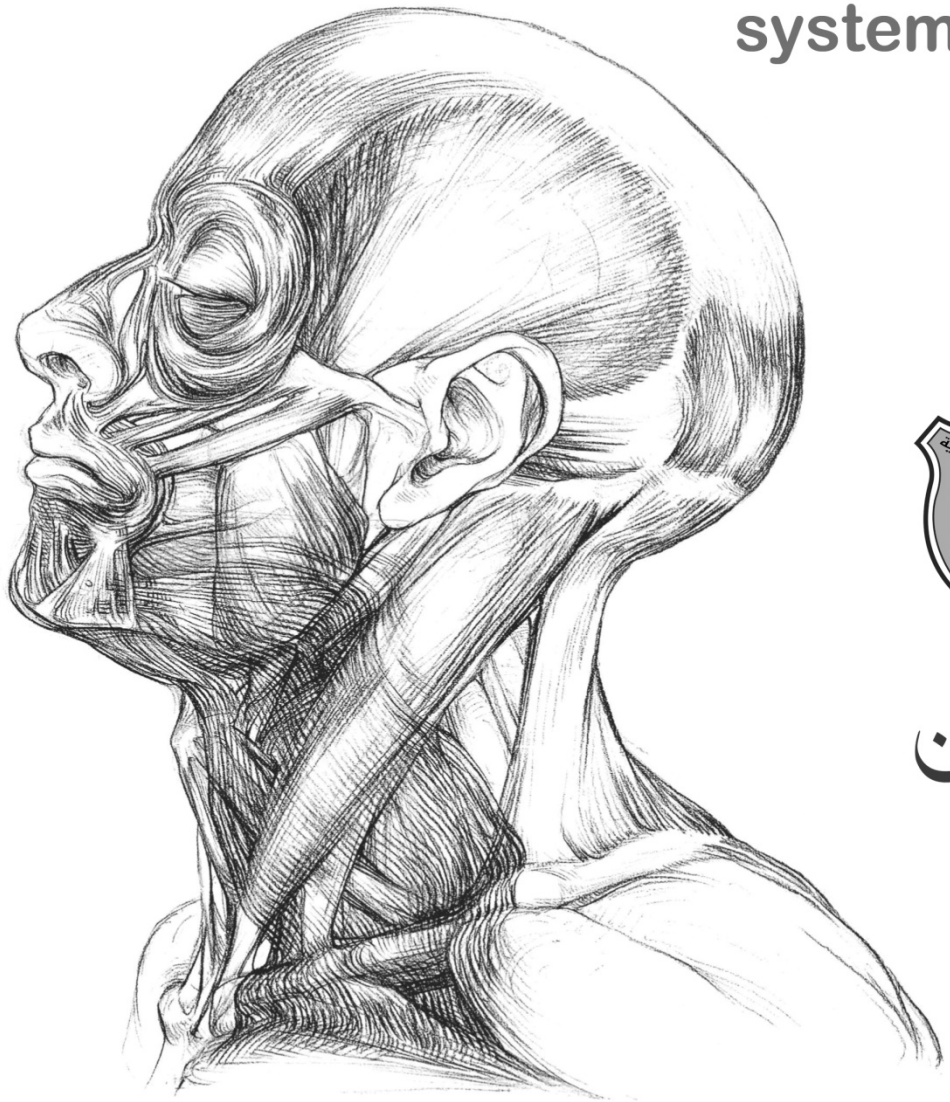
The skin & Musculoskeletal system



PATHOLOGY

SLIDES ☐
SHEET ■
LECTURE # 3

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In this sheet we will discuss chondroid and osteoid tumors in addition to other bone disorders.

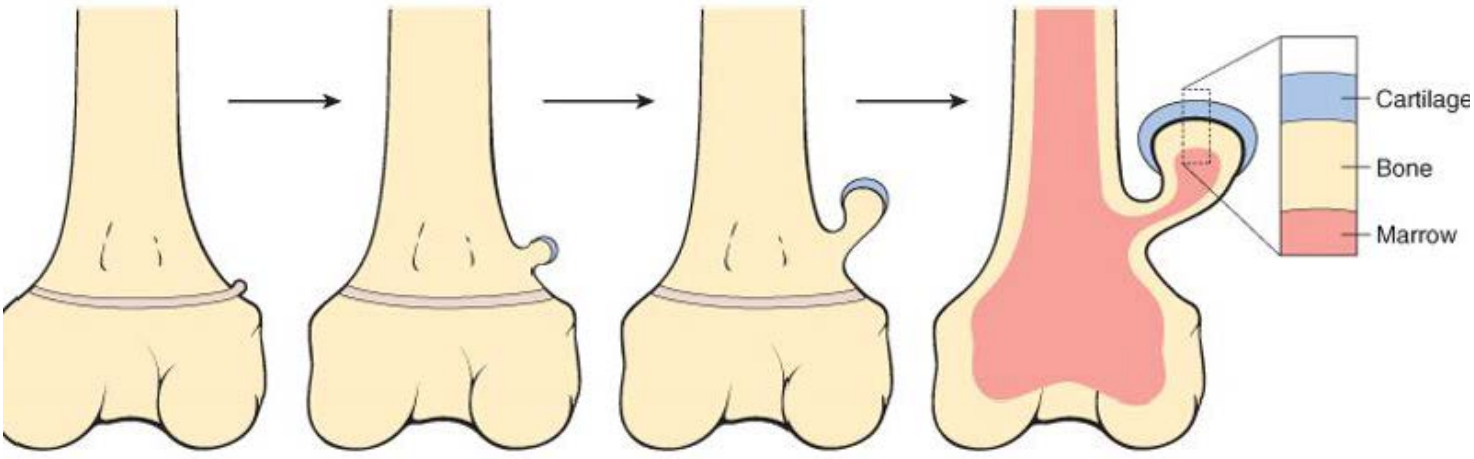
Chondroid Tumors:

1) OSTEOCHONDROMA:

- Clinically, it's called "exostosis", and it is the most common benign chondroid tumor.
- As the name implies; both osteoid (bone) and chondroid (cartilage) can be noticed under the microscope.
- The neoplasm mainly involves the cartilage, hence we call it osteochondroma (not the other way around).
- It can be solitary; single tumor, which is more common in young ages (adolescence and early adulthood). With a ratio of 3:1 males to females.
- As a second case when it is multiple; it's called "Multiple hereditary exostosis"; an autosomal dominant disorder.
- In both situations, there is a mutation(s) in the *EXT gene* in chondrocytes.
- The most common site is the metaphysis of long tubular bones. (Most commonly the femur (around the knee joint). It can also happen in the pelvis, scapula, ribs and phalanges of both upper and lower limbs).

Clinically:

-Osteochondromas have an outgrowth around the bone that is covered by a cartilaginous cap, (the figure below). With the order of : cartilage -> bone ->bone marrow. ((Benign cartilage-capped outgrowth attached by a bony stalk to the underlying skeleton)).



2) CHONDROMA:

- A benign tumor of pure cartilage (hyaline cartilage to be accurate ;)
- **Chondromas can arise from two sites:*

  1-Within the medulla; called ***enchondromas***.

  2-From the outside of the bone (around the bone); called ***juxtacortical Chondromas.*** (Outside the cortex)

  They are the same but we separate them according to the location they arose from.
- Chondromas target individuals at the ages between 20 and 50. And arise solitary in the metaphysis of bones (in case of enchondromas), and the favored sites are the short tubular bones of hands and feet.

Note: *Normally there is no fully-grown cartilage inside the bone, but in these cases, the primitive cells differentiate into cartilage inside the bone.*

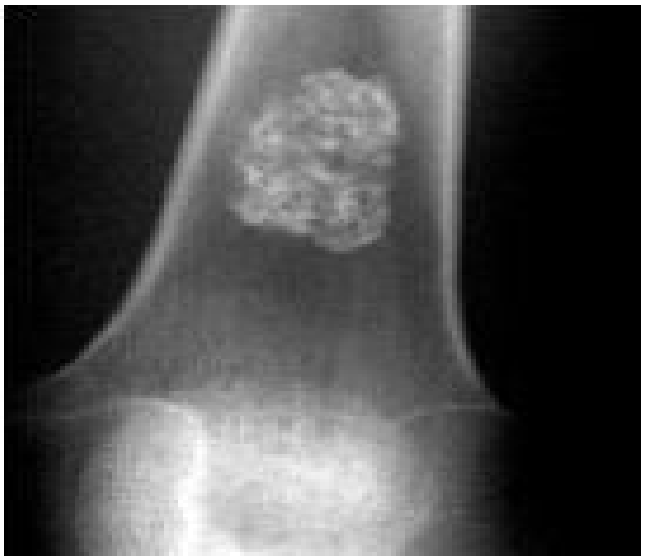
**In case of multiple Chondromas; there are two syndromes:*

1. **Ollier disease**: multiple enchondromas (or just chondromas), and it's unilateral.
2. **Maffucci syndrome**: multiple chondromas associated with benign soft tissue angiomas. (Multiple chondromas with vascular tumors).

Radiology of enchondromas:

It appears as an O-ring sign, with a radiolucent "translucent" region (black), and in the middle there's a white color calcification.

*They are small benign tumors (smaller than 3 cm) with similar morphology to the normal cartilage (well differentiated).



3) CHONDROSARCOMA:

- It's a cartilage-producing malignant neoplasm.
- It can arise from within the bone (intra-medullary), or from the outside (juxtacortical).
- It's a rare tumor which happens mostly in elderly "above 40 years old", (in comparison with osteosarcoma which occurs at any age).
- The most common sites for Chondrosarcomas to grow are: the pelvis, shoulder, and the ribs (bones around the big joints).

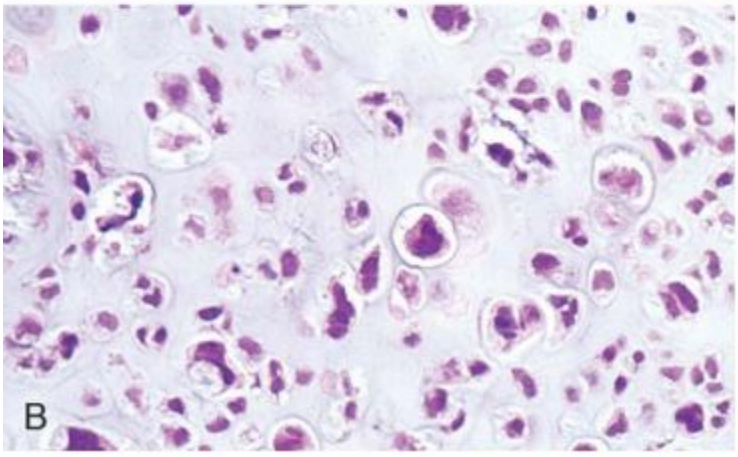
Morphology:

- We see cartilage and malignant cells.
- Although it's a malignant neoplasm; it can be poorly differentiated (high grade), or highly differentiated (low grade).

  Approximately 10% of patients with conventional low-grade chondrosarcomas have a second high-grade poorly differentiated component (if we take a second biopsy from another site of the body it can be of a high grade). So, we take more than one biopsy since the treatment is different for the high-grade tumors.

  Tumor grade is determined by:

  1. *Cellularity*: reflects the number of cells within the lacunae (keep in mind that normally each lacuna contains a single chondrocyte). In high grade cases; the number of cells per lacunae is high, while in low grade cases it is the opposite.
  2. *Cytologic atypia* (pleomorphism): it's how cells are different from each other. High grade types have highly pleomorphic chondrocytes, while low-grade tumors almost resemble normal cartilage.
  3. *Mitosis*: high mitotic activity indicates high grade (poorly differentiated) tumor.



Chondrosarcoma.

A. Gross appearance

Islands of hyaline and myxoid cartilage expand the medullary cavity and grow through the cortex to form a sessile paracortical mass.

B. Microscopic appearance

Anaplastic chondrocytes within the chondroid matrix. Abnormal sizes and shapes with presence of mitotic figures.

Note: Chondrosarcomas appear blue in color, while osteosarcomas appear white, and both of them have similar signs of malignancy.

Before moving on, the doctor emphasized on how important is to know the difference between the three chondroid tumors, in addition to the difference between chondrosarcoma and osteosarcoma.

1) Fibrous Cortical Defect & Nonossifying Fibroma:

- They are the same disease but termed differently according to the size of the defect.

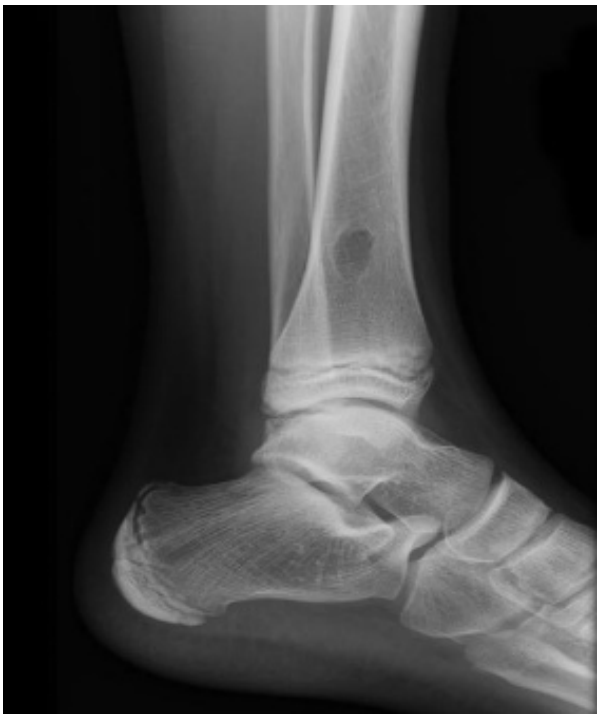
**Fibrous cortical defect:*

- ❖ It's a developmental abnormality rather than a true neoplasm, and it's very common; presents in about 50% of children aged above two years. So it can be looked at as a normal variation or a developmental defect.
- ❖ It's called fibrous cortical defect when the size of the defect is smaller than (0.5) cm.
- ❖ 50% of F.C.D cases are bilateral (affects both sides of the body) or multiple.

- The vast majority of cases are smaller than 0.5cm, and arise in the metaphysis of the distal femur or proximal tibia.
- Larger lesions (5-6 cm) develop into Nonossifying Fibroma (it's not a tumor, but it's large and looks like a tumor).
- In this defect the bone is not yet formed, i.e. still at the fibrous stage.
- This defect appears in the long bones as radiolucent* in radiology.
- Both Fibrous Cortical Defect and Nonossifying Fibroma appear as sharply demarcated radiolucencies surrounded by a thin zone of sclerosis.

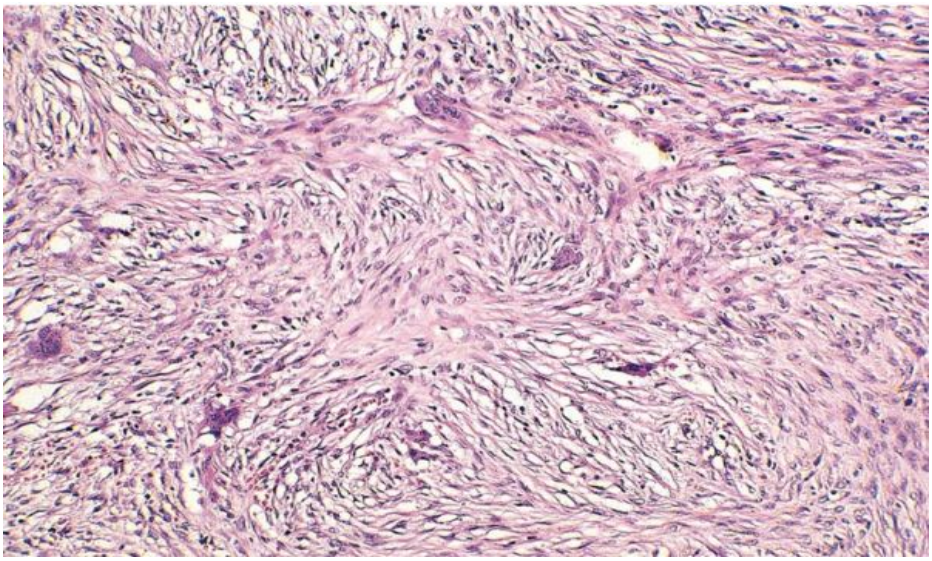
Not included

Radiolucent (black) on film, bone is radiopaque (white) on film…



Microscopic characteristics:

- It's a fibrous tumor; so we will notice proliferating fibroblasts (spindle shaped) and macrophages including multi-nucleated giant cells.
- They form a pattern called storiform (حصيرة) pinwheel pattern.



Fibrous cortical defect or nonossifying fibroma:

Storiform pattern of spindle cells interspersed with scattered osteoclast-type giant cells.

- Generally, this defect is asymptomatic and self-limiting, and discovered indecently. But it may cause a fracture in case it was large (NOF).

2) Fibrous dysplasia:

- It's a benign tumor, but more complicated than the previous fibrous disorder. Better regarded as a developmental arrest, but sometimes it can form a true tumor.
- In FD, there is failure of differentiation (maturation arrest), causing incomplete bone formation (defect in osteogenesis).
- So we see all the components of the normal bone, but they fail to differentiate to the mature form.

Fibrous dysplasia occurs in one of three clinical patterns:

I. Monostotic:
- Involves a single bone
- It's the most common type of FD (70% of cases), and occurs in early adolescence.
- Most common in ribs, then the femur and tibia.
- Asymptomatic, and discovered incidentally as radiolucent area (in radiology)

II. Polyostotic:
- Involves multiple bones. It's restricted to the bone (no cartilage involvement).
- 29% of cases.
- Most common in the femur.

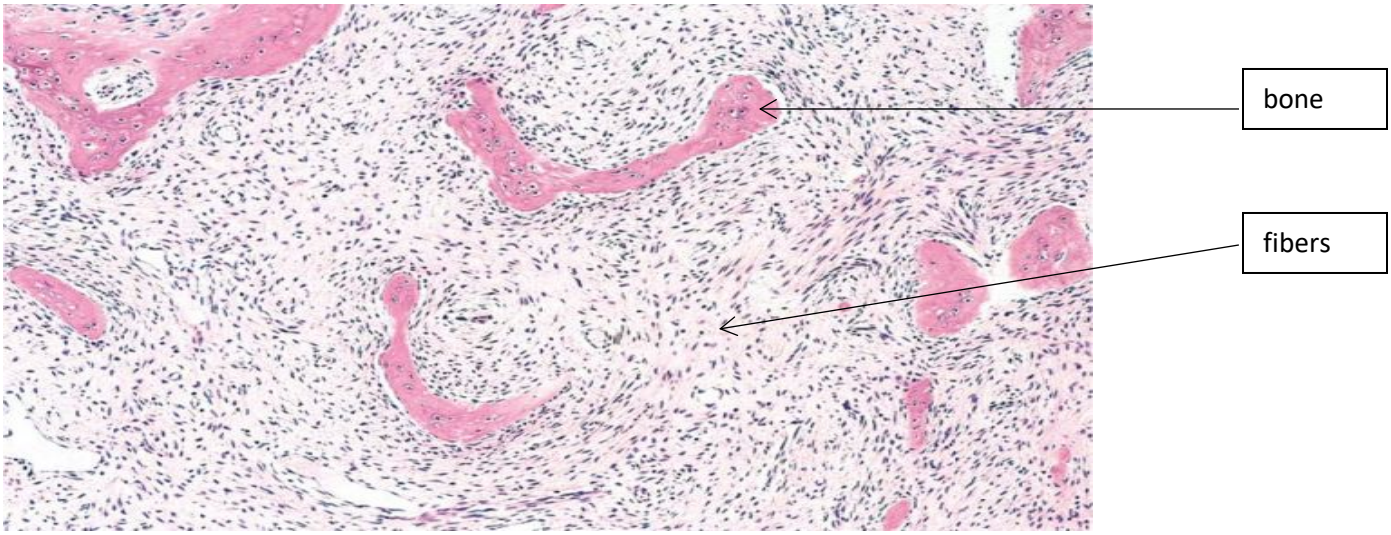
III. Polyostotic associated with disease:
- 1% of cases. (Femur is also the most common site).
- Especially precocious puberty "McCune-Albright syndrome".
  These patients have endocrine abnormalities, which cause precocious puberty (puberty at very young age). They also have skin lesions; dark pigments called "café au lait" along with the fibrous dysplasia.

Note: patients with McCune-Albright syndrome, have a somatic (not hereditary) embryonic mutation yielding a G-protein that constitutively activates adenyl cyclase with a resultant cyclic adenosine monophosphate overproduction and cellular hyper-functioning (precocious puberty).

Note: Fibrous dysplasia can cause marked enlargement and distortion of the bone, so disfigurement can occur if the face or skull is involved,.

Diagnosis of FD:

Under the microscope we have both fiber and bone parts. If we looked at the trabeculae, we can notice that the bone parts don't look normal; they are thin, small and have big spaces between them. They also look like Chinese letters.



In radiology, it has a special appearance called "ground glass appearance"; as broken small pieces of glass, because the osteoids are small and immature with a high number of fibroblasts around them.

- The symptoms are more severe in polyostotic types.
- Rarely, polyostotic disease can transform into osteosarcoma, especially following radiotherapy.

Note: remember that Paget disease also may give rise to osteosarcoma.

Ewing sarcoma:

- Very undifferentiated (primitive) tumor. (Not osteoid, nor chondroid, nor fibrous).
- Historically, there is a similar tumor that arises from outside the bone, and it's called "Primitive neuron-ectodermal tumor (PNET)".
- Ewing sarcoma & PNET are the same disease, but differ in the location. (They share the same mutations (translocations)).

Pathogenesis and Clinical Features:

- The second most common primary malignant tumor of the bone; osteosarcoma is first.
- Targets mainly children (80% are less than 20 years of age (between 10-15)).
- Boys are affected more frequently than girls.
- Rarely affects African (black) people.
- Translocation of the EWS gene on chromosome 22 causes it to fusion with other gene. Most common ones are the FLI-1 gene on chromosome 11, and the ERG gene on chromosome 21.
    - The fusion results in a chimeric protein, which functions as a constitutively active transcription factor to stimulate cell proliferation. The final result is; immature and highly proliferating cells.
- Remember that primitive tumors are very aggressive.

Under the microscope:

- ✓ The cells appear small in size with cleared cytoplasm (only nucleus).
- ✓ Sometimes, the cells form like a ring (rosette)
    - The exact appearance is that tumor cells are circled about a central fibrillary space, and it's called "Homer-Wright rosettes", which is more common in PNET.
- The tumor arises in the medullary cavity. And the most common site is the femur, but it can also arise anywhere else (ex: pelvis).

X-ray:

- ✓ This neoplasm will cause bone destruction. As a response new bone formation is activated (an action of cytokines being produced by the inflammatory cells that respond to the necrotic (destroyed) bone).
- ✓ Here, the new bone is arranged in multiple layers (onionskin fashion under the X-ray) because the destruction is severe, resulting in more activation of osteoid formation.

METASTASIS:

- More common than primary bone tumors.
- Mostly in axial skeleton.
- High vascularization, bone marrow, rich amount of blood with slow perfusion and high amounts of nutrients make the bone a favorite site of metastasis.
- Cancer cells themselves don't destroy the bone. However, they secrete prostaglandins which induces severe pain, interleukins, and PTHRp (parathyroid hormone related peptides).
    - About PTHRp: it seems like PTH but the sequence is different with similar action. It's not normally presented in the body (produced only by cancer cells).
    - One of its functions is to stimulate osteoclasts causing bone resorption, resulting in osteolytic lesions.
- Sometimes for more bone deposition, cancer cells activate osteoblasts; so the patient will have thicker bones. Known as sclerotic lesions (or osteosclerotic lesions).
    - The most common cancer that causes this lesion is prostate cancer.
- Mixed lytic/blastic lesions are also common.

Please refer to the slides 40-54.

"No Stupid Quote"