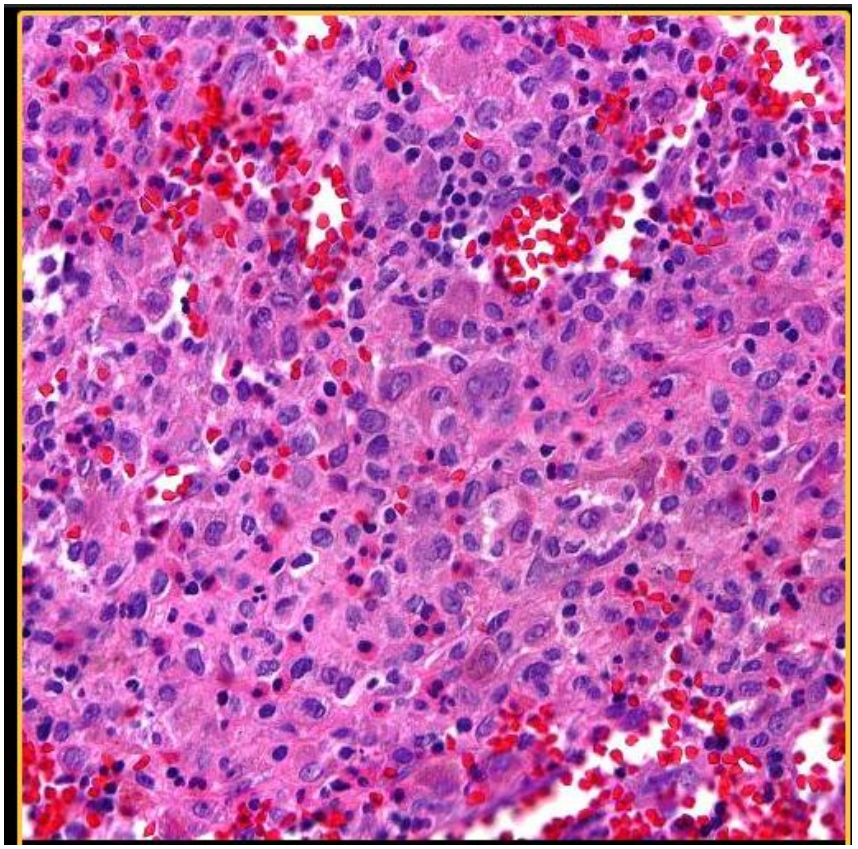

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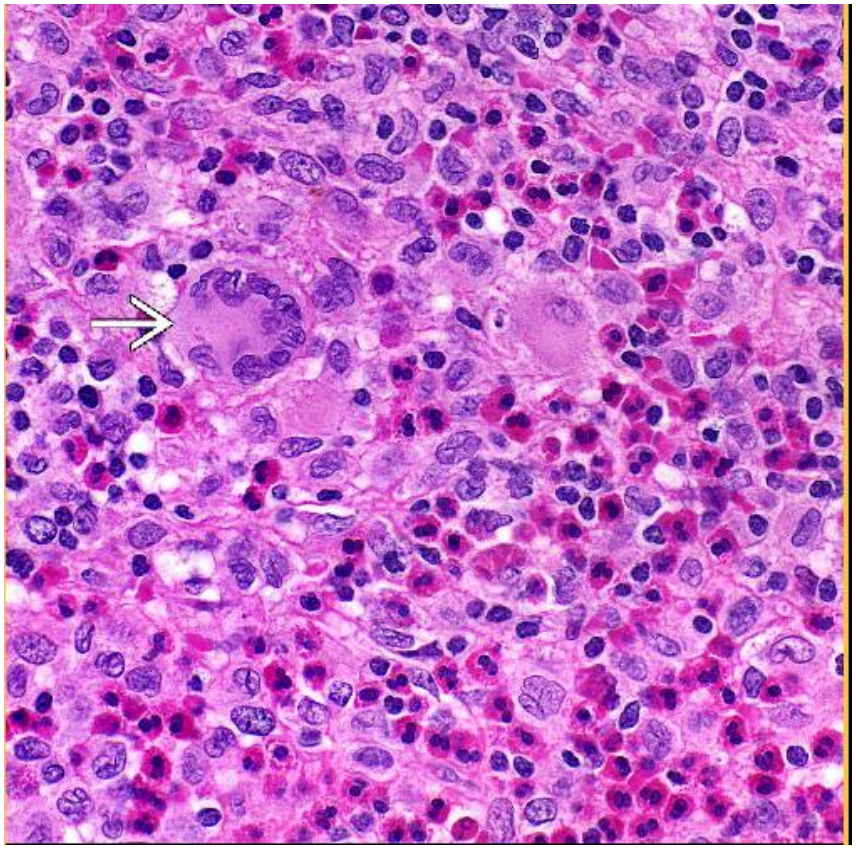
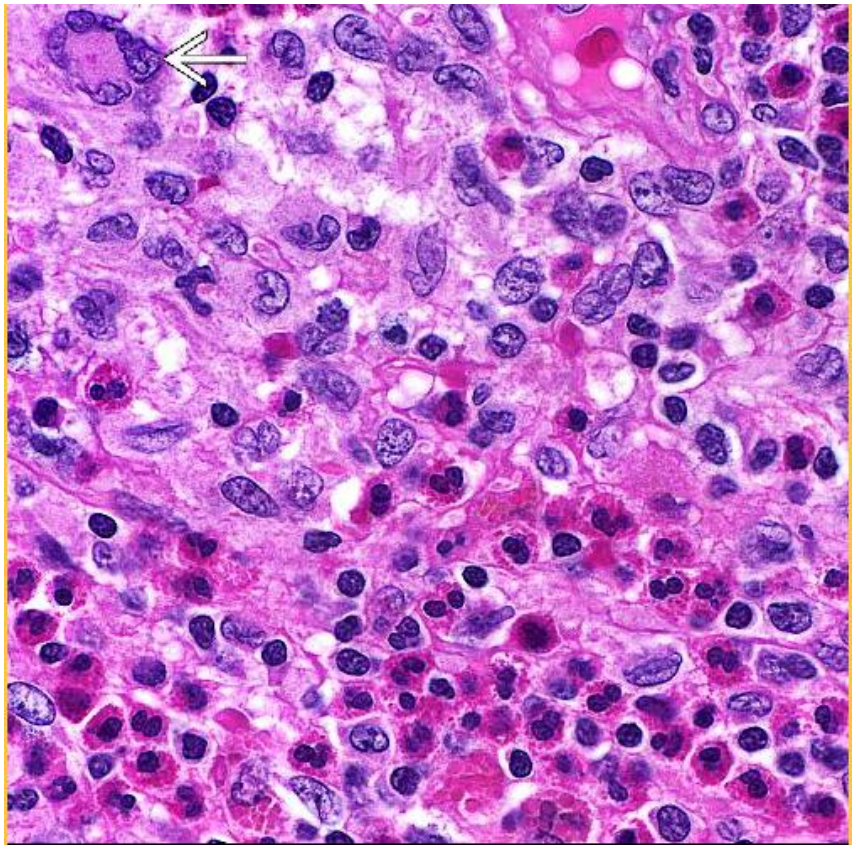


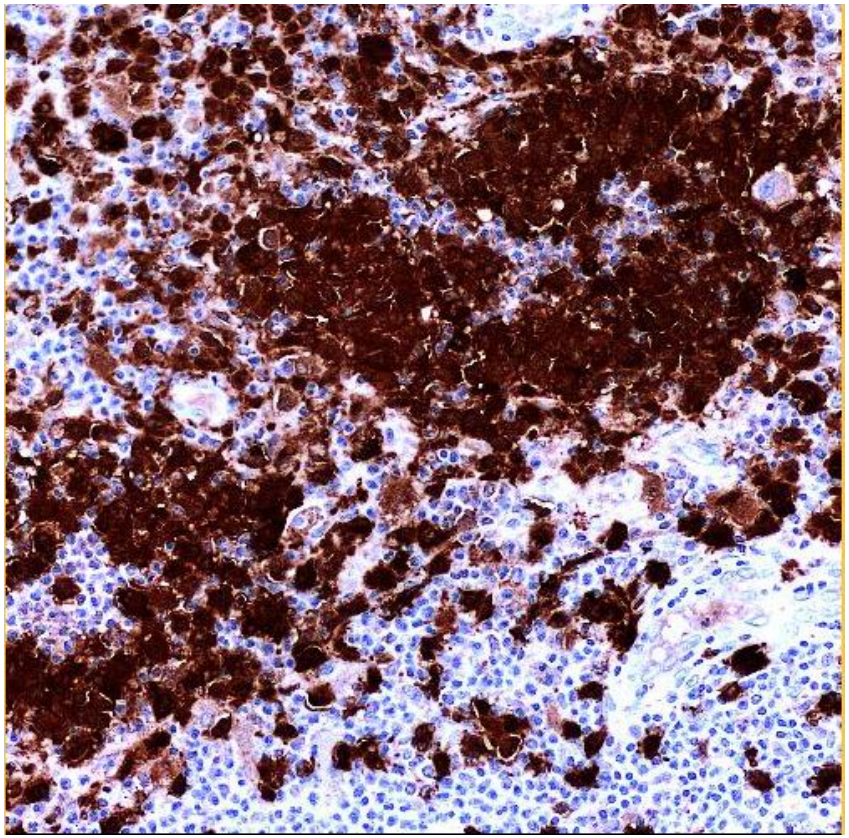


Immunohistochemistry

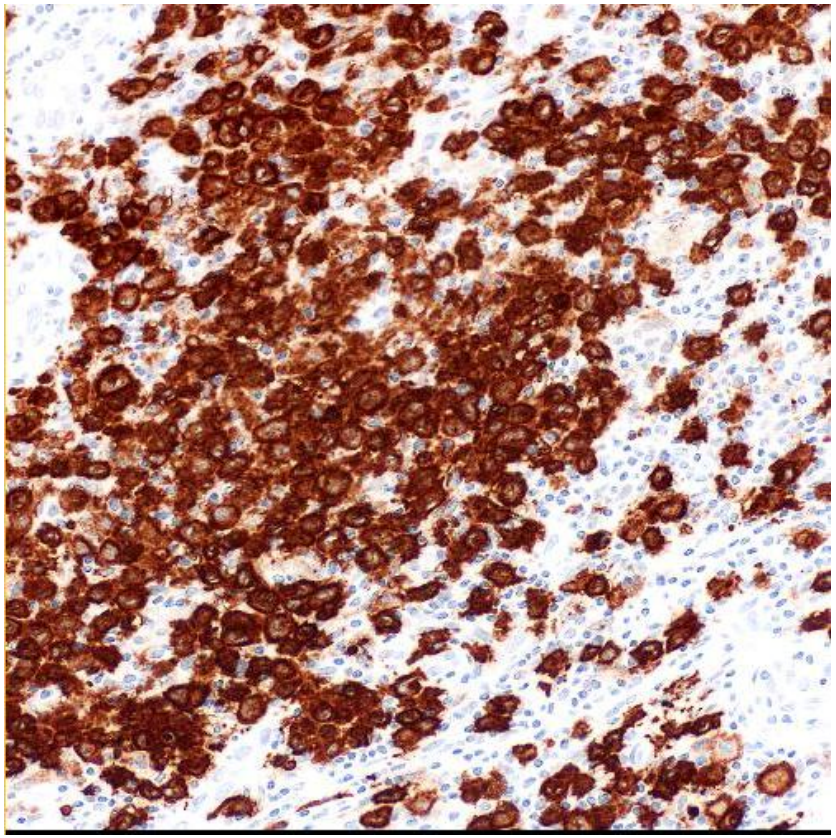
- Langerhans cells express S100 protein, CD1a and Langerin

Immunohistochemistry

IHC for S100-protein



IHC for CD1a



Top differential

- Acute and Chronic Osteomyelitis
- Skeletal diseases with increased eosinophils

Miscellaneous tumors

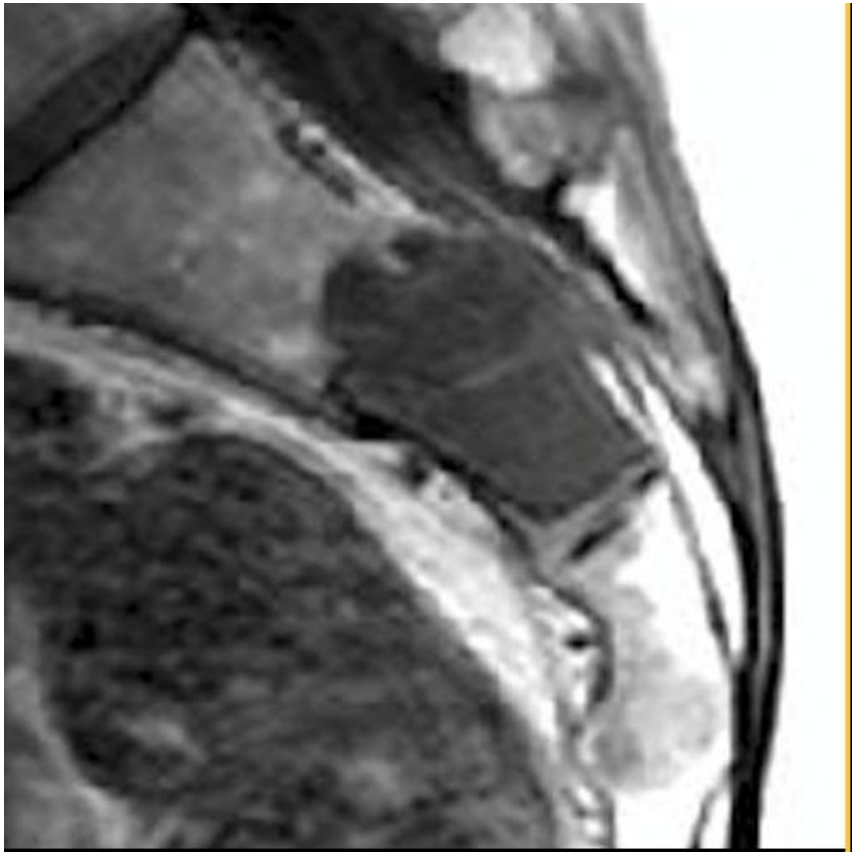
Intraosseous schwannoma

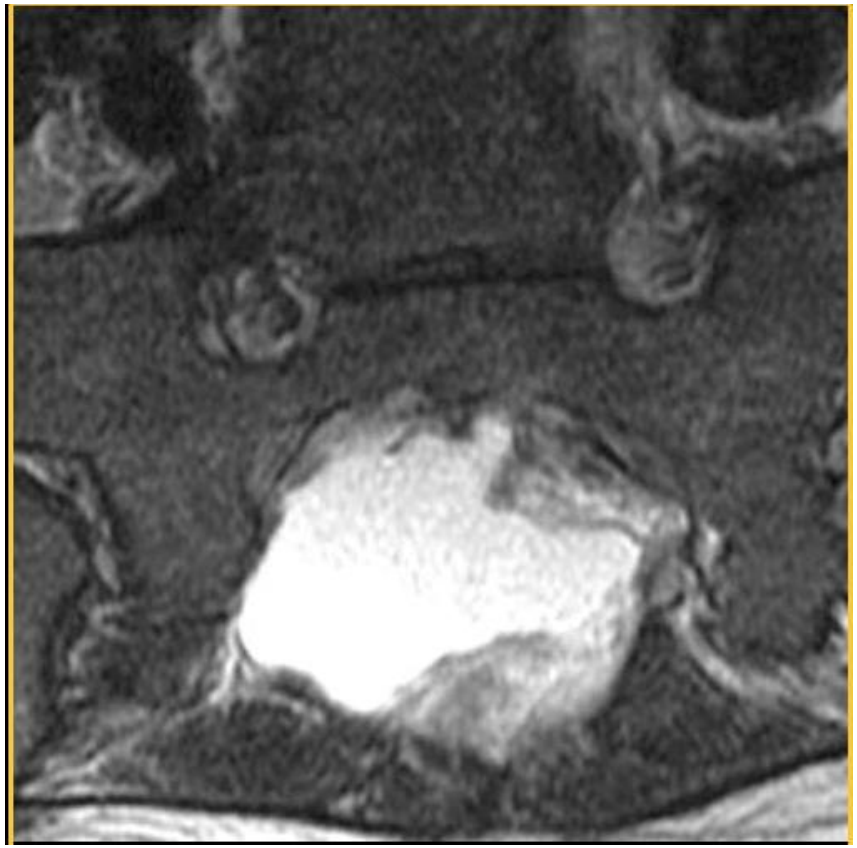
- Primary intraosseous tumor of bone composed entirely os Schwann cells

Etiology/Pathogenesis

- Most tumors are sporadic
- Rare tumors arise in patients with Carney Complex

Image findings





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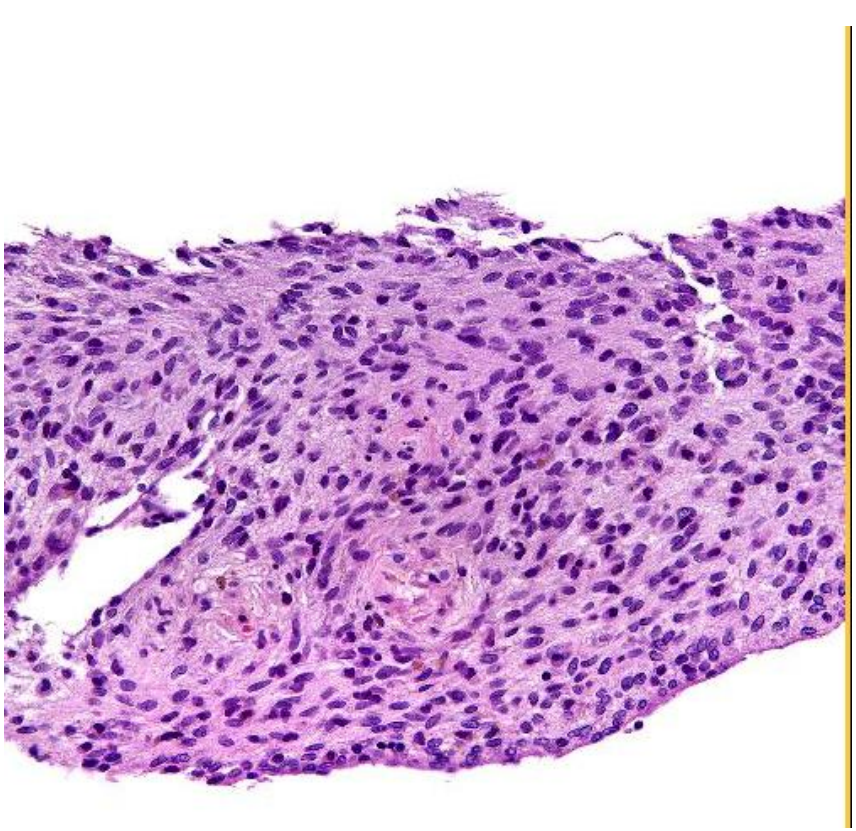

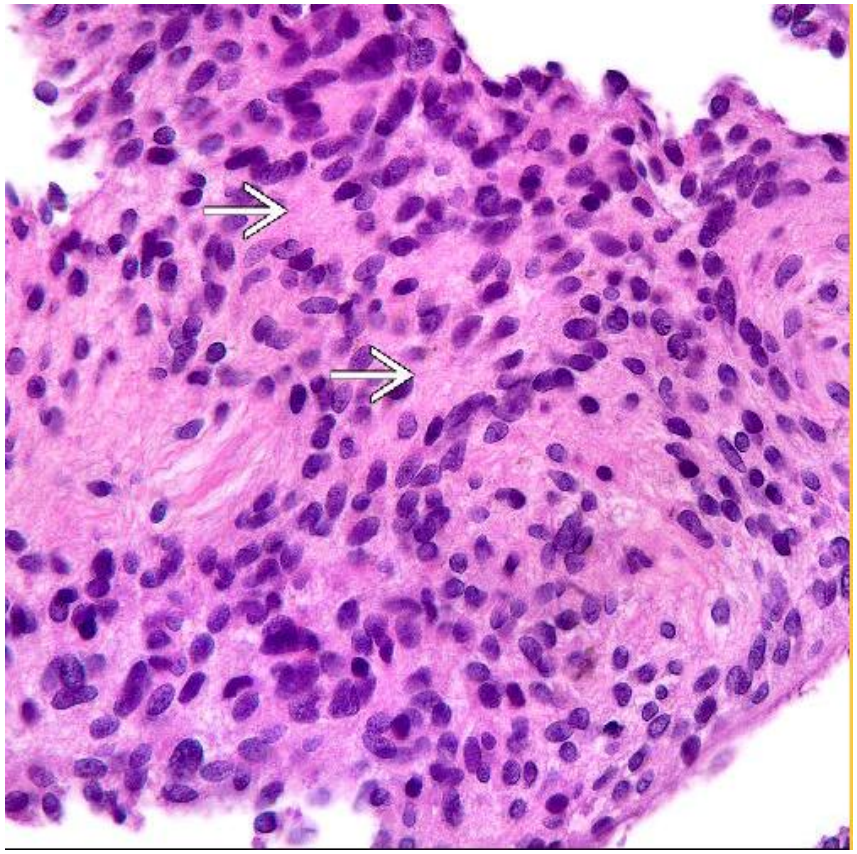

Immunohistochemistry for S100-protein

By Diego Rivera
1886-1954