BONE TUMORS

- Primary bone tumors > metastases from other sites
- *Primary bone tumors widely range -from benign to malignant.*
- Classified according to the normal cell counterpart and line of differentiation.
- Among the **benign** tumors, osteochondromas are most common.
- Osteosarcoma is the most common **primary** bone **cancer**, followed by chondrosarcoma and Ewing sarcoma.
- Benign tumors > malignant (esp. before age 40 yr)
- Bone tumors in elderly are much more likely to be malignant.

- Most bone tumors occur in 1st few decades of life, with few tumors exceptionally affect adults

- Mostly originate in long bones of extremities.
- One of the exceptions: Chondrosarcomas tend to develop during mid- to late adulthood and involve the trunk, limb girdles, and proximal long bones.

- Most bone tumors arise without any previous known cause (no known risk factors)

- **Risk factors of bone cancers** (esp. osteosarcoma) include:
- genetic syndromes (e.g., Li-Fraumeni and retinoblastoma syndromes)→ associated with osteosarcomas
- bone infarcts
- chronic osteomyelitis
- Paget disease
- irradiation
- use of metal orthopedic devices

- **Clinical presentation**

- benign lesions frequently are **asymptomatic** and are detected as **incidental** findings.
- Others produce **pain** or a slowly growing **mass**.
- Occasionally, a pathologic **fracture** is the first manifestation.

- **Radiologic imaging :** critical in the evaluation of bone tumors
- **biopsy** and histologic study and, in some cases, molecular tests are necessary for diagnosis

Bone-Forming Tumors

- **The tumor cells in these neoplasms produce *bone***

- ***Osteomas*** **:**
- **benign**
- **most common in head and neck (e.g. paranasal sinuses).**
- **present in middle age**
- **solitary, slowly growing, hard, exophytic masses on bone surface.**
- **On histologic examination: are composed of a mixture of bone.**
- **may cause local mechanical problems (e.g., obstruction of a sinus cavity) and cosmetic deformities**
- **are not locally aggressive; do not undergo malignant transformation.**

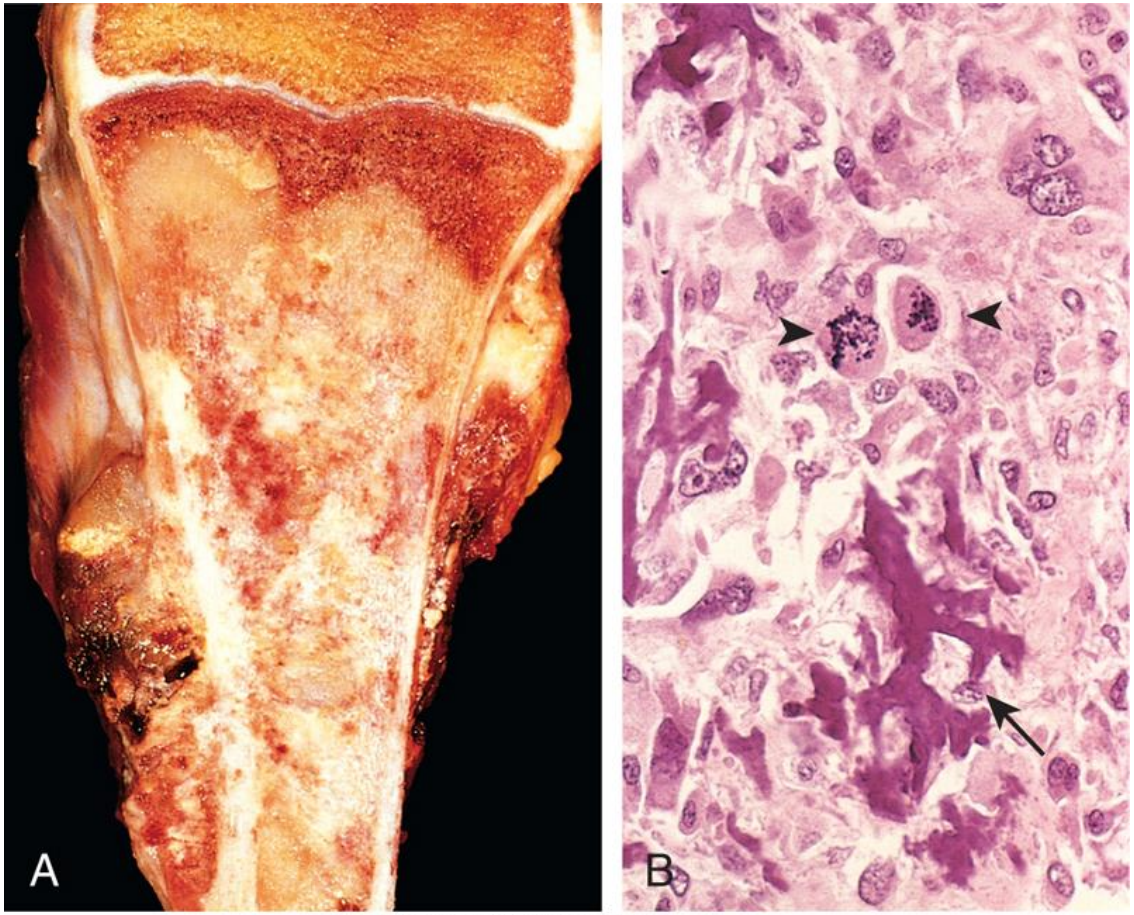
Osteoid osteomas and *osteoblastomas*

- are benign neoplasms with very similar histologic features.
- teenage years and 20s
- a male predilection (2:1).
- They are distinguished from each other by their size and clinical presentation:
- ***Osteoid osteomas:*** arise beneath the periosteum or in the cortex in the proximal femur and tibia; **by definition less than 2 cm in diameter ;** Localized **pain**, most severe at night, usually is **relieved by aspirin**.
- ***Osteoblastomas:*** are **larger**; mostly in the **vertebral** column; they also cause **pain**, although it often is more difficult to localize and is **not** responsive to aspirin.
- **Microscopically**: both neoplasms are composed of interlacing trabeculae of bone surrounded by osteoblasts; vascular connective tissue contains variable numbers of giant cells.
- **Treatment:** Local excision; incompletely resected lesions can recur.
- Malignant transformation is **rare**

Osteosarcoma

- *is a bone-producing malignant tumor.*
- the most common primary malignant tumor of bone (20% of primary bone cancers- After myeloma and lymphoma)
- 75% of patients are **younger than 20 years** of age
- a second peak occurs in elderly persons, usu. with risk factors (including: Paget disease, bone infarcts, and previous irradiation).
- **Men** > than women (1.6:1).
- Most tumors arise in the **metaphyseal region of the long bones of the extremities** (60% **knee**, 15% hip, 10% shoulder, and 8% jaw.).
- the most common form of osteosarcoma is poorly differentiated, producing a predominantly bony matrix

lacelike pattern of neoplastic bone (*arrow*) produced by anaplastic tumor cells. Note the wildly abnormal mitotic figures (*arrowheads*).



Morphology

- **The production of bone (osteoid) by malignant cells is essential for diagnosis of osteosarcoma**
- Cartilage and fibroblastic differentiation can also be present in varying amounts.

PATHOGENESIS

- usu. develop at sites of greatest bone growth
- Several mutations are associated with osteosarcoma:

1- ***RB*** **gene mutations→ most common** (60% to 70% of sporadic cases); hereditary retinoblastomas (germline mutations in the *RB* gene have a thousand-fold greater risk for osteosarcoma).

2- **mutations in** ***TP53*** **(in** spontaneous osteosarcomas)

3- **mutations in genes that regulate the cell cycle. (e.g.** cyclins, CDKs, and kinase inhibitors).

Clinical Features

- painful enlarging mass (most typical pesentation)
- a pathologic fracture can be the first sign.

- **Radiographic image** ➔ a large, destructive, mixed lytic and blastic **mass** with infiltrating margins.

- The tumor may break through the cortex and lift 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 pulmonary metastases

- **Standard treatment**: Despite aggressive behavior, chemotherapy and limb salvage therapy currently yields long-term survivals of 60% to 70%.

- **Secondary osteosarcomas:**
- occur in older adults
- Ass. With risk factors, most commonly Paget disease or previous radiation exposure.
- are highly aggressive tumors
- they do **not** respond well to therapy and are usually fatal.

Cartilage-forming tumors

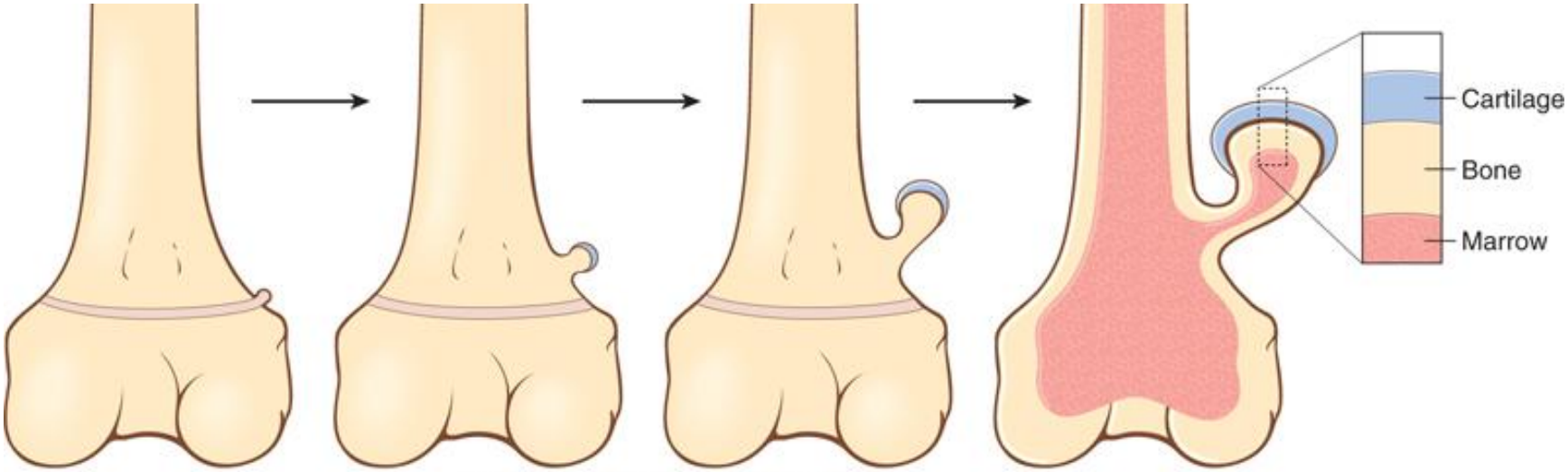
- produce cartilage
- a spectrum from benign, self-limited growths to highly aggressive malignancies
- benign cartilage tumors > than malignant ones.

- **Osteochondromas (exsostosis):**
- are common benign, cartilage-capped tumors attached by a bony stalk to the underlying skeleton.
- late adolescence and early adulthood
- male-to-female ratio of 3:1
- Inactivation of both copies of ***EXT1*** or ***EXT2*** genes in chondrocytes of the growth plate (tumor suppressor genes encode proteins essential for polymerization of heparan sulfate).

Osteochondromas

- develop only in bones of **endochondral** origin
- at the metaphysis near the growth plate of long bones
- most common about the knee
- tend to stop growing once the normal growth of the skeleton is completed
- **Clinical features:**
- Usually incidental findings.
- slow-growing mass, can be painful if impinge on a nerve or if the stalk is fractured.
- **Rarely** progress to chondrosarcoma or other sarcomas
- Malignant transformation occurs more frequently in multiple hereditary osteochondromas

The development of an osteochondroma, beginning with an outgrowth from the epiphyseal cartilage



Chondromas

- are benign neoplasms of hyaline cartilage.
- *Enchondromas* → arise within the medulla;
- *juxtacortical chondromas* → when on the bone surface
- usually diagnosed in 20s to 50s
- the metaphyseal region of tubular bones
- favored sites: **the short tubular bones of the hands and feet.**
- **Hereditary chondromas:**
- *Ollier disease= multiple chondromas* involving one side of the body
- *Maffucci syndrome = multiple chondromas associated with soft tissue spindle cell hemangiomas*

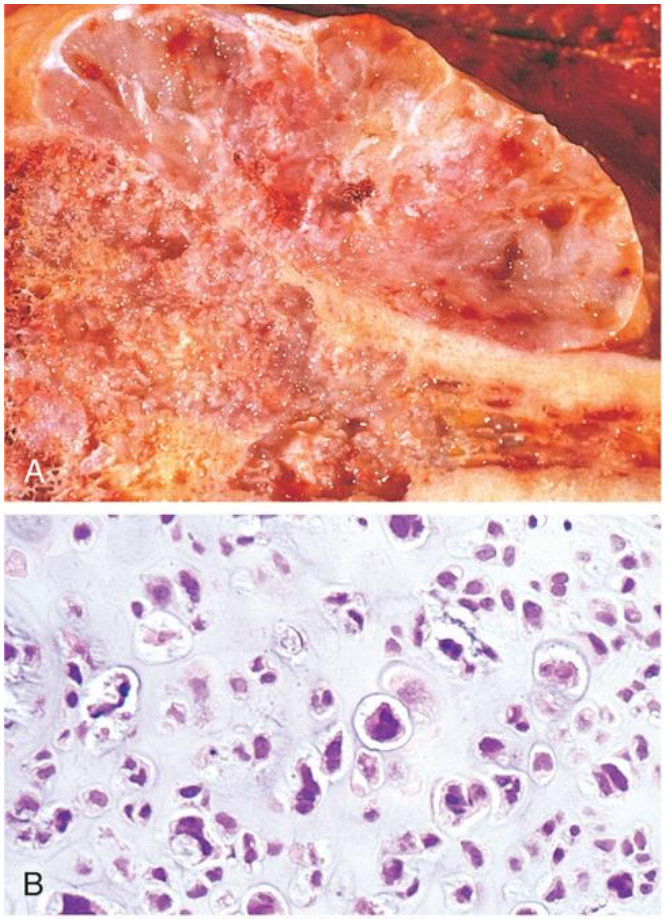
- MORPHOLOGY
- gray-blue, translucent nodules usually < 5 cm.
- Microscopically: well circumscribed, composed of hyaline cartilage containing cytologically benign chondrocytes.
- In the hereditary multiple chondromatoses→greater cellularity and atypia (difficult to distinguish from chondrosarcoma)
- Clinical features:
- incidental findings; occasionally painful or cause pathologic fractures.
- On x-ray: well-circumscribed oval lucencies surrounded by thin rims of radiodense bone (*O-ring sign*).
- Solitary chondromas→ rarely malignant transformation,
- hereditary enchondromatoses→ increased risk of malignant transformation

Chondrosarcoma

- a malignant sarcoma whose cells produce neoplastic cartilage.
- most pts are age 40 or older
- men to women ratio is 2:1
- commonly arise in the pelvis, shoulder, and ribs; **rarely** involve the distal extremities.
- painful, progressively enlarging masses.
- destroy the cortex and forms a soft tissue mass
- chondrosarcomas are either:
- **low-grade**: 5-year survival rate of 80- 90%; rarely metastasize; smaller than 10 cm
- **high-grade**: 5-year survival rate of 40%; metastasis in 70%; usu. larger than 10 cm
- metastasize hematogenously (esp. to lungs and skeleton).
- **Treatment**: wide surgical excision; chemotherapy is added for the aggressive variants

Chondrosarcoma-- Morphology:

form an expansile glistening mass that often erodes the cortex. It is composed of malignant hyaline and myxoid cartilage



Metastatic tumors of bone

- *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 a distinct skeletal preference.
- In adults: 75% of bone mets→ prostate, breast, kidney, and lung cancers.
- In children→ neuroblastoma, Wilms tumor, Ewing sarcoma, and rhabdomyosarcoma.
- Most common sites for mets→ the axial skeleton (vertebral column, pelvis, ribs, skull, sternum); proximal femur, and humerus

- **The radiologic appearance**: can be purely lytic, purely blastic, or both.
- lytic lesions (e.g., kidney and lung tumors and melanoma)➔ HOW? the metastatic cells secrete substances (e.g. prostaglandins, interleukins, and PTH-related protein (PTHrP)) that stimulate osteoclastic bone resorption; the tumor cells themselves do **not** directly resorb bone.
- Mets with osteoblastic response (e.g., prostate ca) do so by stimulating osteoblastic bone formation.
- Many metastases induce a mixed lytic and blastic reaction