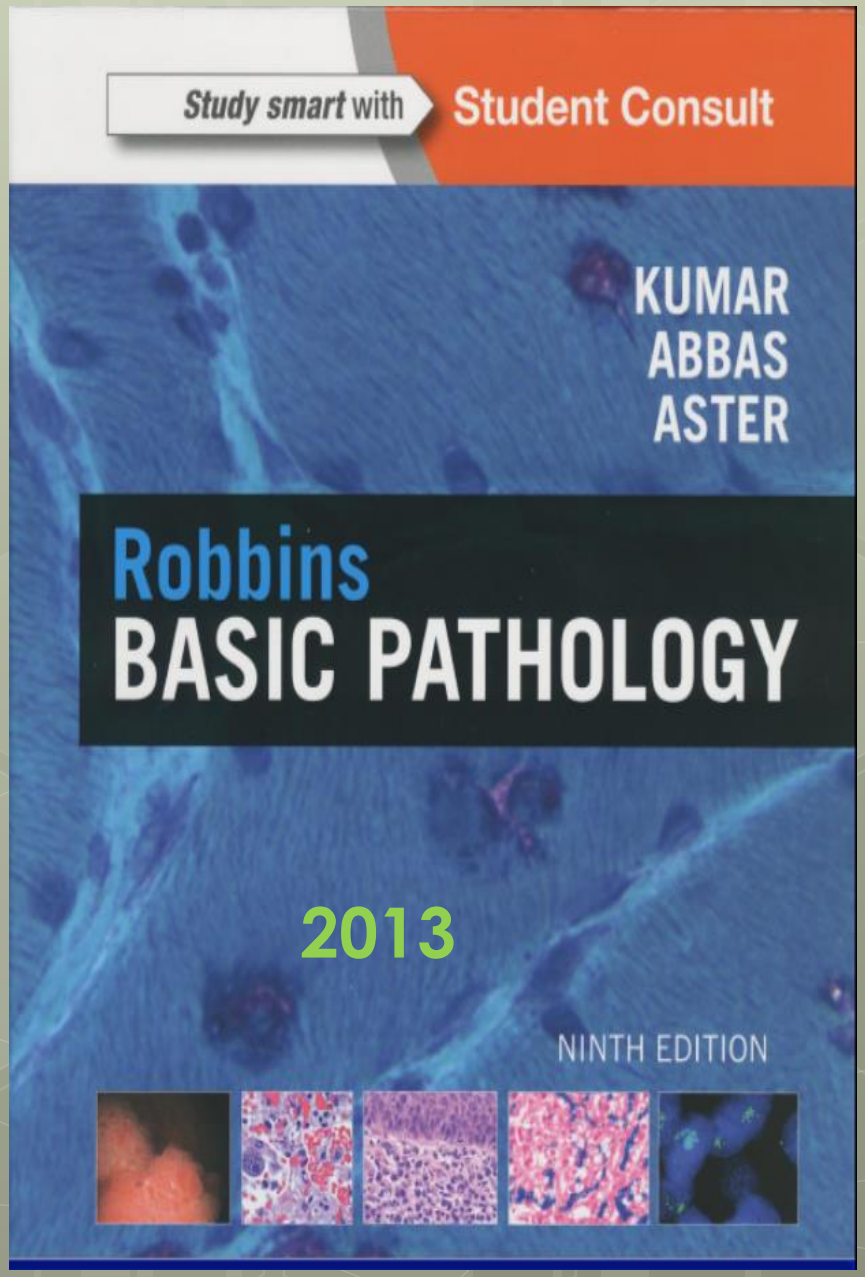
IN THE NAME OF GOD



chapter 20, pp 765-781

BONE PATHOLOGY

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- Osteosarcoma
- Cartilage-Forming Tumors
  - Osteochondroma
  - Chondroma
  - Chondrosarcoma
- Fibrous and Fibroosseous Tumors
  - Fibrous Cortical Defect and Nonossifying Fibroma
  - Fibrous Dysplasia
- Miscellaneous Bone Tumors
  - Ewing Sarcoma and Primitive Neuroectodermal Tumor
  - Giant Cell Tumor of Bone
- Metastatic Disease

Osteosarcoma

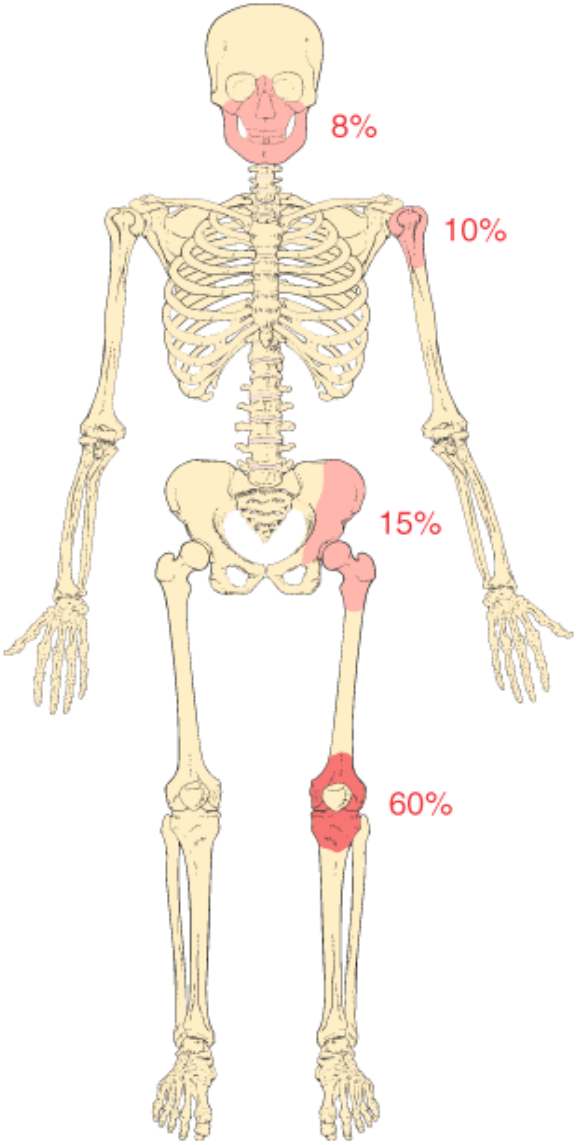
- Osteosarcoma is a bone-producing malignant mesenshymal tumor
- After myeloma and lymphoma, osteosarcoma is the most common primary malignant tumor of bone,
- approximately 20% of primary bone cancers;
- a little over 2000 cases are diagnosed annually in the United States.

Osteosarcoma

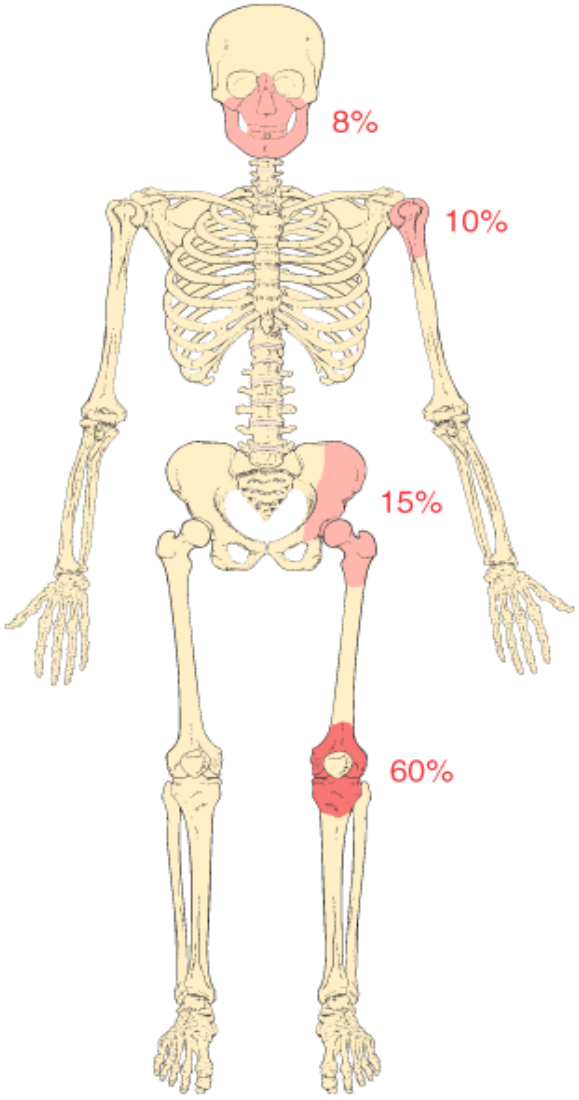
- Osteosarcomas occur in all age groups,
- 75% of patients are younger than 20 years of age,
- second peak occurring in elderly persons,
- usually in association with other conditions,
  - including Paget disease,
  - bone infarcts,
  - previous irradiation.
- Men are more commonly affected than women (1.6: 1).

OSTEOSARCOMA

- any bone can be involved,
- metaphyseal region
- 60% about the knee
- 15% around the hip,
- 10% at the shoulder,
- 8% in the jaw.



(OSTEOGENIC SARCOMA)



LATE TEENS
KNEES
METAPHYSES
PAINFUL!!!

Several subtypes of osteosarcoma

- Site of involvement within the bone
  - medullary versus cortical
- Degree of differentiation,
- Number of involved sites,
- Presence of underlying disease,
- Histologic features;

- the most common type of osteosarcoma is
- primary,
- solitary,
- intramedullary,
- poorly differentiated,
- producing a predominantly bony matrix.

Morpholpgy

- On gross evaluation,
- osteosarcomas are gritty-appearing,
- gray-white tumors,
- often exhibiting hemorrhage
- Cystic degeneration.
- Tumors frequently destroy the surrounding cortices, producing soft tissue masses (Fig. 20-9, A).
- They spread extensively in the medullary canal,
- infiltrating and replacing the marrow
- infrequently penetrating the epiphyseal plate or entering the joint space

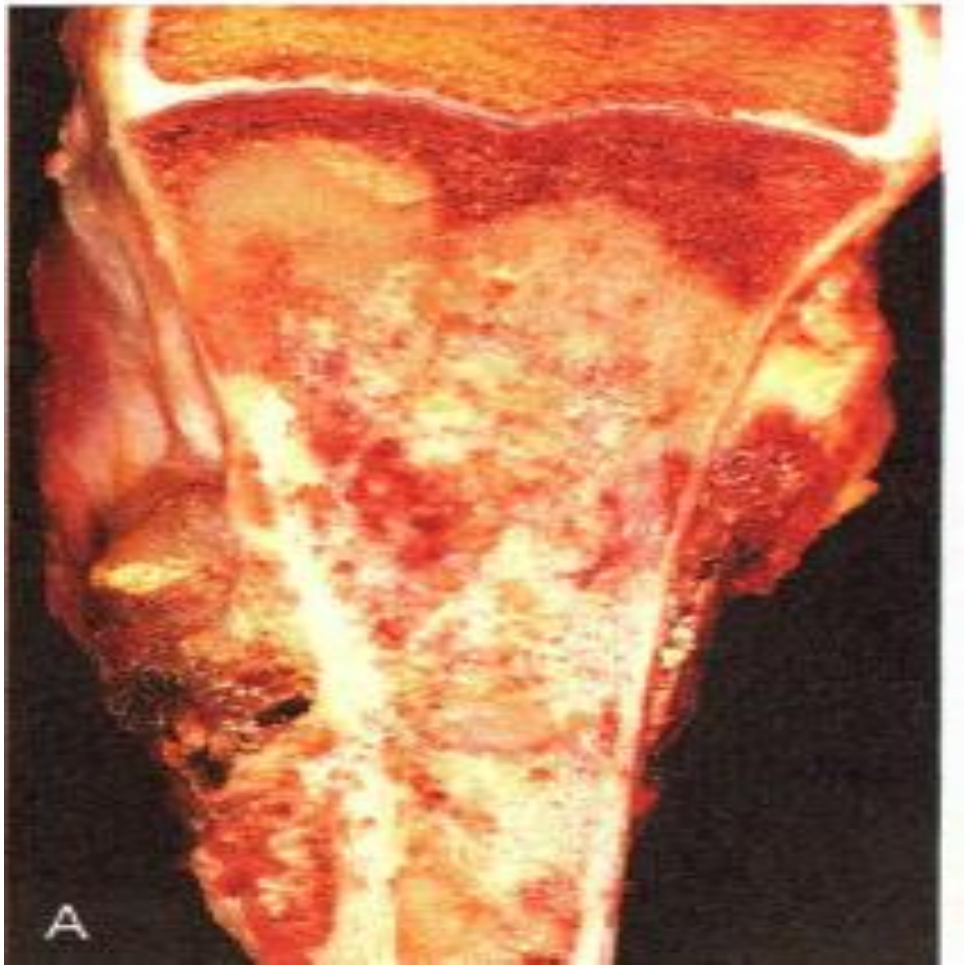


Figure 20-9 Osteosarcoma. A, Mass involving the upper end of the tibia. The tan-white tumor fills most of the medullary cavity of the metaphysis and proximal diaphysis. It has infiltrated through the cortex, lifted the periosteum, and formed soft tissue masses on both sides of the bone.

- Tumor cells vary in size and shape and frequently have large hyperchromatic nuclei; bizarre tumor giant cells are common, as are mitotic figures.
- The production of mineralized or unmineralized bone (osteoid) by malignant cells is essential for diagnosis of osteosarcoma (Fig. 20-9. B).

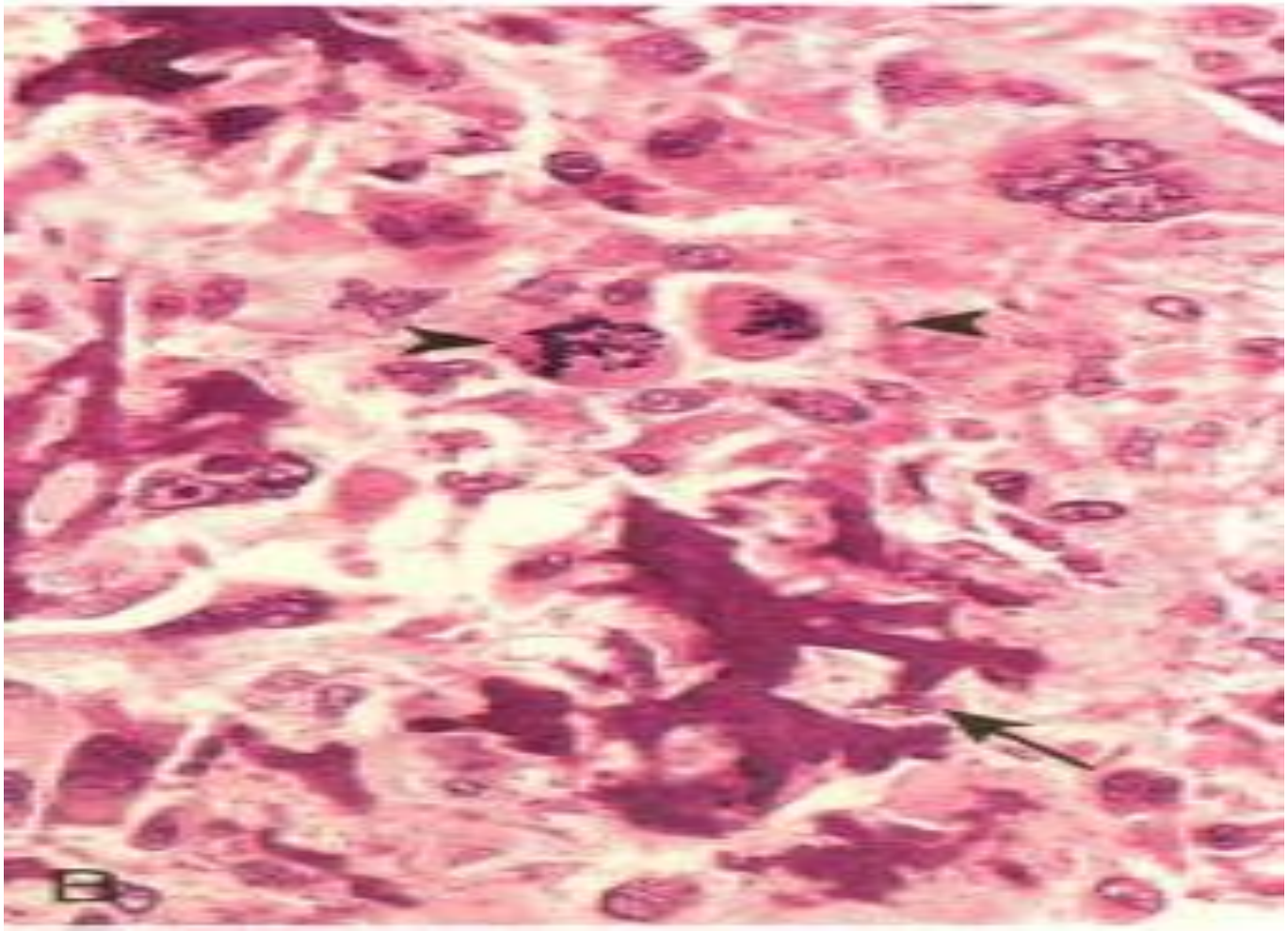


Figure 20-9 Osteosarcoma. B, Histologic appearance .with coarse. Lacelike pattern of neoplastic bone (arrow) produced by anaplastic tumor cells. Note the wildly aberrant mitotic figures (arrowheads).

- The neoplastic bone typically is coarse and lacelike but also can be deposited in broad sheets.
- Cartilage and fibroblastic differentiation can also be present in varying amounts.
- When malignant cartilage is abundant, the tumor is called a chondroblastic osteosarcoma.
- Vascular invasion is common, as is spontaneous tumor necrosis.

PATHOGENESIS

- Several mutations are closely associated with the development of osteosarcoma.
- In particular. RB gene mutations occur in 60% to 70% of sporadic tumors, and persons with hereditary retinoblastomas (due to germline mutations in the RB gene) have a thousand-fold greater risk for development of osteosarcoma.

- Spontaneous osteosarcomas also frequently exhibit mutations
- TP53
- Genes that regulate the cell cycle,
  - Cyclins .
  - Cyclin dependent kinases,
  - Kinase inhibitors.

- Many osteosarcomas develop at sites of greatest bone growth, perhaps because rapidly dividing cells provide a fertile soil for mutation

Clinical Features

- Osteosarcomas typically manifest as painful enlarging masses, although a pathologic fracture can be the first sign.

- Radiographic imaging usually shows a large, destructive, mixed lytic and blastic mass with indistinct infiltrating margins.

- The tumor frequently breaks through the cortex and lifts the periosteum, resulting in reactive periosteal bone formation.

- A triangular shadow on the x-ray film between the cortex and raised periosteum (Codman triangle) is characteristic of osteosarcomas.

- Osteosarcomas typically spread hematogenously; at the time of diagnosis,
- approximately 10% to 20% of patients have demonstrable pulmonary metastases,
- a larger number have microscopic metastases.
- Despite aggressive behavior, standard treatment with chemotherapy and limb salvage therapy currently yields long-term survivals of 60% to 70%.

- Secondary osteosarcomas occur in older adults most commonly in the setting of Paget disease or previous radiation exposure.
- Like primary osteosarcomas, secondary osteosarcomas are highly aggressive tumors, but they do not respond well to therapy and are usually fatal.

Cartilage-Forming Tumors

- Cartilage-forming tumors produce hyaline or myxoid cartilage;
- fibrocartilage and elastic cartilage are rare components.
- Spectrum from benign, self-limited growths to highly aggressive malignancies;
- Benign cartilage tumors are much more common than malignant ones.

Osteochondroma

- Osteochondromas are relatively common benign, cartilage capped tumors attached by a bony stalk to the underlying skeleton.
- Solitary osteochondromas typically are first diagnosed in late adolescence and early adulthood
- (male-to female ratio of 3: 1);
- multiple osteochondromas become apparent during childhood,
- occurring as multiple hereditary osteochondromas, an autosomal dominant disorder.

- Inactivation of both copies of the EXT1 or EXT2 genes through mutation and loss of heterozygosity in chondrocytes of the growth plate is implicated in both sporadic and hereditary osteochondromas.

- These tumor suppressor genes encode Glycosyl transferases essential for polymerization of heparin sulfate, an important component of cartilage.
- This finding and other molecular genetic studies support the concept that osteochondromas are true neoplasms and not developmental malformations.

- Osteochondromas develop only in bones of endochondral origin arising at the metaphysis near the growth plate of long tubular bones, especially about the knee; they tend to stop growing once the normal growth of the skeleton is completed (Fig. 20-10).

OSTEOCHONDROMA (EXOSTOSIS)

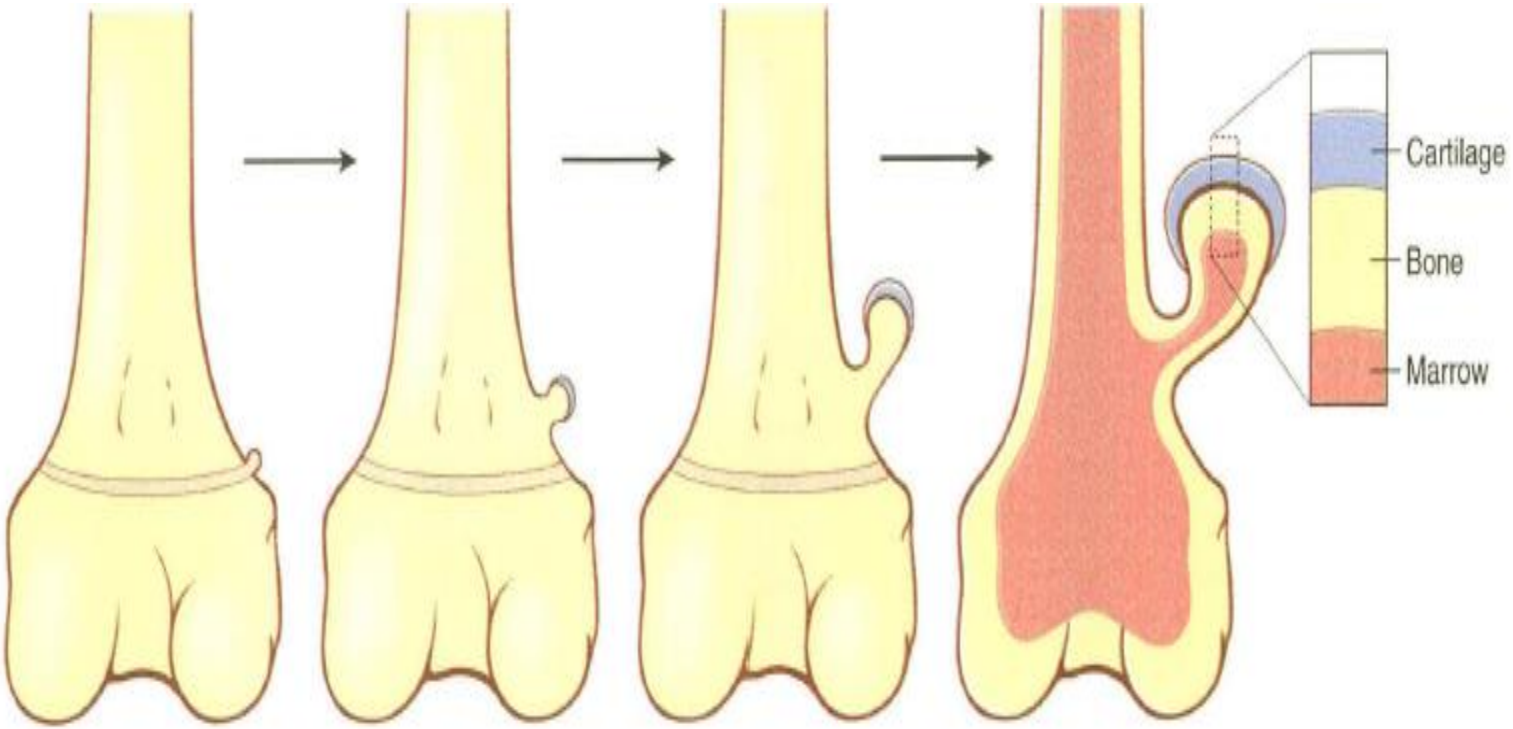
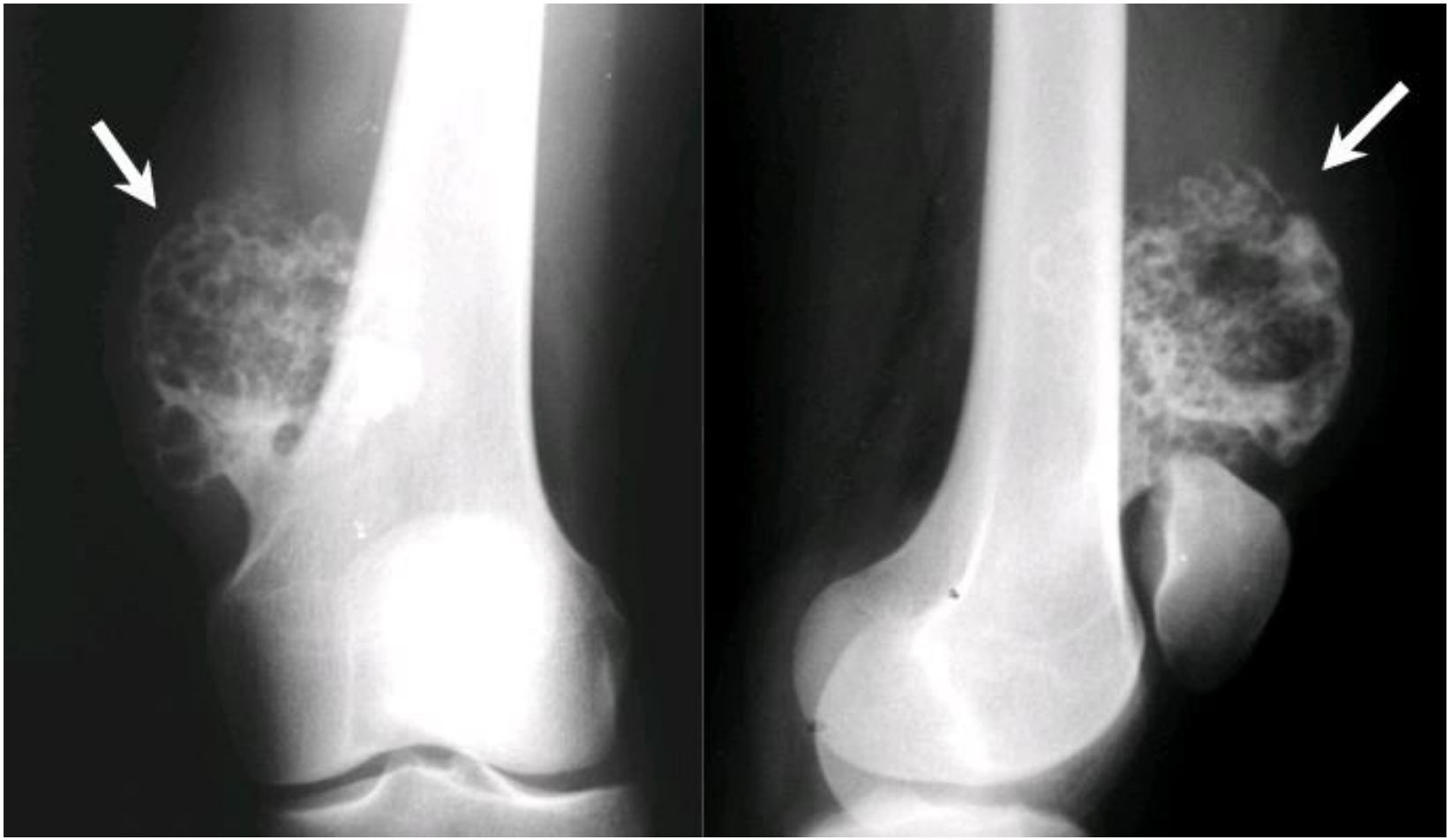


Figure 20-10 The development of an osteochondroma. beginning with an outgrowth from the epiphyseal cartilage.

OSTEOCHONDROMA (EXOSTOSIS)



- Occasionally they develop from bones of the pelvis, scapula, and ribs and in these sites frequently are sessile.
- Rarely, osteochondromas arise in the short tubular bones of hands and feet

MORPHOLOGY

- Osteochondromas range from I to 20 cm in size and have a cartilaginous cap that is usually less than 2 cm in thickness.
- The hyaline cartilage resembles a disorganized growth plate undergoing endochondral ossification.

- Newly formed bone forms the inner portion of the head and stalk, with the stalk cortex and central region merging with the cortex and medullary cavity. respectively, of the host bone.

Clinical Features

- Osteochondromas are slow-growing masses that can be painful if they impinge on a nerve or if the stalk is fractured.
- In many cases, they are incidental findings.
- In multiple hereditary osteochondromas, deformity of the underlying bone suggests an associated disturbance in epiphyseal growth.

Clinical Features

- Solitary osteochondromas rarely progress to chondrosarcoma or other sarcomas, but malignant transformation occurs more frequently in those with multiple hereditary osteochondromas

Chondroma

- Chondromas are benign neoplasms of hyaline cartilage.
- When they arise within the medulla, they are termed enchondromas;
- when on the bone surface, they are called juxtacortical chondromas.

- Enchondromas usually are diagnosed in persons between the ages of 20 and 50 years;
- they typically are solitary
- Located in the metaphyseal region of tubular bones,
- the favored sites being the short tubular bones of the hands and feet

- Ollier disease is characterized
  - Multiple chondromas preferentially involving one side of the body, and
- Maffucci syndrome is characterized
  - by multiple chondromas associated
  - soft tissue spindle cell hemangiomas.

PATHOGENESIS

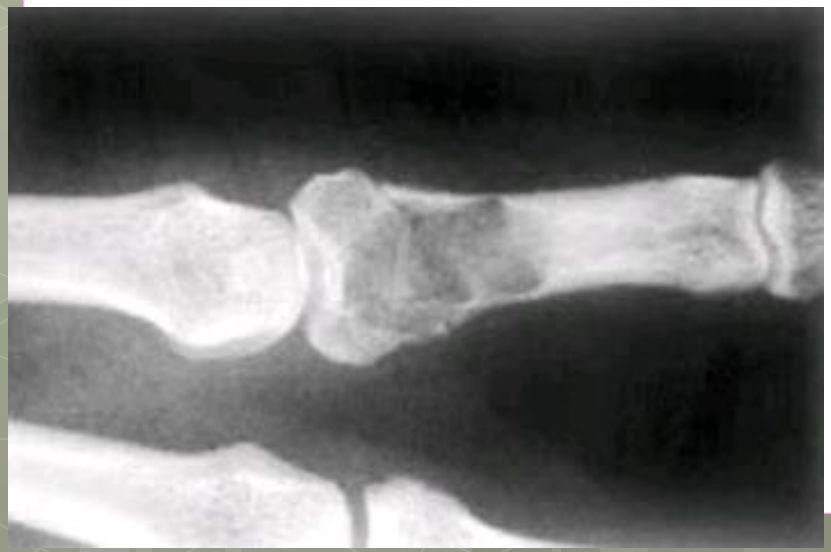
- Enchondromas occurring in Oilier disease and Maffucci syndrome
- frequently contain point mutations in either isocitrate dehydrogenase I (IDH I) or IDH2 that create a new enzyme activity.
- The same IDH mutations occur as somatic mutations in acute myeloid leukemias and gliomas.
- in Oilier and Maffucci disease the mutations are also found at low frequency in normal tissues, suggesting the mutations occurred early during embryonic development. an example of genetic mosaicism.

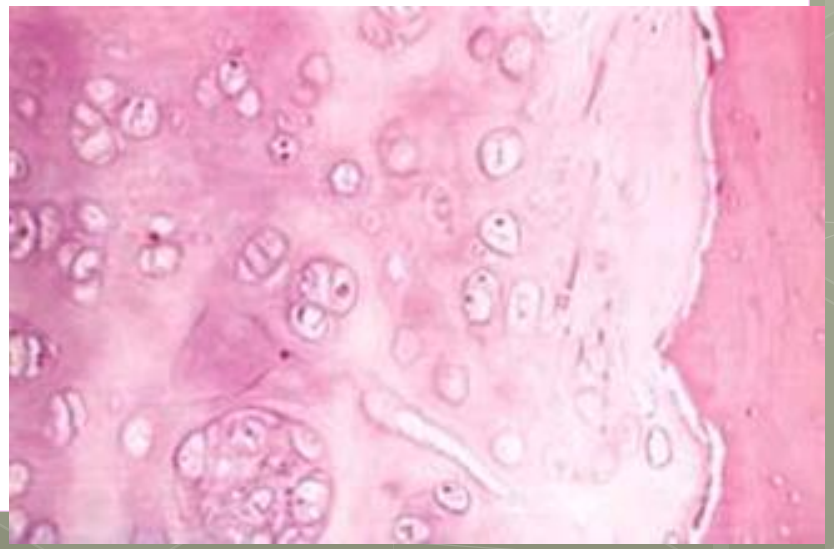
Morpholpgy

- Enchondromas are gray-blue, translucent nodules
- Usually smaller than 5 cm in greatest dimension.
- On microscopic examination. they are well circumscribed and composed of hyaline cartilage containing cytologically benign chondrocytes.
- At the periphery. there is endochondral ossification,
- while the center frequently calcifies and dies.
- In the hereditary multiple chondromatoses, the islands of cartilage exhibit greater cellularity and atypia. making them more difficult to distinguish from chondrosarcoma.

CHONDROMA

- Chondroma vs. EN-chondroma
- PURE Hyaline Cartilage
- MULTIPLE enchondromas = Ollier's dis.
- Maffucci Synd. if hemangiomas present





Clinical Features

- Most enchondromas are detected as incidental findings;
- occasionally they are painful or cause pathologic fractures.
- On x-ray imaging, the unmineralized nodules of cartilage produce well-circumscribed oval lucencies surrounded by thin rims of radiodense bone (O-ring sign).
- Calcified matrix manifests as irregular opacities.

- The growth potential of chondromas is limited, and most remain stable, although they can recur if incompletely excised.
- Solitary chondromas rarely undergo malignant transformation, but those associated with enchondromatoses are at increased risk for such change.
- Maffucci syndrome is associated with an increased risk for development of other types of malignancies, including ovarian carcinomas and brain gliomas.

Chondrosarcoma

- a malignant connective tissue tumor (sarcoma) whose cells manufacture and secrete neoplastic cartilage matrix.
- It is subclassified according
  - site (intramedullary versus juxtacortical)
  - histologic variants
- Chondrosarcomas occur roughly half as
- frequently as osteosarcomas;
- most patients are age 40 or older,
- men affected twice as frequently as women.

MORPHOLOGY

- Conventional chondrosarcoma, the most common variant, arises within the medullary cavity of the bone to form an expansile glistening mass that often erodes the cortex (Fig. 20-1 I, A).
- It is composed of malignant hyaline and myxoid cartilage.
- Myxoid chondrosarcomas are viscous and gelatinous in consistency. and the matrix oozes from the cut surface.
- The adjacent cortex is thickened or eroded, and the tumor grows with broad pushing fronts into marrow spaces and the surrounding soft tissue.
- Tumor grade is determined by cellularity, degree of cytologic atypia, and mitotic activity (Fig. 20-1 I. B).

Figure 20-11 Chondrosarcoma. A,Islandsof hyalineand myxoidcartilage expand the medullary cavity and grow through the cortex to form a sessile paracortical mass.

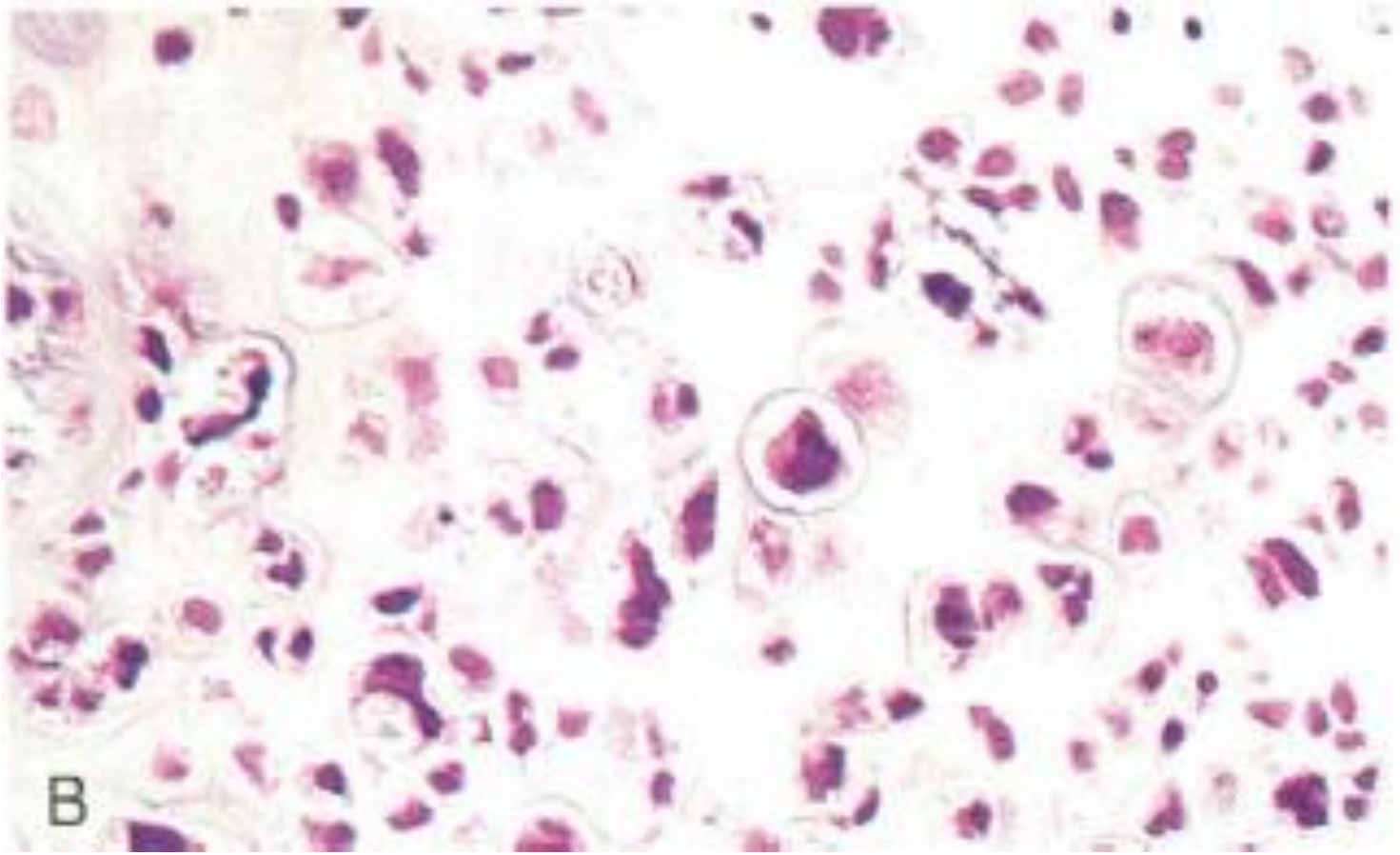
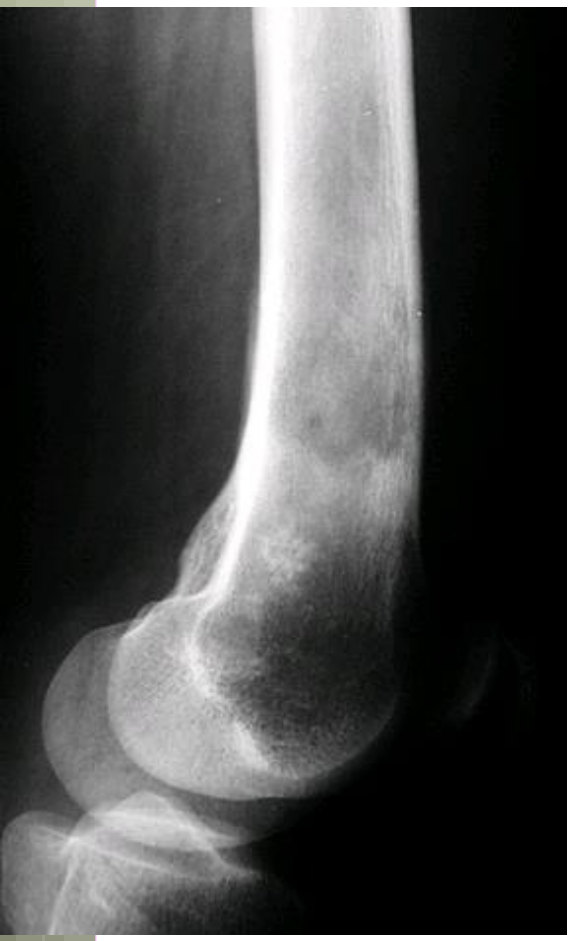


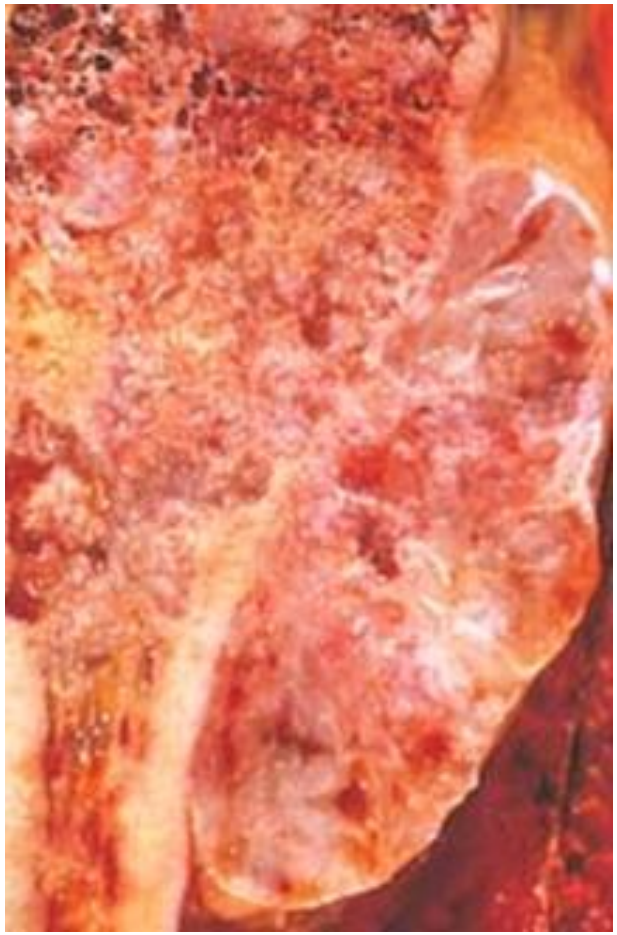
Figure 20-11 Chondrosarcoma. B, Anaplastic chondrocytes within a chondroid matrix.

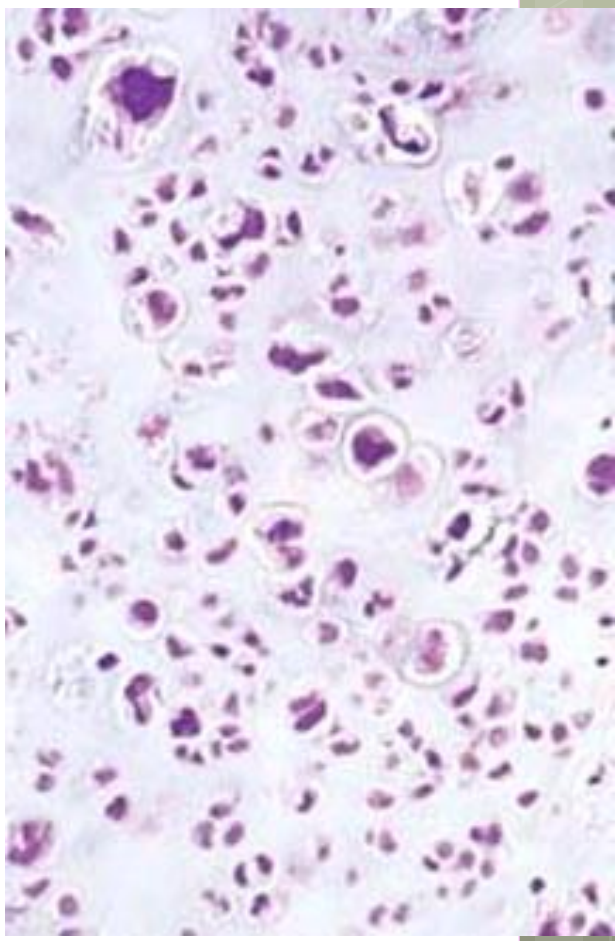
CHONDROSARCOMA

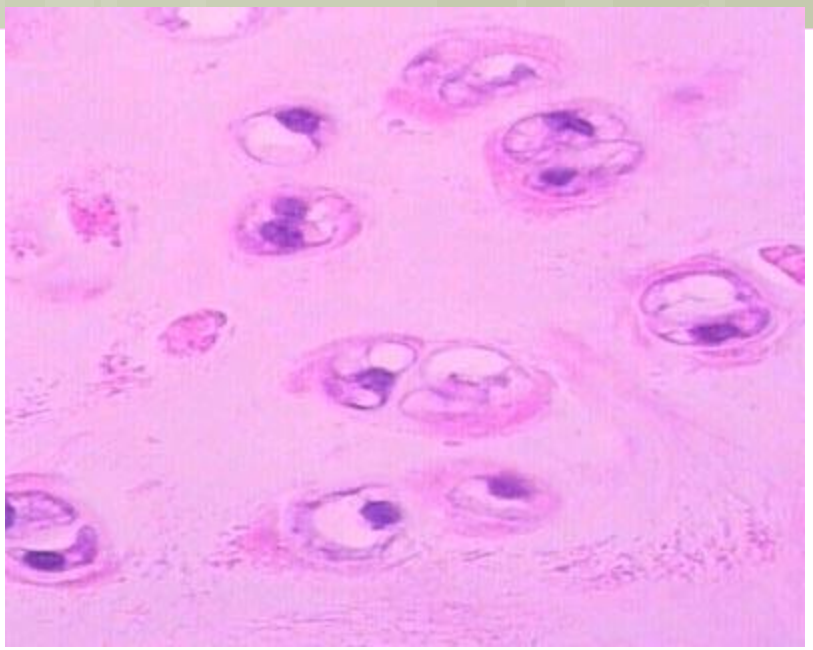
- Low-grade tumors may be difficult to distinguish from enchondroma.
- Higher-grade lesions contain pleomorphic chondrocytes with frequent mitotic figures.
- Approximately 10% of patients with conventional low grade chondrosarcomas have a second high-grade poorly differentiated component (dedifferentiated chondrosarcomas) that includes foci of fibro- or osteosarcomas.
- Other histologic variants include clear cell and mesenchymal chondrosarcomas

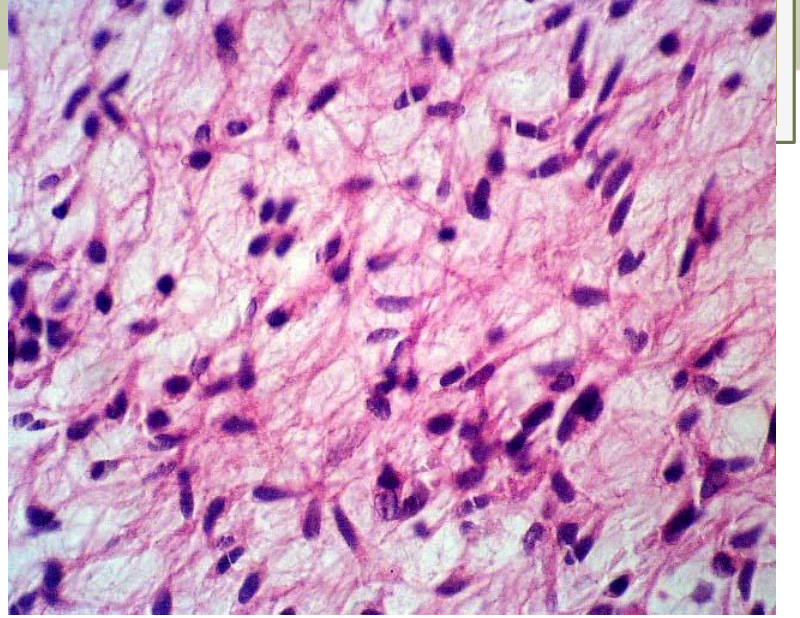
CHONDROSARCOMA

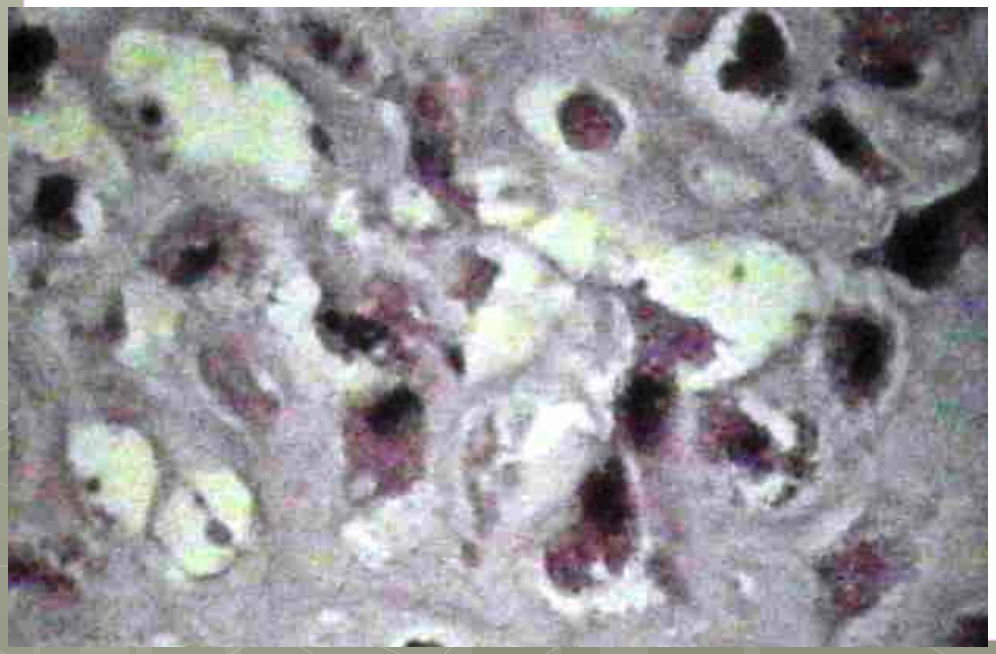


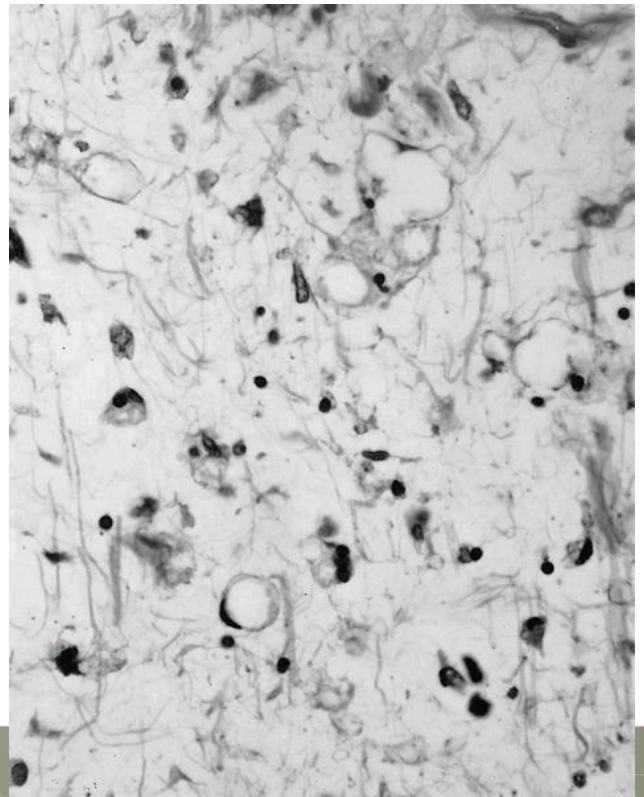












Clinical Features

- Chondrosarcomas commonly arise in the
  - pelvis,
  - shoulder,
  - ribs;
- in contrast with enchondromas, chondrosarcomas rarely involve the distal extremities.

- They typically manifest as painful, progressively enlarging masses.
- A slowly growing low-grade tumor causes reactive thickening of the cortex,
- whereas a more aggressive high-grade neoplasm destroys the cortex and forms a soft tissue mass;
- the more radiolucent the tumor the greater the likelihood that it is high grade.

- There is also a direct correlation between grade and biologic behavior of the tumor.
- Fortunately, most conventional chondrosarcomas are indolent and low-grade, with a 5-year survival rate of 80% to 90% (versus 43% for grade 3 tumors); grade 1 tumors rarely metastasize, whereas 70% of the grade 3 tumors disseminate.

- Size is another prognostic feature,
  - with tumors larger than 10 cm being significantly more aggressive than smaller tumors.
- Chondrosarcomas metastasize hematogenously,
- preferentially to the lungs and skeleton.

- Conventional chondrosarcomas are treated with wide surgical excision;
- chemotherapy is added for the mesenchymal and dedifferentiated variants because of their aggressive clinical course.

Fibrous and Fibroosseous Tumors

- Fibrous tumors of the skeleton are extremely common and exhibit a wide diversity of morphologic variants.

Fibrous Cortical Defect and Nonossifying Fibroma

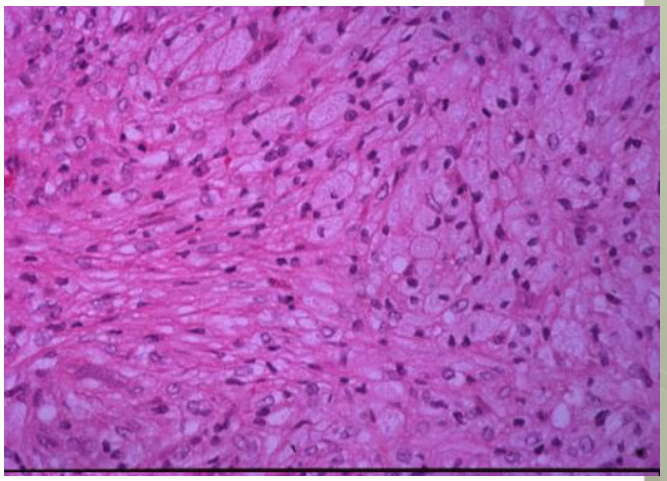
- Fibrous cortical defects are probably developmental abnormalities rather than true neoplasms.
- The vast majority are smaller than 0.5 cm in diameter and arise eccentrically in the metaphysis of the distal femur or proximal tibia; almost 50% are bilateral or multiple.
- Larger lesions (5 to 6 cm)develop into non ossifying fibromas.

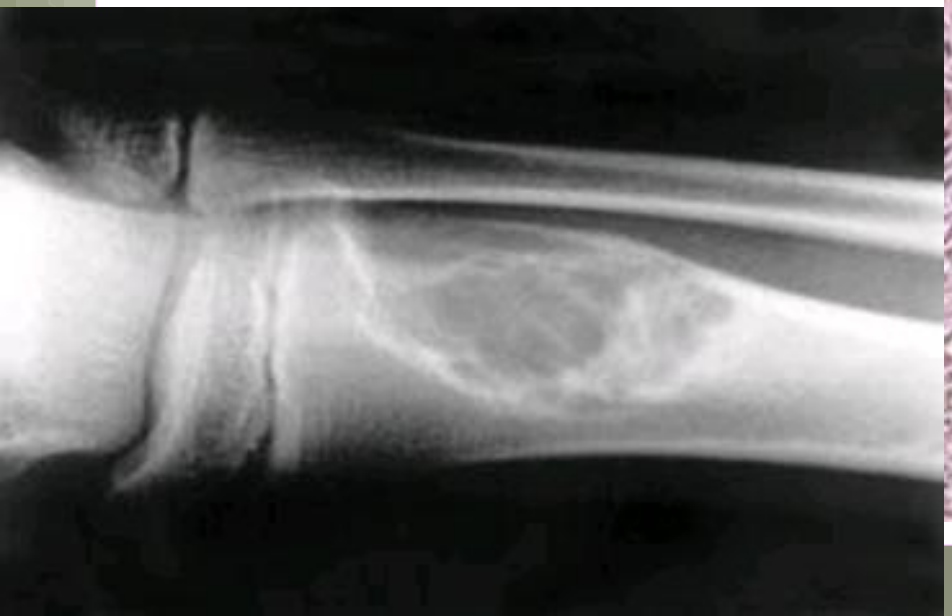
MORPHOLOGY

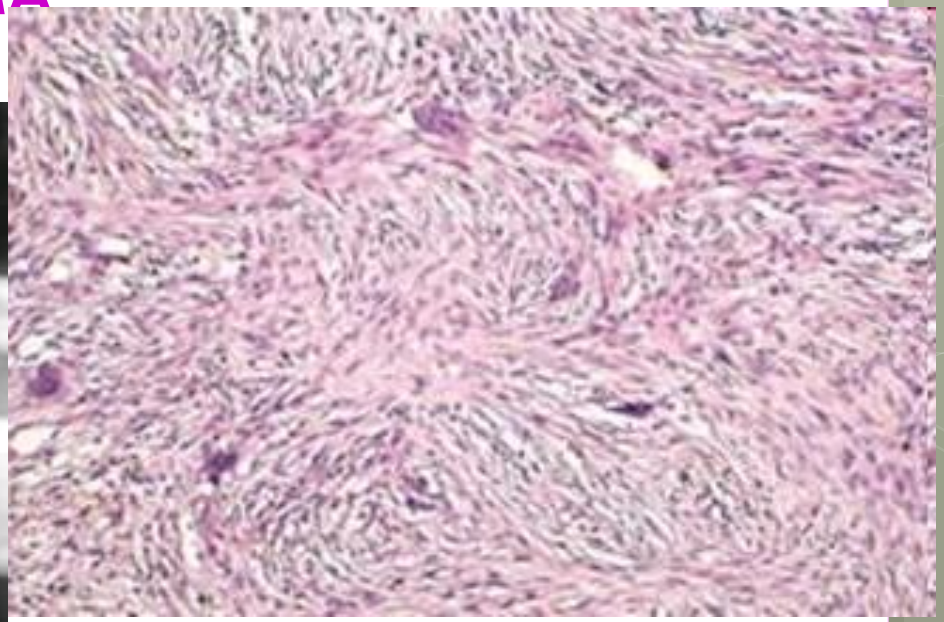
- Fibrous cortical defects and non ossifyingfibromas both manifest
- as sharply demarcated radiolucencies surrounded by a thin zone of sclerosis.
- On gross inspection, they are gray to yellow-brown;
- microscopic examination shows cellularlesions composed of cytologically benign fibroblasts and activated macrophages, including multinucleate forms.
- The fibroblasts classically exhibit a storiform (pinwheel) pattern (Fig. 20-12).
- Hemorrhage and hemosiderin deposits are a common finding.

FIBROUS CORTICAL DEFECT

- COMMON, usually LESS THAN 1 CM
- CHILDREN >2
- IF MORE THAN 5-6 CM, they are then called NON-OSSIFYING FIBROMA







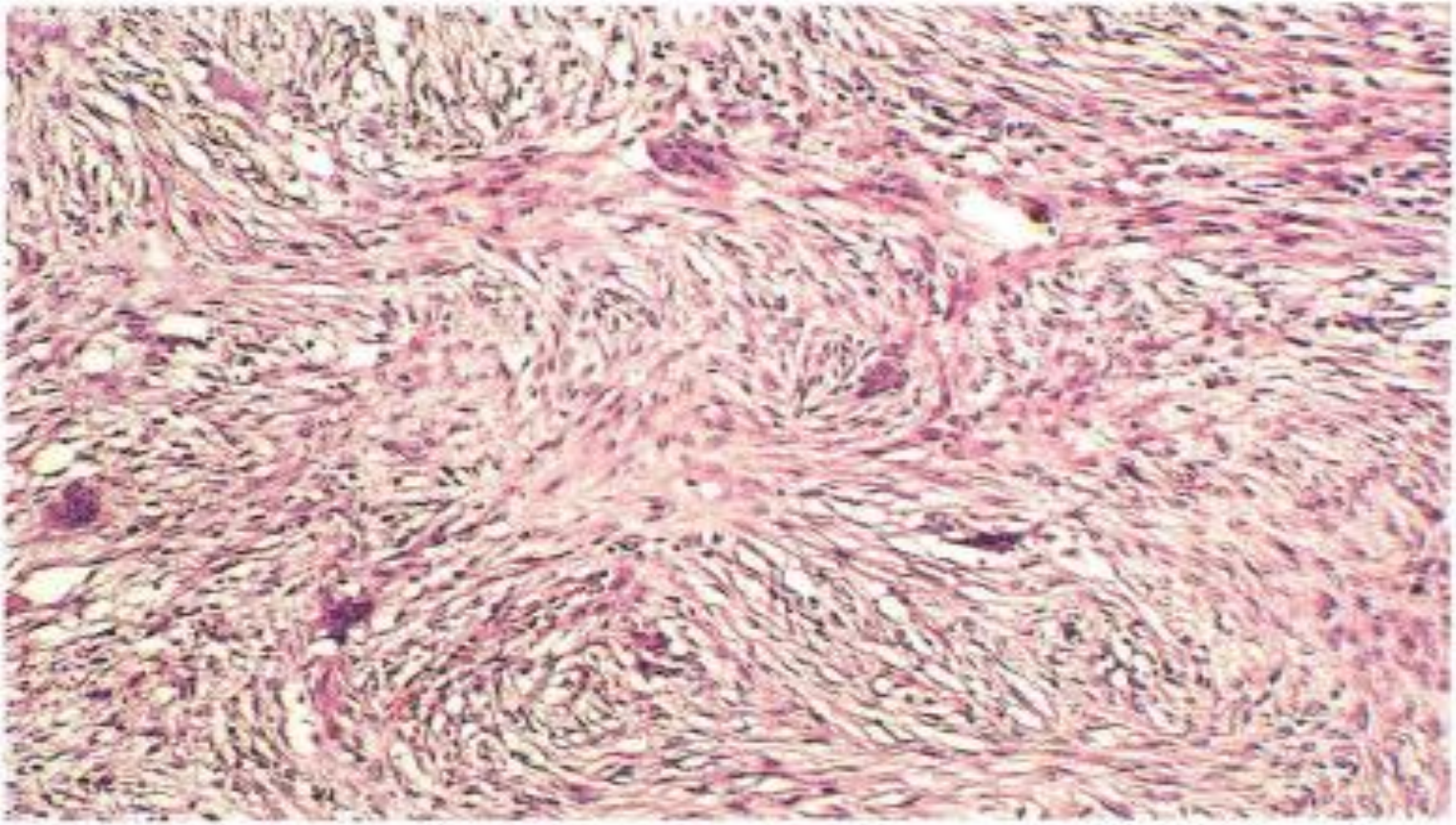


Figure 20–12 Fibrous cortical defect or nonossifying fibroma. Characteristic storiform pattern of spindle cells interspersed with scattered osteoclast-type giant cells.

Clinical Features

- Fibrous cortical defects are asymptomatic and typically are detected only as incidental radiographic lesions.
- The usual clinical course is characterized by spontaneous differentiation into normal cortical bone within a few years,so as a rule, biopsy is not required.
- The few that enlarge into nonossifying fibromas can manifest with pathologic fracture; in such cases, biopsy is necessary to rule out other tumors.

Fibrous Dysplasia

- Fibrous dysplasia is a benign tumor in which all components of normal bone are present, but they fail to differentiate into mature structures.

- Fibrous dysplasia manifests with one of three clinical patterns:
- (1) involvement of a single bone (monostotic)
- (2) involvement of multiple bones (polyostotic)
- (3) polyostotic disease, associated with cafe au lait skin pigmentations and endocrine abnormalities, especially precocious puberty (McCune-Albright syndrome).

- Mutations of the GNAS gene, resulting in a constitutively active Gs protein, are responsible for all forms of fibrous dysplasia.
- The mutation occurs during embryogenesis (somatic mutations) resulting in mosaicism in the fetus and adult.

- The extent of manifestation (mono-ostotic, polyostotic, or McCune-Albright syndrome)depends on
- (1) the stage of embryogenesis when the mutation is acquired
- (2) the fate of the cell harboring the initial mutation.

- Monoostotic fibrous dysplasia accounts for 70% of cases.
- The tumor usually arises during the second and third decades of life;
- there is no gender predilection.
- In descending order of frequency, ribs, femur, tibia, jawbones, calvariae, and humerus are most commonly affected.

- Lesions often are asymptomatic and frequently are discovered incidentally.
- However, fibrous dysplasia can cause marked enlargement and distortion of bone, so that if the face or skull is involved,
- disfigurement can occur, or it can cause pain and pathologic fracture.

- Polyostotic fibrous dysplasia without endocrine dysfunction accounts for a majority of the remaining cases.
- It manifests at a slightly earlier age than that for the monostotic type.
- In descending order of frequency, femur, skull, tibia, and humerus are most commonly involved.

- Craniofacial involvement is present in 50% of patients with moderate skeletal involvement and in 100% of patients with extensive skeletal disease.
- Polyostotic disease tends to involve the shoulder and pelvic girdles, resulting in severe deformities and spontaneous fractures.

- McCune-Albright syndrome accounts for 3% of all cases.
- The associated endocrinopathies include sexual precocity (girls more often than boys), hyperthyroidism, growth hormone-secreting pituitary adenomas, and primary adrenal hyperplasia.

- The severity of manifestations depends on the number and cell types that harbor the G protein mutation.
- The bone lesions may be unilateral, and the skin pigmentation usually is limited to the same side of the body.
- The cutaneous macules classically are large, dark to light brown (cafe au lait), and irregular in configuration.

MORPHOLOGY

- On gross inspection, fibrous dysplasia is characterized by well-circumscribed, intramedullary lesions of varying sizes; large masses expand and distort the bone.

- Lesional tissue is tan-white and gritty-appearing; on microscopic examination, it exhibits curved trabeculae of woven bone (mimicking Chinese characters), without osteoblastic rimming, surrounded by a moderately cellular fibroblastic proliferation (Fig. 20-13).

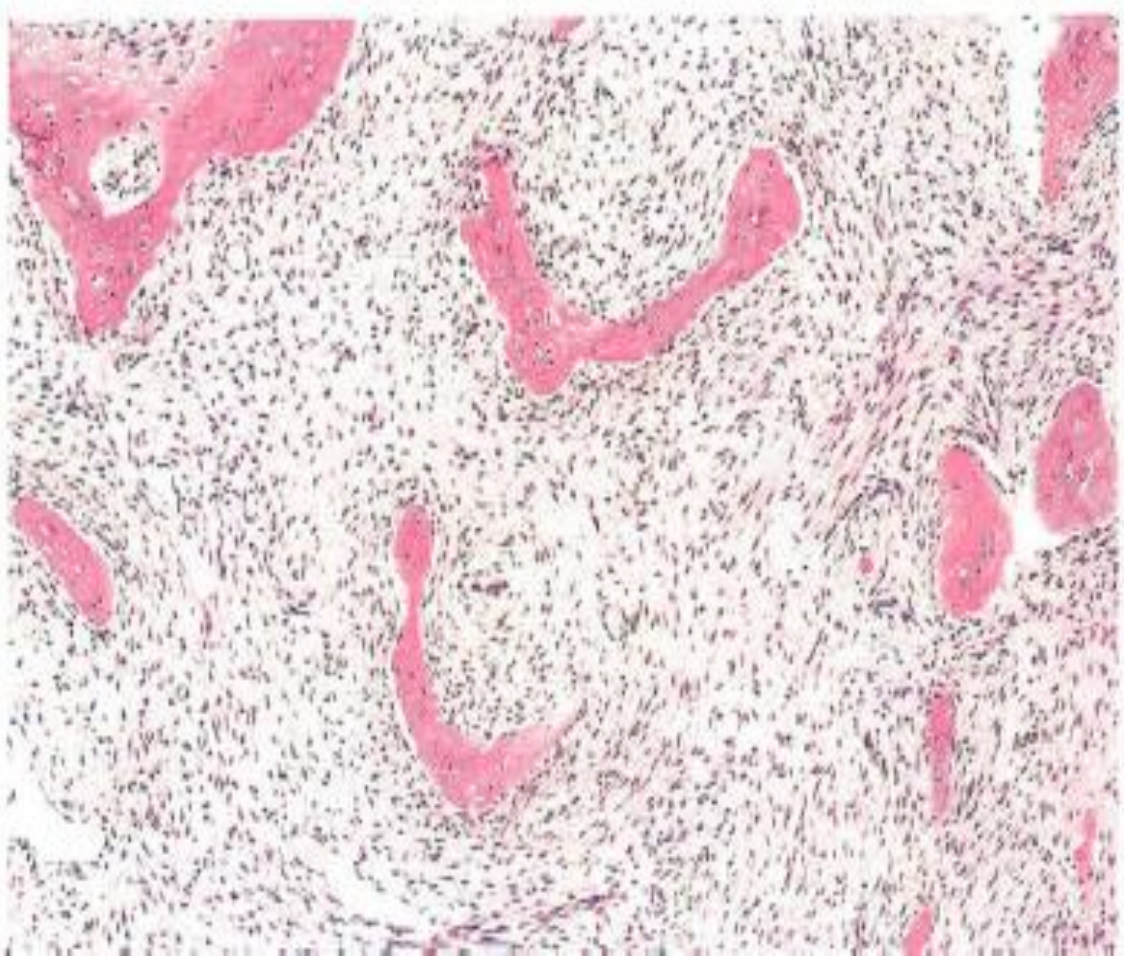


Figure 20-13 Fibrous dysplasia. Curved trabeculae of woven bone arisingin a fIbroustissue. Note the absence of osteoblasts rimming the bone

Clinical Course

- The natural history depends on the extent of skeletal involvement; patients with monostotic disease usually have minimal symptoms.
- On x-ray imaging, lesions exhibit a characteristic ground glass appearance with well-defined margins.
- Symptomatic lesions are readily cured by conservative surgery.

- Polyostotic involvement frequently is associated with progressive disease and more severe skeletal complications (e.g., fractures, long bone deformities, craniofacial distortion).

- Rarely, polyostotic disease can transform into osteosarcoma, especially after radiotherapy.

Miscellaneous Bone Tumors
Ewing Sarcoma and Primitive Neuroectodermal Tumor

- Ewing sarcoma and primitive neuroectodermal tumors (PNETs) are primary malignant small round cell tumors of bone and soft tissue.
- They share certain molecular features (described below) and are best viewed as variants of the same tumor, differing only in degree of neuroectodermal differentiation and clinical features.
- PNETs demonstrate clear neural differentiation, whereas Ewing sarcomas are undifferentiated.

- Ewing sarcoma accounts for 6% to 10% of primary malignant bone tumors.
- After osteosarcoma, it is the second most common pediatric bone sarcoma.
- Most patients are 10 to 15 years of age, and 80% are younger than 20 years.
- Boys are affected slightly more frequently than girls,
- there is a striking racia predilection for whites; blacks and Asians are rarely afflicted.

- The common chromosomal abnormality is a translocation that causes fusion of the EWS gene on 22q12 with a member of the ETS family of transcription factors.
-

- The most common fusion partners are the HI gene on llq24 and the ERG gene on 21q22. The resulting chimeric protein functions as a transcription factor, but precisely how it contributes to oncogenesis remains uncertain; effects on differentiation, proliferation, and survival have all been proposed.

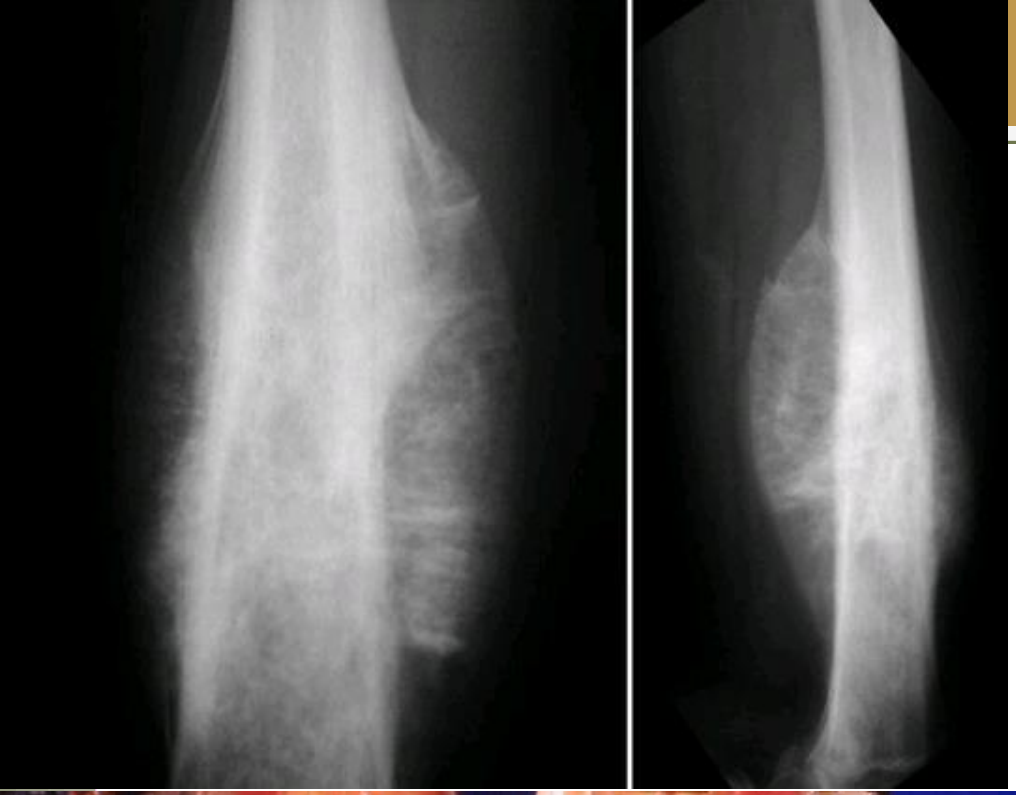
- At a practical level, these translocations are of diagnostic importance, as approximately 95% of tumors have t(11;22)(q24;ql2) or t(21;22) (q22;ql2

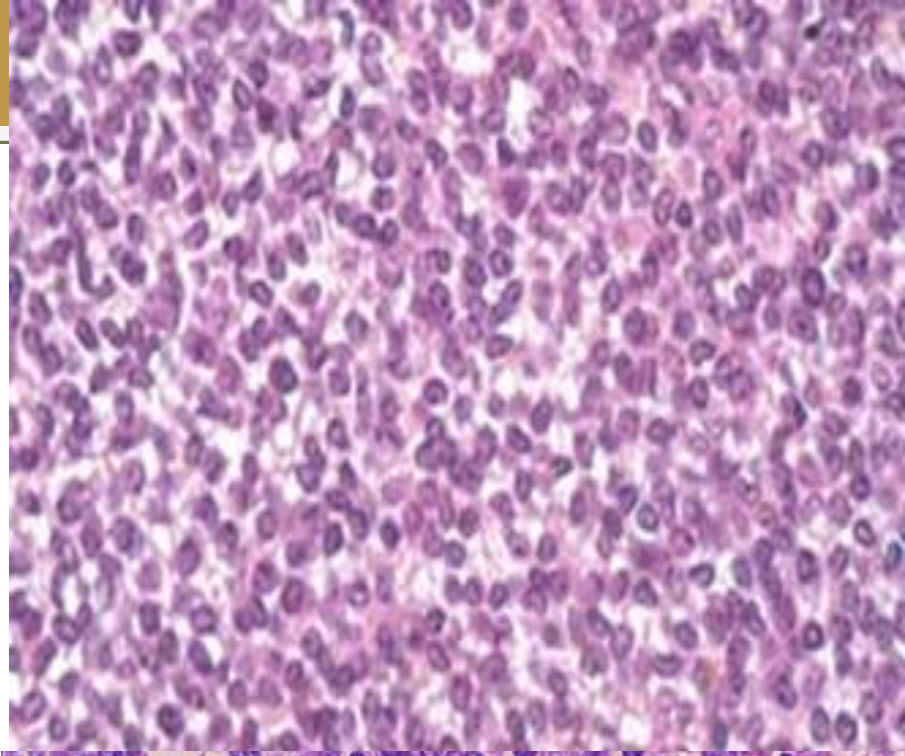
MORPHOLOGY

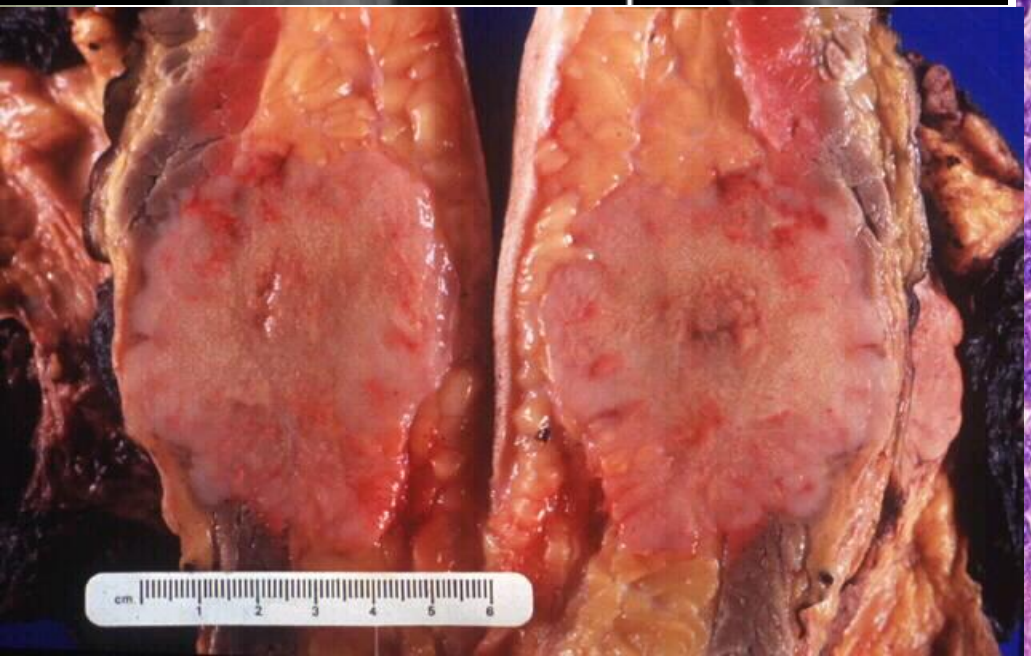
- Ewing sarcoma/PNET arises in the medullary cavity and invades the cortex and periosteum to produce a soft tan white tumor mass, frequently with hemorrhage and necrosis.

- It is composed of sheets of uniform small, round cells that are slightly larger than lymphocytes; typically, there are few mitotic figures and little intervening stroma (Fig. 20-14).

- The cells have scant glycogen-rich cytoplasm.
- The presence of Homer-Wright rosettes (tumor cells circled about a central fibrillary space) indicates neural differentiation



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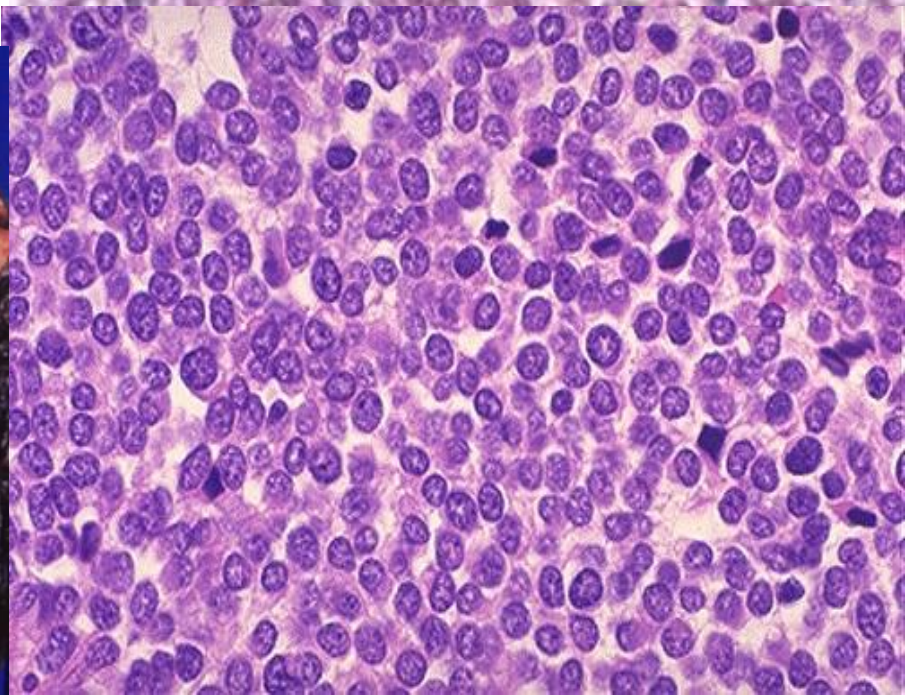


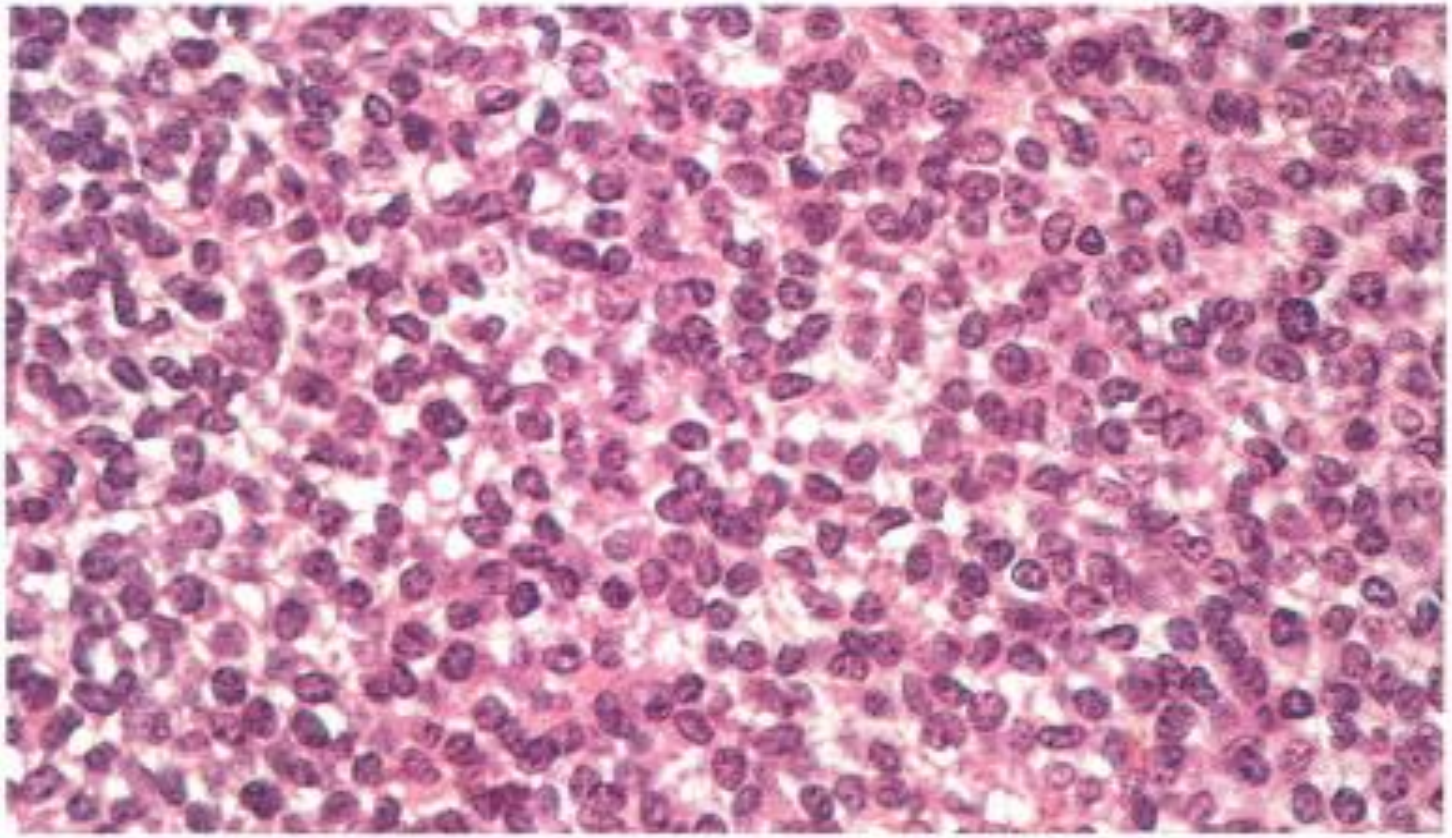


Figure 20-14 Ewingsarcoma. Sheets of small round cells with scant.clear cytoplasm.

Clinical Features

- Ewing sarcoma/PNET typically manifests as a painful enlarging mass in the diaphyses of long tubular bones (especially the femur) and the pelvic flat bones.

- Some patients have systemic signs and symptoms suggestive of infection. Imaging studies show a destructive lytic tumor with infiltrative margins and extension into surrounding soft tissues.

- There is a characteristic periosteal reaction with deposition of bone in an onion-skin pattern.
- Treatment includes chemotherapy and surgical excision with or without irradiation. The 5-year survival rate is currently 75% for patients presenting with localized tumors.

Giant Cell Tumor of Bone

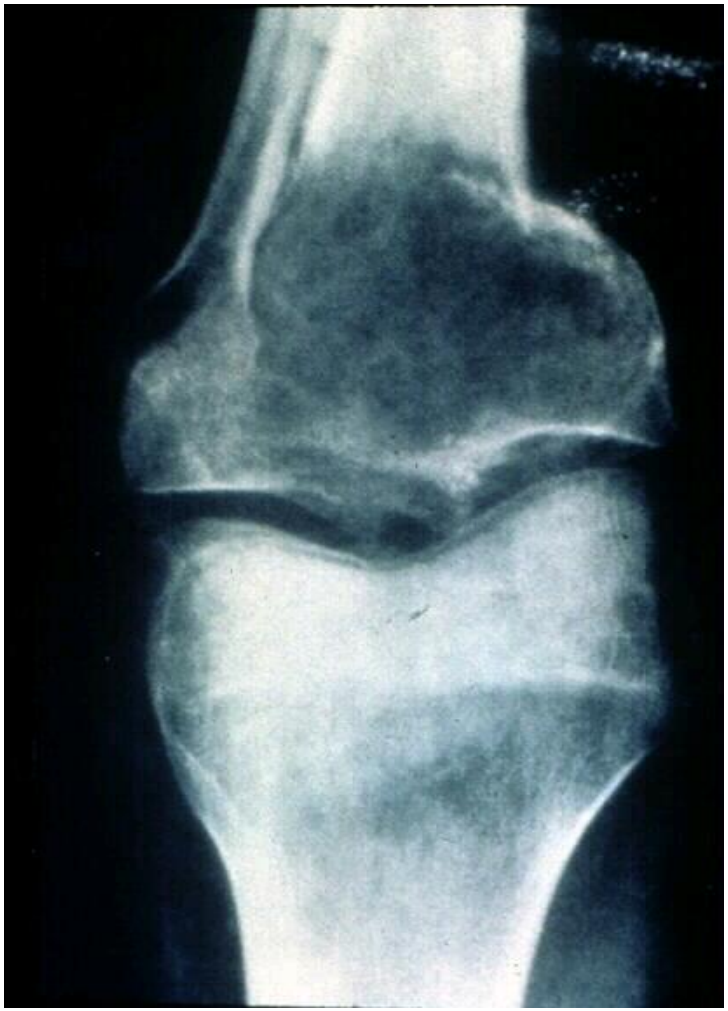
- Giant cell tumors (GCTs) contain prominent by multinucleate osteoclast-type giant cells - hence the synonym osteoclastoma.
- GCT is a relatively common benign but locally aggressive bone tumor,
- usually arising in persons in their 20s to 40s.
-

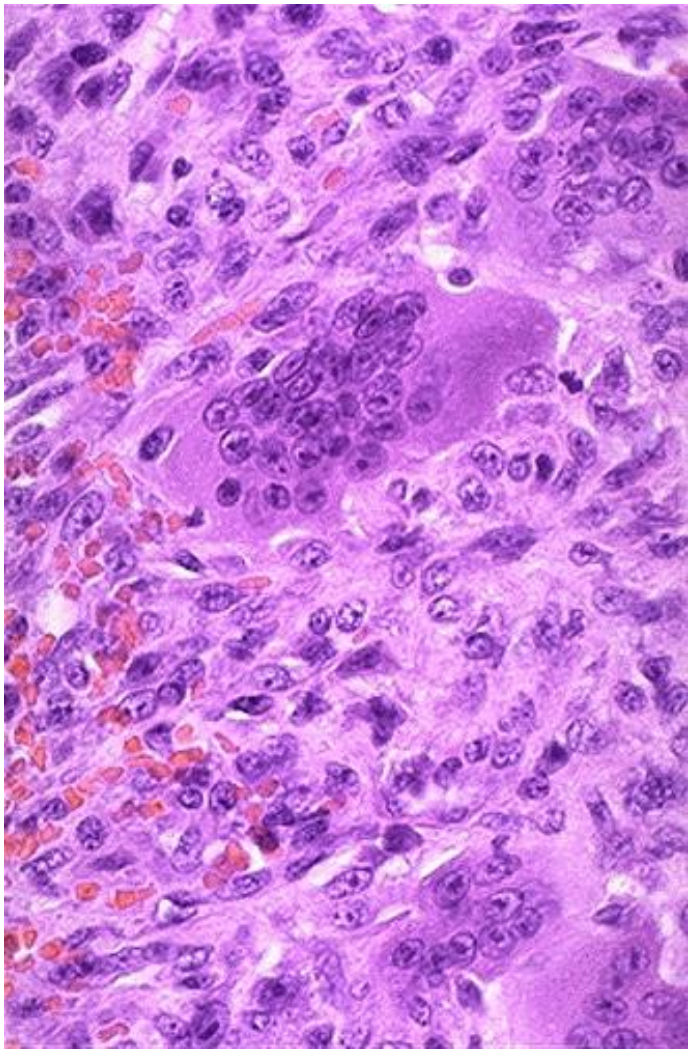
- Despite the name, molecular analyses have shown that it is the mononuclear cells in the tumor that are neoplastic.
- These cells may be related to osteoblast precursor cells, as they express RANK ligand, which may stimulate the development of surrounding non-neoplastic osteoclast-like cells

MORPHOLOGY

- GeTs are large and red-brown, and often show cystic degeneration.
- They are composed of uniform oval mononuclear
- cells and scattered osteoclast-type giant cells containing 100or more nuclei (Fig. 20-15). Mitotic figures are typically frequent.
- Necrosis. hemorrhage. and reactive bone formation also are commonly present.

GCT (Giant Cell Tumor), BONE





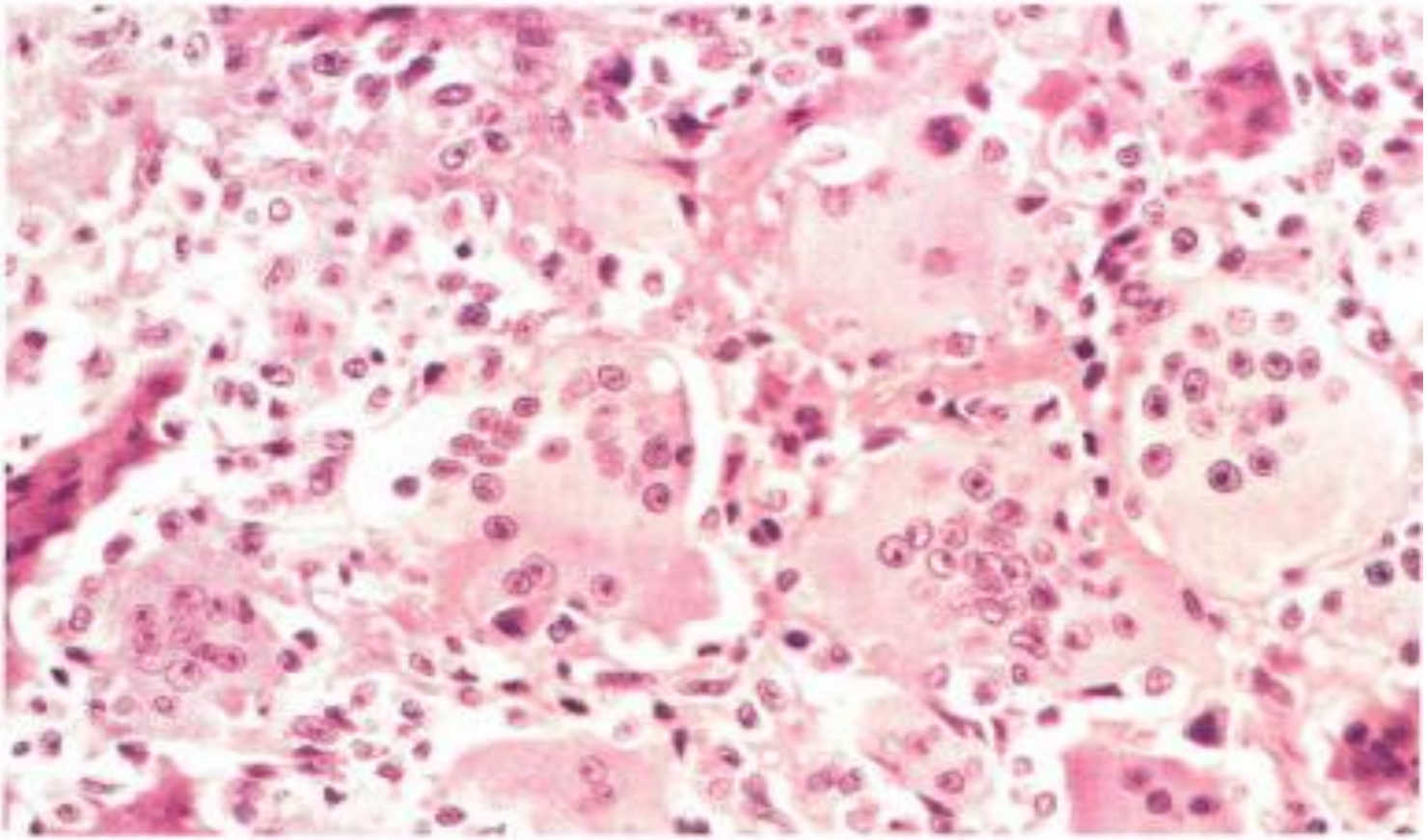


Figure 20-1 5 Benigngiant celltumor showingabundant multinucleate giant cellsand a backgroundof mononuclearcells.

Clinical Course

- Although almost any bone may be involved, a majority of GCTs arise in the epiphysis and involve the metaphysis of long bones around the knee (distal femur and proximal tibia), frequently cilusing pain.

- Occasionally, GCTs manifest with pathologic fractures.
- Most are solitary tumors.
- Radiographically, GCTs ilre lilrge, purely lytic, and eccentric;
- the overlying cortex frequently is destroyed, producing a bulging soft tissue mass with a thin shell of reactive bone.
- Although GCTs are considered benign, roughly half recur after simple curettage, and as many as 2% spread to the lungs as lociolized lesions that are cured by local excision.

Metastatic Disease

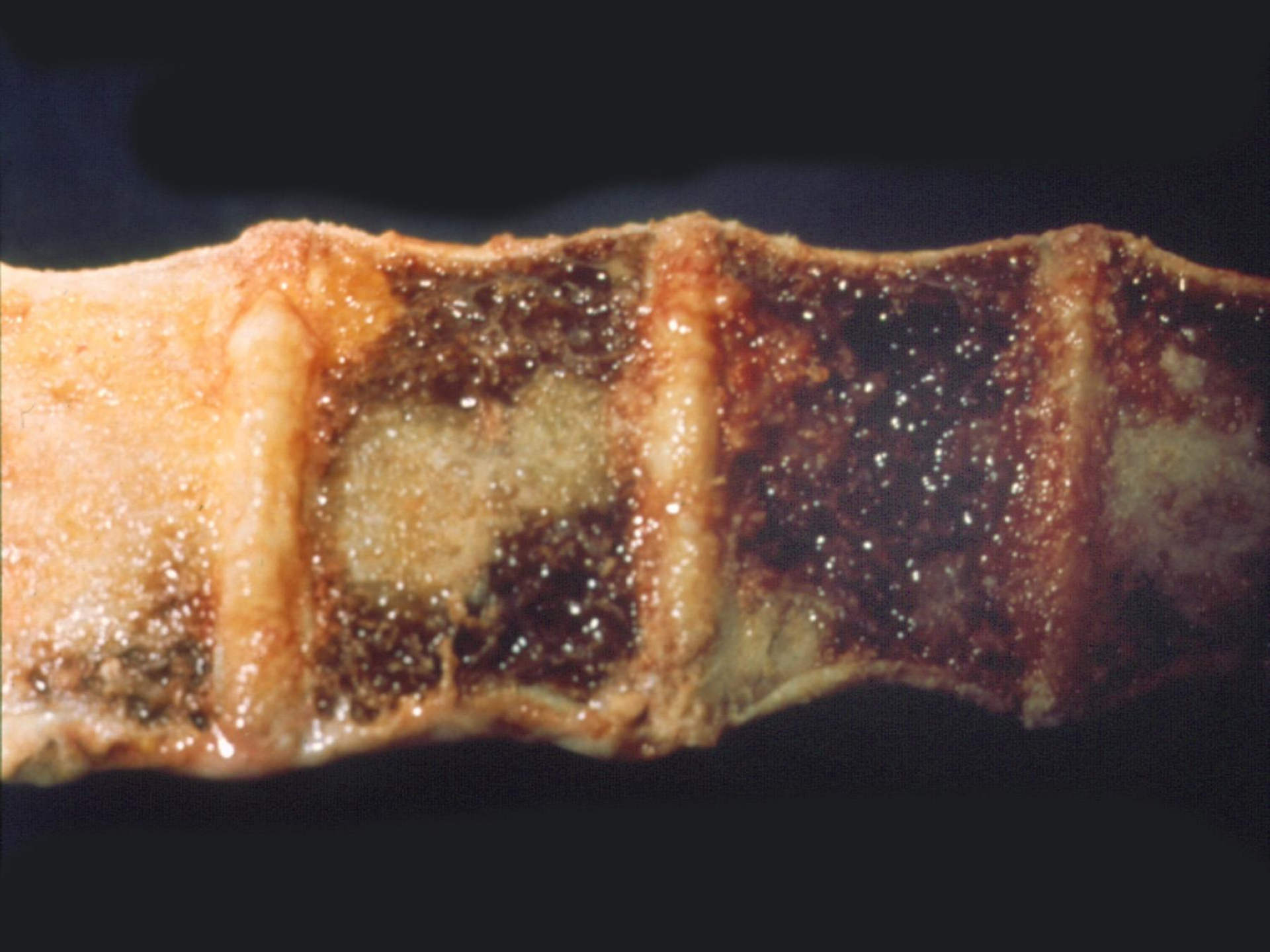
- Metastatic tumors are the most common malignant tumors involving bone. Pathways of spread include
- (1) direct extension,
- (2) lymphatic or hematogenous dissemination,
- (3)intraspinal seeding.
- Any cancer can spread to bone, but certain tumors exhibit il distinct skeletal predilection.

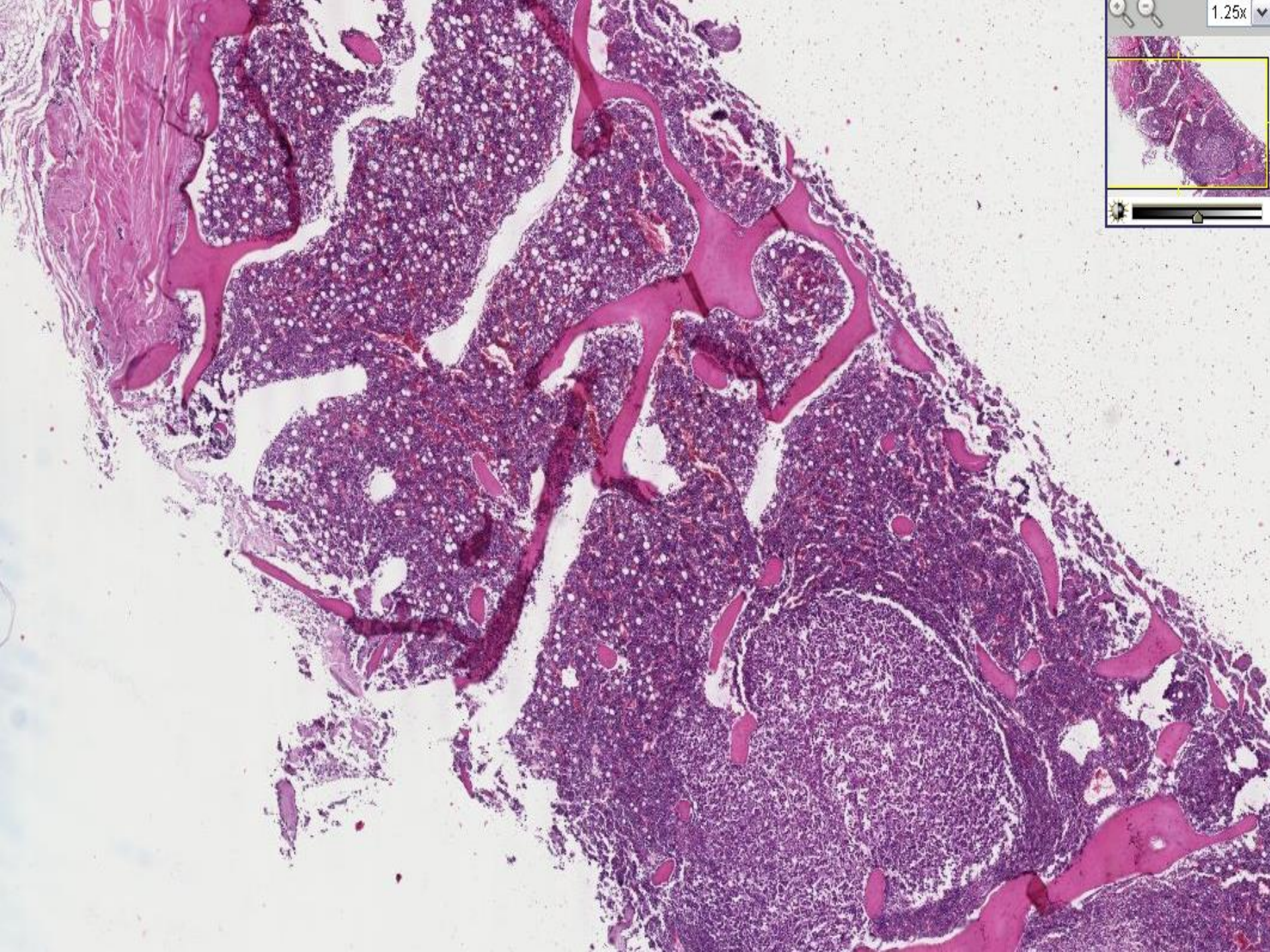
- In adults more than 75% of skeletal metastases originate from cancers of the prostate, breast, kidney, and lung.
- In children, neuroblastoma, Wilms tumor, osteosarcoma, Ewing sarcoma, and rhabdomyosarcoma are the common sources of bony metastases.

- Most metastases involve the axial skeleton (vertebral column, pelvis, ribs, skull, sternum), proximal femur, and humerus, in descending order.
- The red marrow in these areas, with its rich capillary network, slow blood flow, and nutrient environment rich in growth factors, facilitates tumor cell implantation and growth.

- The radiologic appearance of metastases can be purely lytic, purely blastic, or both.
- In lytic lesions (e.g., with kidney and lung tumors and melanoma), the metastatic cells secrete substances such as prostaglandins, interieukins, and PTH-related protein (PTHrP) thilt stimulate osteoclastic bone resorption; the tumor cells themselves do not directly resorb bone.

- Similarly, metastatic tumors that elicit an osteoblastic response (e.g., prostate adenocarcinoma) do so by stimulating osteoblastic bone formation.
- Most metastases induce a mixed lytic and blastic reaction.

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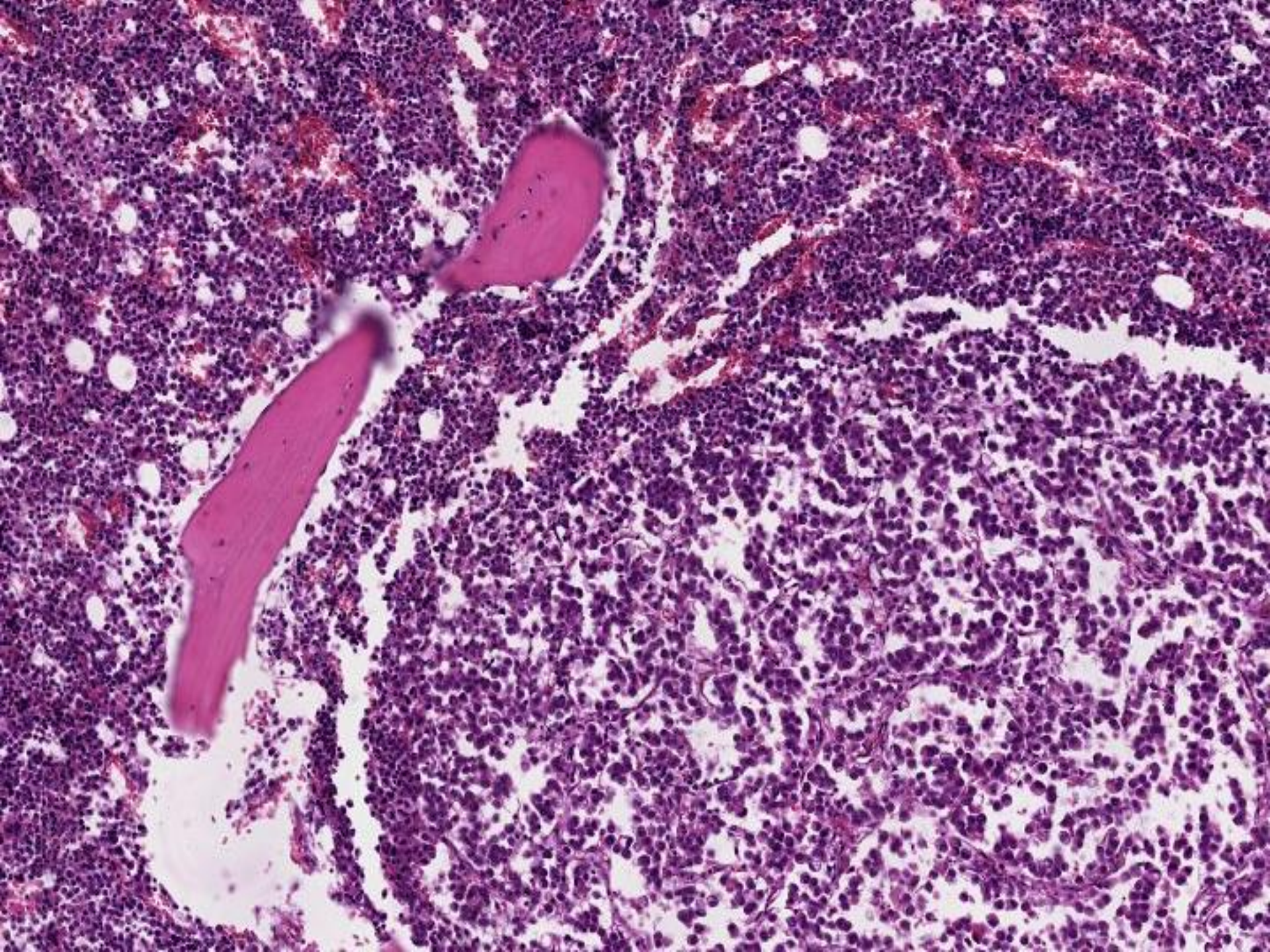

ANY QUESTION