Unit VII – Problem 6 – Pathology: Bone Tumors

- **Classification of bone tumors:**
  - **Age-gender-bone-site related classification.**
  - **Behavioral classification:**

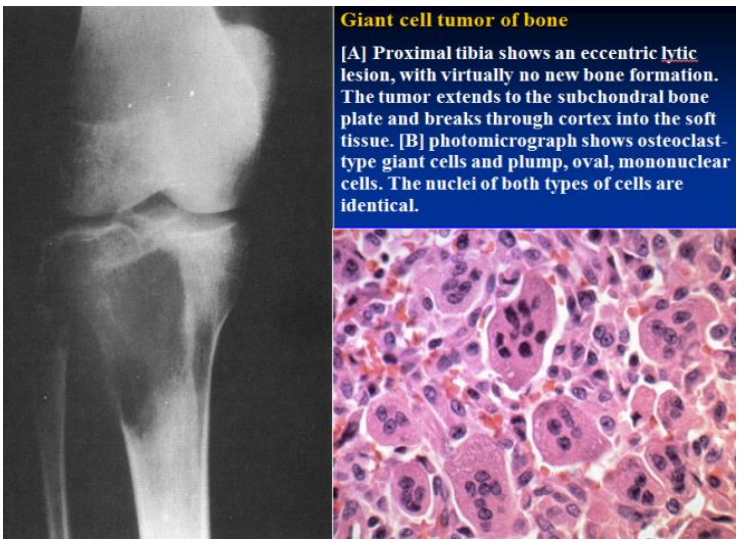
0	Benign
1	Unknown behavior (whether benign or malignant)
2	Non-invasive/ in situ
3	Primary malignant
6	Metastatic tumors
9	Unknown whether the malignant tumor is primary or metastatic

  - **Histogenesis-based classification:**
    - ✓ Bone-forming tumors:
      - ❖ *Benign*: osteomas (slow-growing benign tumors composed of compact cortical type of bone), osteoid-osteoma, osteoblastoma.
      - ❖ *Malignant*: osteosarcoma.
    - ✓ Cartilage-forming tumors:
      - ❖ *Benign*: enchondroma (composed of well-differentiated hyaline cartilage), enchondromatosis, osteochondroma, chondroblastoma, chondromyxoid fibroma.
      - ❖ *Malignant*: chondrosarcoma.
    - ✓ Giant cell tumors (osteolastomas): producing lytic multiloculated lesion of the bone.
    - ✓ Bone marrow tumors: Primitive Neuroectodermal Tumors of Childhood (PNET) or also known as Ewing sarcoma, lymphoma, leukemia, myeloma.
    - ✓ Vascular tumors:
      - ❖ *Benign*: hemangioma, lymphanioma, hemangioendothelioma, hemangiopericytoma.
      - ❖ *Malignant*: angiosarcoma.
    - ✓ Other connective tissue tumors:
      - ❖ *Benign*: desmoplastic fibroma, infantile myofibromatosis, muscle and adipose tissue tumors.
      - ❖ *Malignant*: fibrosarcoma, malignant fibrous histiocytoma.
    - ✓ Other primary tumors: lymphomas, adamantinoma of long bone, peripheral nerve tumors, xanthoma, fibrocatilagenous mensenchymoma.
    - ✓ Metastatic tumors.
  - **Tumor-like lesions of the bone (all of them produce lytic lesions of the bone)**
    - ✓ Fibrous dysplasia.
    - ✓ Metaphyseal fibrous defect (non-ossifying fibroma):
      - ❖ Benign tumor of childhood occurring in the metaphysis of long bones (commonly femur & tibia) and characteristically regress thereafter.
    - ✓ Eosinophilic granuloma.
    - ✓ Bone cysts:
      - ❖ *Aneurysmal bone cyst.*
      - ❖ *Simple (unicameral) bone cyst.*
      - ❖ *Subchondral cyst.*
      - ❖ *Ganglion cyst of bone.*
- **Principles in the diagnosis of bone tumors:**
  - **Age of the patient (adult vs child).**
  - **Bone involved.**
  - **Specific anatomic location**: epiphysis, metaphysis, diaphysis, cortex, medulla, periosteum.
  - **Radiological appearance:**
    - ✓ Onion skin of Ewing sarcoma.

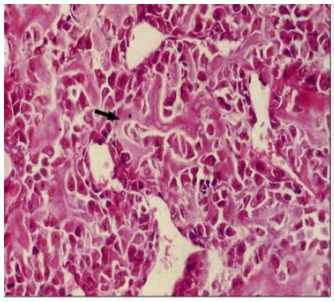
- ✓ Sunburst of osteosarcoma.
- ✓ Codman's triangle.

- **Histogenesis of tumor**: developmental, defective, neoplastic… etc.
- **Biopsy procedure and microscopic appearance.**
- **Immunohistochemistry, cytogenetics, molecular studies.**
- **Tumor-like conditions.**
- **Clinical-radiological-pathological correlation.**

- **Presentation of bone tumors:**
  - **Clinical presentation**: asymptomatic, pain, functional limitations of movements, local swelling, pathological fracture, vertebral collapse, metastasis.
  - **Radiological appearance.**
  - **Laboratory findings:**
    - ❖ ↑ serum alkaline phosphatase: secreted by osteoblasts in carcinoma of the breast and lung.
    - ❖ ↑ serum acid phosphatase: secreted by neoplastic cells of prostatic carcinoma.
- **Pathogenesis of bone tumors:**
  - **Most malignant bone tumors arise de novo** (starting from the beginning) but some tumors arise within pre-existing conditions.
  - **There are some predisposing benign bone lesions which can transform to malignancy such as:**
    - ✓ Paget's disease.
    - ✓ Chondromatosis (benign cartilage-forming tumor).
    - ✓ Osteochondromatosis.
    - ✓ Fibrous dysplasia (tumor-like lesion).
    - ✓ Osteofibrous dysplasia.
  - **Malignant bone tumors can also be caused by exposure to radiation such as:**
    - ✓ Radium: in watch makers.
    - ✓ External therapeutic radiation.
  - **Following prosthesis in hip replacement.**
  - **Genetic implication:**
    - ✓ Ewing's sarcoma: t(11,22) and t(21,22).
  - **Pathogenesis of osteosarcoma:**
    - ✓ Rb suppressor gene: especially in children treated with chemotherapeutic alkylating agents for retinoblastoma and other malignancies.
    - ✓ Mutation in p53 gene.
    - ✓ Amplification of MDM2, CDK-4, PRIM.
    - ✓ Overexpression of MET and POS
- **Giant cell tumors of bone (details):**
  - Locally aggressive, potentially malignant tumors characterized by the presence of osteoclastic giant cells in a background of proliferating mononuclear cells.
  - These tumors usually originate at the junction between epiphysis and metaphysis of long bones (especially in humerus, distal end of the radius, knee area and fibula).
  - **Pathogenesis**: two lineages of mononuclear stromal cells:
    - ✓ Non-neoplastic macrophage monocyte system.
    - ✓ Cells with chromosomal abnormalities and molecular alterations in oncogens (TP53 and c-myc).



- **Osteosarcoma (details):**
  - Arises proximal to the knee (but any other metaphysis can be affected).
  - There will be bone destruction and neoplastic bone formation due to the mutations which will result in the pathogenesis of this disease (mentioned above).
  - **Gross appearance:**
    - ✓ Variable: depending on the amount of neoplastic bone which is found, cartilage, stroma and blood vessels.
    - ✓ Cut surface: combination of hemorrhagic, cystic, soft and bony areas.

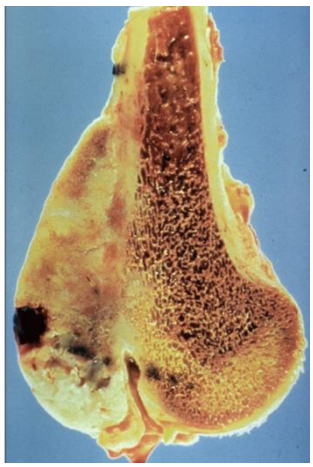


Osteosarcoma.
Cut surface and histological appearances of a rapidly growing tumour in the distal femur of a 16 years old boy

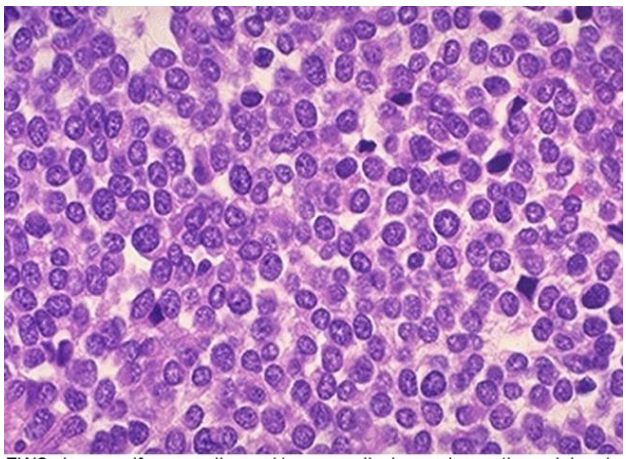
  - **Microscopy:**
    - ✓ Malignant osteoblasts forming malignant osteoid and tumor bone (which is woven and lack structural arrangement).
    - ✓ There are also malignant giant cells and malignant cartilage.
    - ✓ Immunohistochemistry: malignant cells stain for alkaline phosphatase and osteonectin.
  - **Spread:**
    - ✓ Direct into: bone marrow, periosteum, epiphysis and joint space.
    - ✓ Direct to nearby structures: muscle, nerve or soft tissue.
    - ✓ Blood stream metastasis to lungs.

- **Juxtacortical osteosarcoma:**
  - Variant of osteosarcoma occur on periosteal surface of bone particularly lower posterior metaphysic of femur.
  - Low-grade lesion which does not invade the cortex or medulla of bone but grows externally to the shaft.
  - No Codman's triangle because the periosteum is not elevated.

Juxtacortical osteosarcoma
The lower femur contains a malignant tumor arising from the periosteal surface of the bone and sparing the medullary cavity.



- **Ewing's sarcoma (PNET):**
  - Occurs as midshaft or metaphyseal lesion.
  - Tends to parallel the distribution of red marrow.
  - Tumor cells are rich in glycogen.
  - Onion-skin appearance: represents alternate circumferential discontinuous layer of periosteal new bone and lytic bone.



EWS shows uniform small round tumour cells, hyperchromatic nuclei and poorly defined (glycogen-rich) cytoplasm

- **Metastatic bone tumors:**
  - Commonest malignant bone tumors.
  - Mostly carcinomas (thyroid, breast, lung, kidneys and prostate).
  - Carried by blood stream.
  - Commonly vertebral column and end of long bones.