MSS

pathology

LEC no.5

Writer: Aisha mohammad
Shahd mohammed

Corrector: Farah thaher

Doctor: Tariq Aladily

MUSCULOSKELETAL PATHOLOGY-5 BONE TUMORS-2

Professor Tariq Aladily

Department of Pathology

The University of Jordan

tnaladily@ju.edu.jo

EWING SARCOMA

It is a highly malignant tumor
The cells don't form bone or cartilage or any other material

- Uncommon malignant, undifferentiated tumor
- 10% of primary malignant bone tumors
- Second most common bone sarcoma in children → REMEMBER:first one is osteosarcoma
- 80% of patients are <20 year-old — They are children or adolescnce
- M>F
- 20% of cases arise extra-skeletal

It is arises in soft tissue NOT only in the bone these a difference from osteosarcoma

PATHOGENESIS

The cell of origin of this tumor still UNKNOWN exactly bcz it is primitive tumor it was thought that this tumor arise from stem cells of mesenchymal in soft tissue
Another theory : this tumor build the structure of neuron BUT is NOT complete

- Arise from primitive cell (mesenchymal stem cell vs neuroectodermal cell)
- >90% have balanced translocation

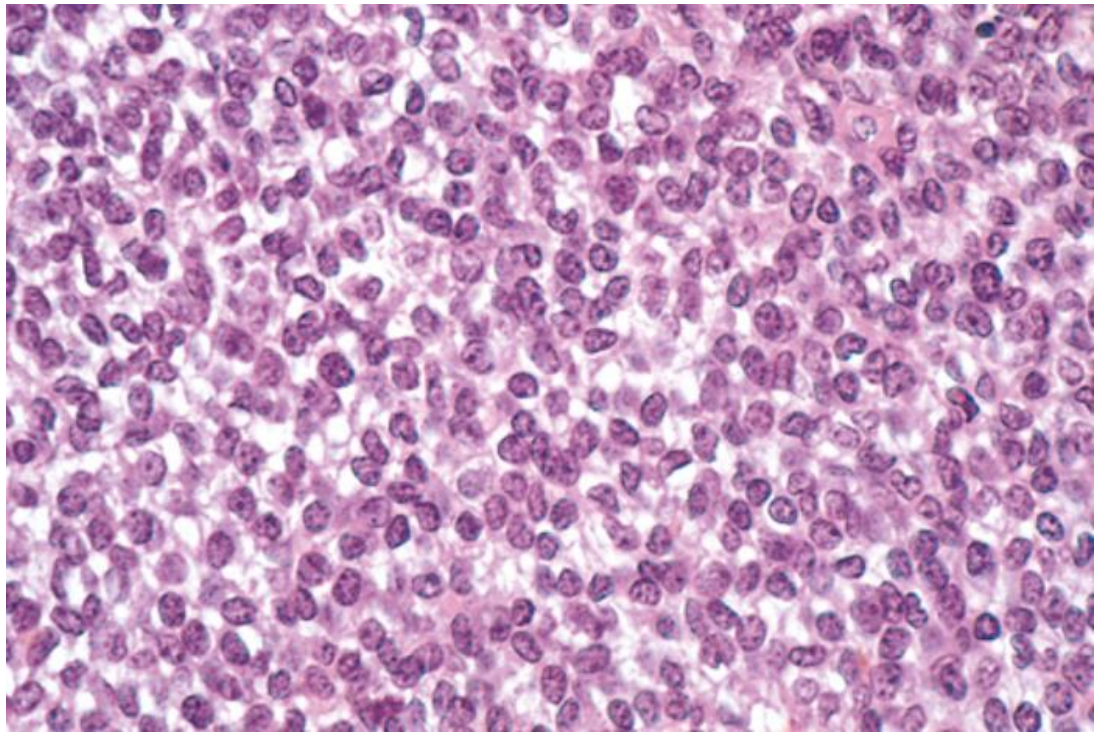
Which mean there is translocation between two chromosome without loos of DNA material

- Fusion of EWSR1 gene (chr 22) and FLI1 gene (chr 11).
- The resultant protein binds DNA, dysregulate transcription and lead to uncontrolled growth and abnormal differentiation
- Tumor arise in the medulla In long bone in the middle part diaphysis
- Severe necrosis and destruction, periosteal reaction of multiple layers, appear in X-ray as "onion skin"

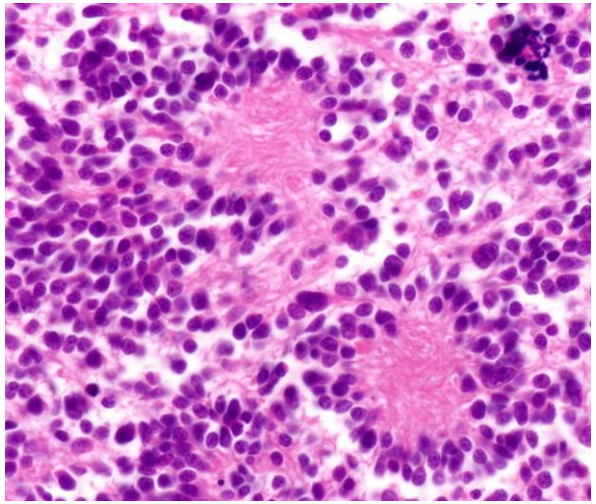
After this fusion there is transcription of DNA and new protein is formed which is oncogene
This protein dysregulate transcription

And it can activation of new bone synthesis BUT multi layers اكثر من تحفيز نمو العظام إذا تم تصويرها رح تظهر مثل البصلة نتيجة طبقة من العظام بالتالي

MORPHOLOGY



In the left side we see under the LM very primitive cells (small / round) and it is mainly a nucleus it DOSE NOT take any shape bcz abnormal differentiated so it looks like a lymphocyte لانو انويتها صغيرة



In the right side sometimes they can take the form of primitive neuron called Homer-Wright rosettes و شكلها دائري لانهم مثل الوردة اللون الوردي بالصورة عبارة عن fibrillary part of neuron

- Left: Ewing sarcoma composed of sheets of small round cells with minimal clear cytoplasm
- Right: Homer-Wright rosettes: circular arrangement of cells with a central fibrillary material

GIANT CELL TUMOR

These tumor in the middle between completely benign and malignant SO it is more benign صح انو حميد لكنه شوي عنيف اكثر من المعتاد
It can make more damage BUT still it can be controlled by surgery .

- Mostly benign tumor, but locally aggressive (may recur)
- Third decade of life
- Epiphyseal tumor, causes destruction of overlying cortex and bulge into soft tissue (arthritis-like symptoms)
- Most common site: distal femur and proximal tibia
- 4% develop lung metastasis, but controlled by surgical removal
- Tumor is composed of two population of cells: primitive osteoblast precursors (neoplastic) that secrete RANKL, and reactive osteoclasts (non-neoplastic)

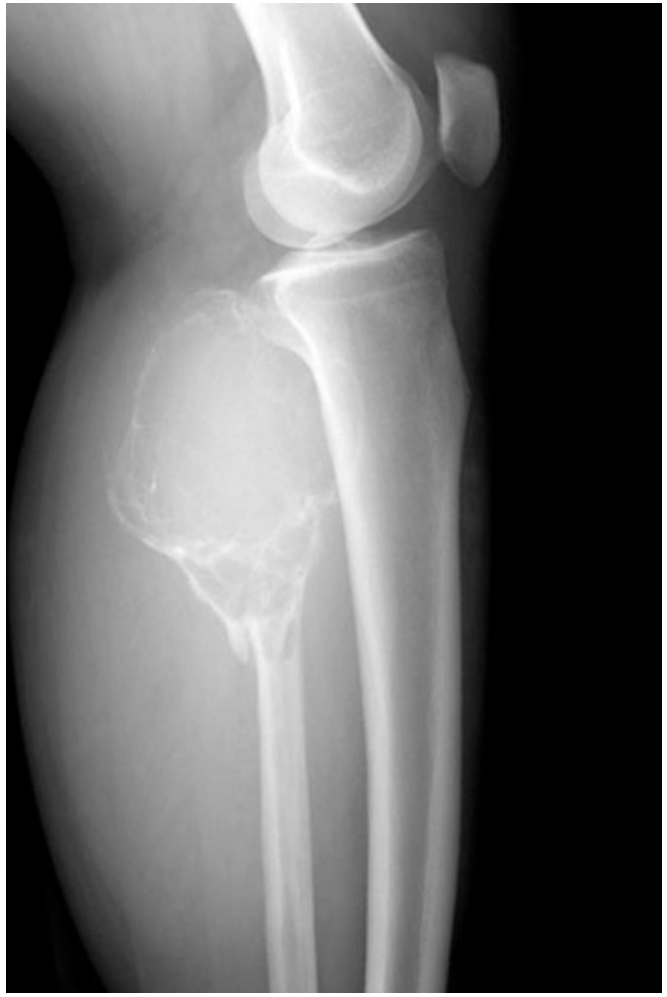
This is the first tumor arise from Epiphyseal of long bone at the end of long bone

It can affect joint

They can take form of mononuclear cells

- Radiographically, giant cell tumor of the proximal fibula is predominantly lytic and expansile with destruction of the cortex. A pathologic fracture is also present.

This is X-ray of GIANT CELL TUMOR in the fibula you can see there is a large tumor in the Epiphysial at the end of the bone .



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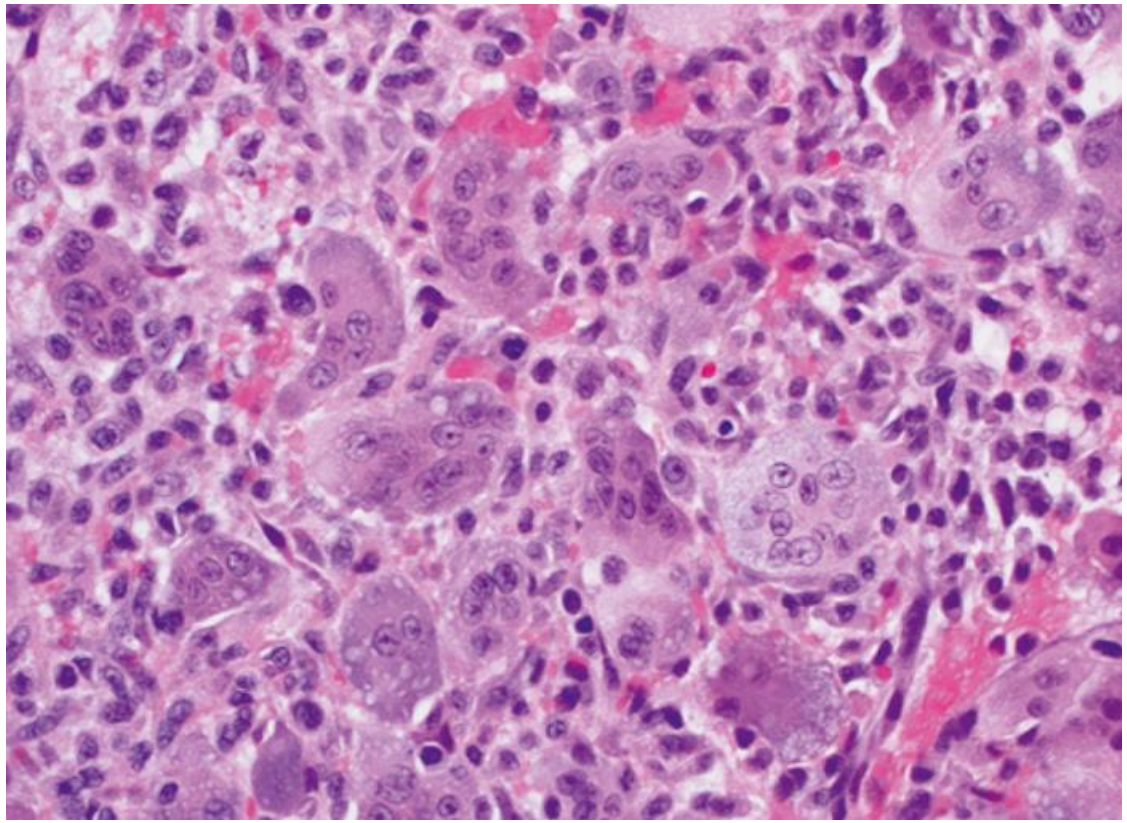


There is a lot of multinucleated giant cells which is osteoclast .

In the background you can see small cells contain single nuclei (neoplastic cell)

- Giant cell tumor illustrating an abundance of multinucleate giant cells with background mononuclear stromal cells.

ANEURYSMAL BONE CYST (ABC)

- Multiloculated blood-filled spaces
- Affects all age groups, but most commonly in adolescents
- Affects femur, tibia MOST common site or vertebra
- Arise in metaphysis
- Appear well-defined lesion with internal septa and filled with blood
- Septa are composed of plump uniform fibroblasts, multinucleated giant cells and woven bone
- Causes pain, swelling, pathologic fracture
- Locally aggressive (may recur)

It can remove by surgery .

You can not see a sold bone SO no neoplastic cell.

ANEURYSMAL mean balloon like cavity in the tisse .
بمعنى منفوخ و فاضي
It is a tumor cases a mass and bone damage BUT it forms a cavity

CYST means cavity

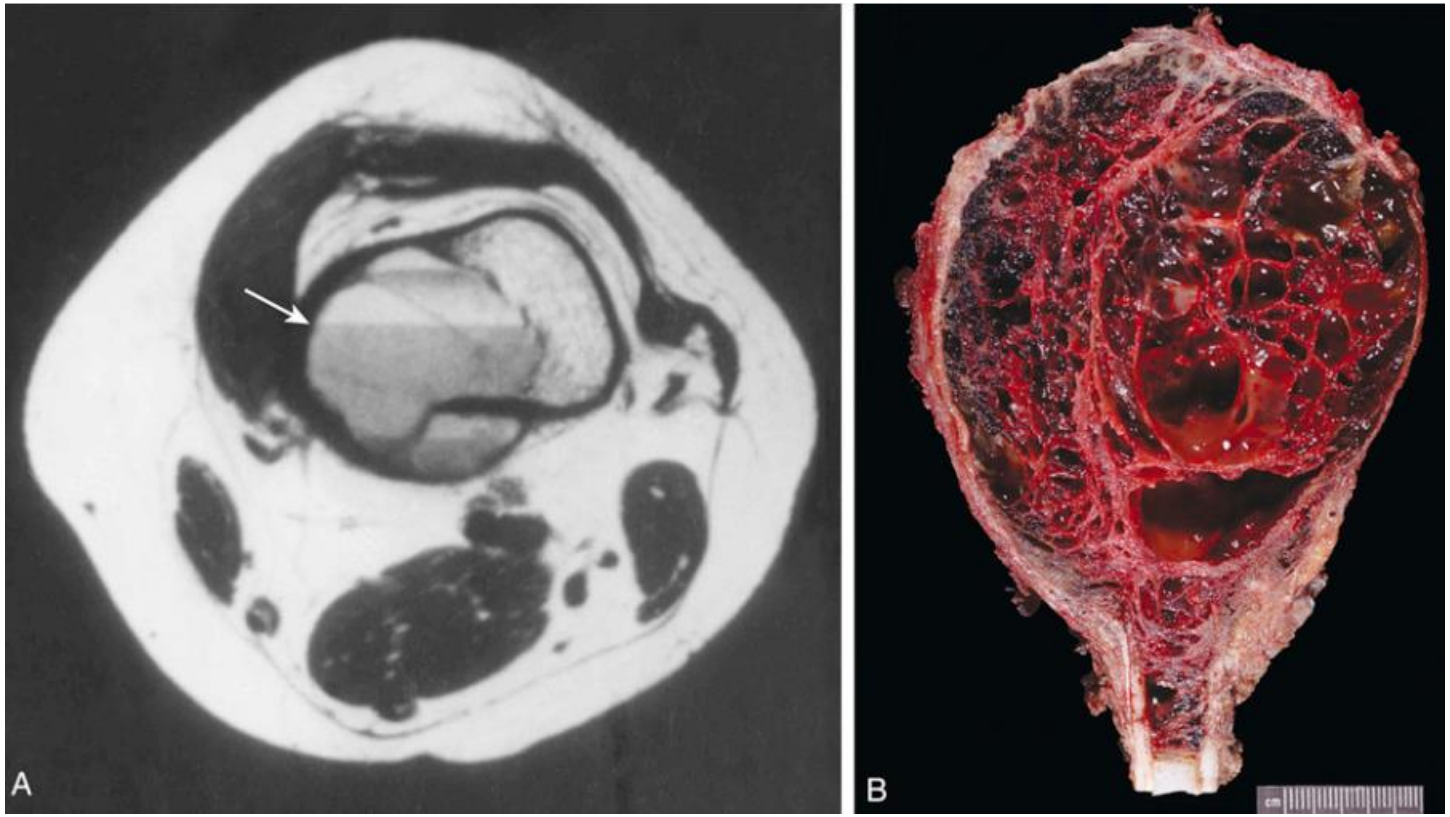
The number of cells is little

The bone has cavity filled with blood .
العظام بصير فيه تجاويف مليئة في الدم

PATHOGENESIS

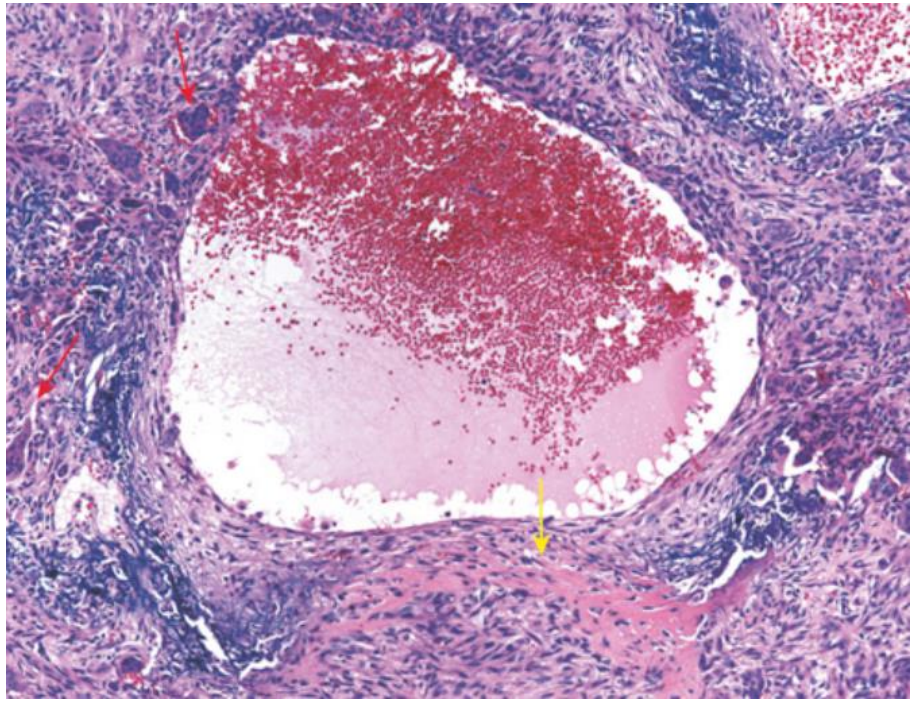
- Neoplastic cells are spindle, unknown origin
- Rearrangement of chromosome 17p13
- Fusion of USP6 with COL1A1 genes
- Results in overexpression of USP6
- Activation of NF-kB pathway
- Increase in matrix metalloproteases, leading to cystic bone resorption

MORPHOLOGY



- Aneurysmal bone cyst. (A) Axial magnetic resonance image demonstrating characteristic fluid-fluid levels (arrow). (B) Gross appearance of aneurysmal bone cyst. The lesion appears hemorrhagic and spongelike in this bisected portion of proximal fibula

MORPHOLOGY



- Aneurysmal bone cyst with blood-filled cystic space surrounded by a fibrous wall containing proliferating fibroblasts, reactive woven bone (yellow arrow), and osteoclast-type giant cells (red arrows).

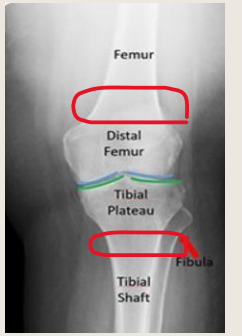
Developmental defects: Occur when there is a disturbance in the development of the body

FIBROUS CORTICAL DEFECT AND NONOSSIFYING FIBROMA

This is not a true tumor

- Developmental defects, where fibrous tissue replaces bone. (part of the bone is fibrous tissue)
- Present in 50% of children >2 years(it's a very common condition, but it's generally very small and not important), incidental finding (it's not symptomatic, and it's discovered by chance when they take an X-ray for another region)
- Most commonly in metaphysis of distal femur or proximal tibia
- 50% multiple and bilateral (more than one lesion)
- Fibrous cortical defect: small (<0.5 cm)
- Non-ossifying fibroma: large (may reach 5 cm)
- Both are well-demarcated (characteristic of benign tumer), appear radiolucent in X-ray (it appears black in color)

Remember: the Metaphysis Of bone

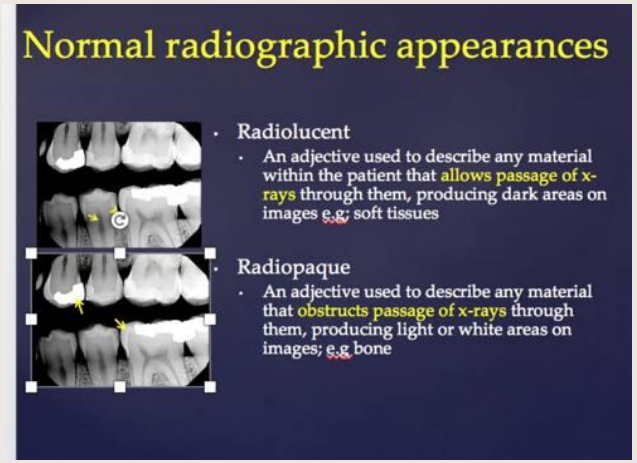


Well-demarcated: the boundary or limits of a mass are clearly defined

Radiopaque: the bone reflect the X-ray because of calcium, and it appears white.

Radiolucent: when the X-ray penetrate the bone (without calcium only with fibrous tissue), it appears black.

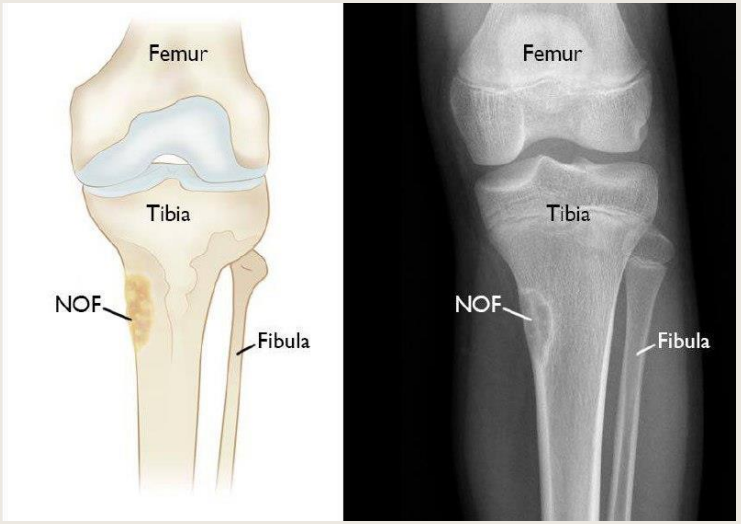
Additional:



- Fibrous cortical defect: small (<0.5 cm)
- Non-ossifying fibroma: large (may reach 5 cm)

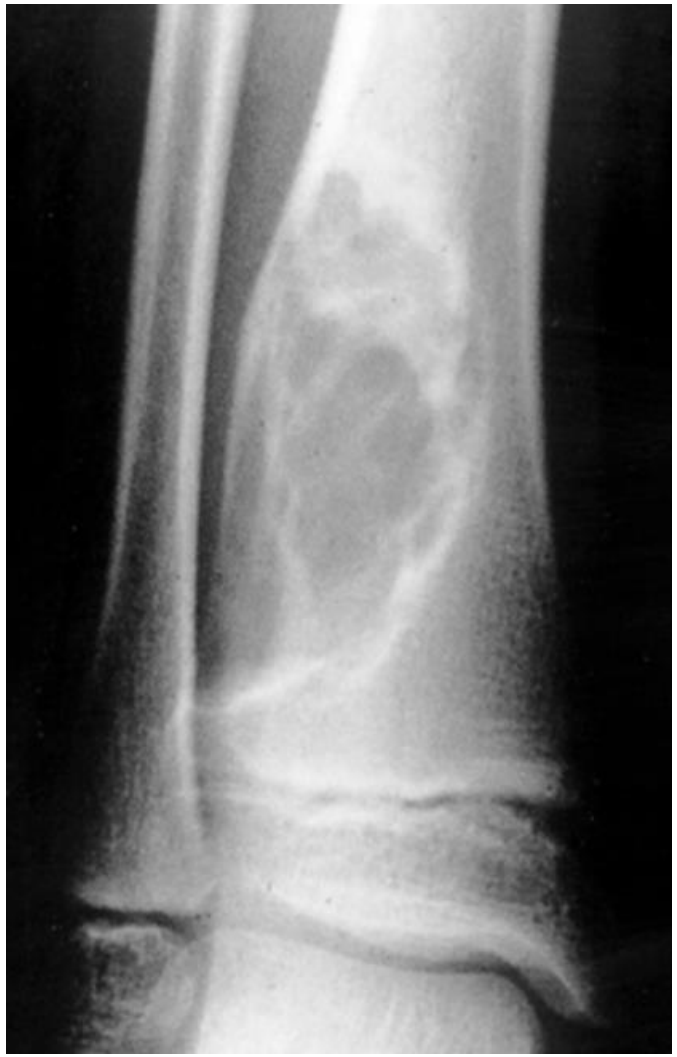
If it's small we call it: Fibrous cortical defect. Sometimes it becomes large, we call it: Non-ossifying fibroma (it looks like a tumor. fibroma and doesn't have an ossification that's why we call it "non-ossifying fibroma")

Additional:



- Nonossifying fibroma of the distal tibia metaphysis producing an eccentric lobulated radiolucency surrounded by a sclerotic margin.

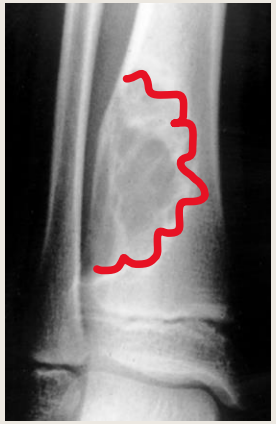
The term **"Sclerotic Margin"** for intraosseous lesions refers to a thin or thick, complete or incomplete rim of bone at the interface of the lesion with cancellous bone.



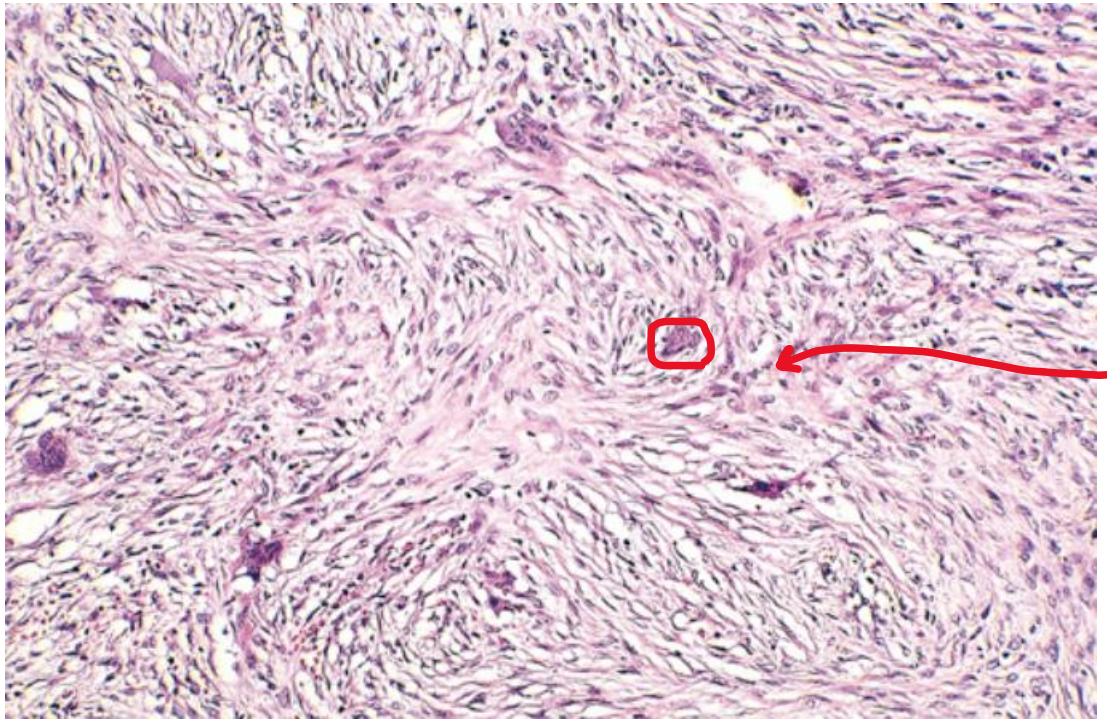
This is how it appears in X-ray:
-Notice the darker area
-well-demarcated (you can identify the borders easily)
So it's a non-ossifying fibroma

Eccentric : له سلوك مختلف
unconventional and slightly strange views or behaviour

Lobulated: having lobes



MORPHOLOGY



- Pinwheel (storiform) fibroblasts and multinucleated giant cells

By microscopy:
-It has a characteristic morphology :
pinwheel زي المروحة
In pathology, we call it **storiform**

-The fibroblasts are not arranged as normal, rather they take curves and form a big circle و ما بشبهو بعض بكونو يلفو حوالين بعض

-and in between you can see
multinucleated giant cells

Locations of Giant cells:
1-Aneurysmal bone cyst
2-Giant cell tumer
3- Nonossifying fibroma
But each one has different charactaristic, in this one the Pinwheel appearance of the fibroblast

It's not a real tumor; rather it's a developmental abnormality of bone genesis due to mutation

Remember 😀
Dysplasia: abnormal pattern of growth of the bone.

FIBROUS DYSPLASIA (FD)

- Benign tumor, results from localized development arrest (components of normal bone are present but do not differentiate into mature structures)
- May grow and cause disfigurement (especially in the face or in the skull)

Disfigurement= تشوه

- Might be sporadic or syndromic
- Can be:
- Monostotic (only one bone with tumor)
- Polyostotic (multiple) (may transform to osteosarcoma)
- Mazabraud syndrome: FD and soft tissue myxoma
- McCune Albright syndrome: polyostotic FD, endocrine diseases, skin pigmentation

There is a bone in the tissue, but it's not a mature bone. Most of the tissue is consist of other materials. And **it behaves like a tumor** (the defect in the bone grows like tumors)

Most cases are sporadic, but sometimes it's syndromic
Remember:
Sporadic --> acquired, single bone
Syndromic --> appears early in life, multiple bones

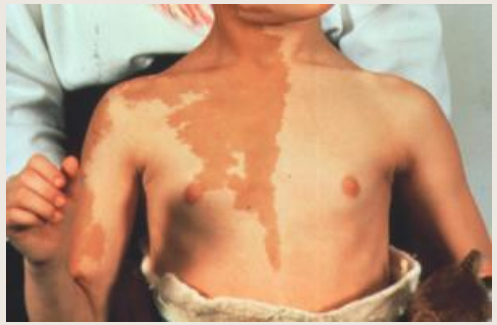
- **Mazabraud syndrome**: FD and soft tissue myxoma
- **McCune Albright syndrome**: polyostotic FD, endocrine diseases, skin pigmentation

Sometimes we have polyostotic fibrous dysplasia with other diseases in the body = forms **syndromes**

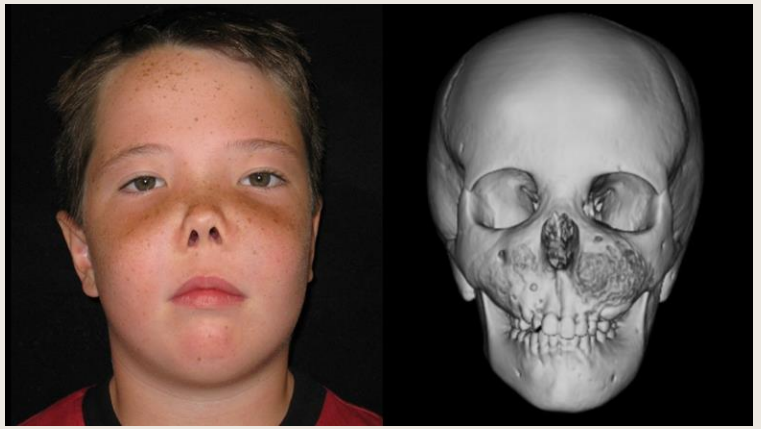
It's a rare syndrome, but it's commonly asked in medicine.

Additional:
McCune Albright syndrome

-Notice the brown lesion



- Notice the **disfigurement** التشوه(as we said it's more common in the face or the skull)



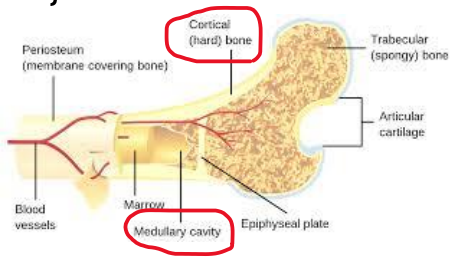
PATHOGENESIS

The most important mutation in this disease is GNAS1 gene mutation, it makes gain of function

- Gain of function mutation in GNAS1 gene
- Constitutively active Gs-protein (will not be suppressed)
- Increase level of cAMP (cAMP is a **potent mitogen)**
- Promotes cell proliferation and disrupts osteoblast differentiation (so we will have tumor with little osteoblast without full maturation)

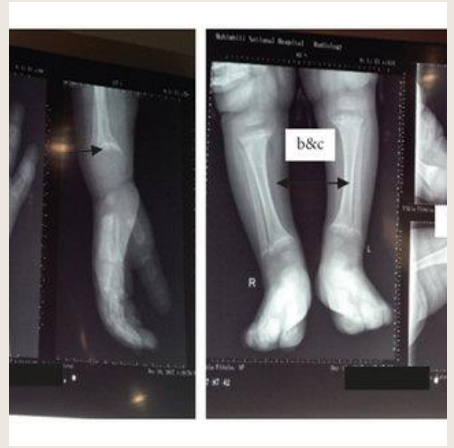
GNAS1 gene mutation --> Gs-protein is permanently active without suppression --> increase cAMP in the cytoplasm --> Proliferation of the cells and distruption of OB

- Tumor arise in medulla, causes cortical thinning and bowing



A mitogen: is a small bioactive protein or peptide that induces a cell to begin cell division, or enhances the rate of division

Additional:
Notice the bowing !!

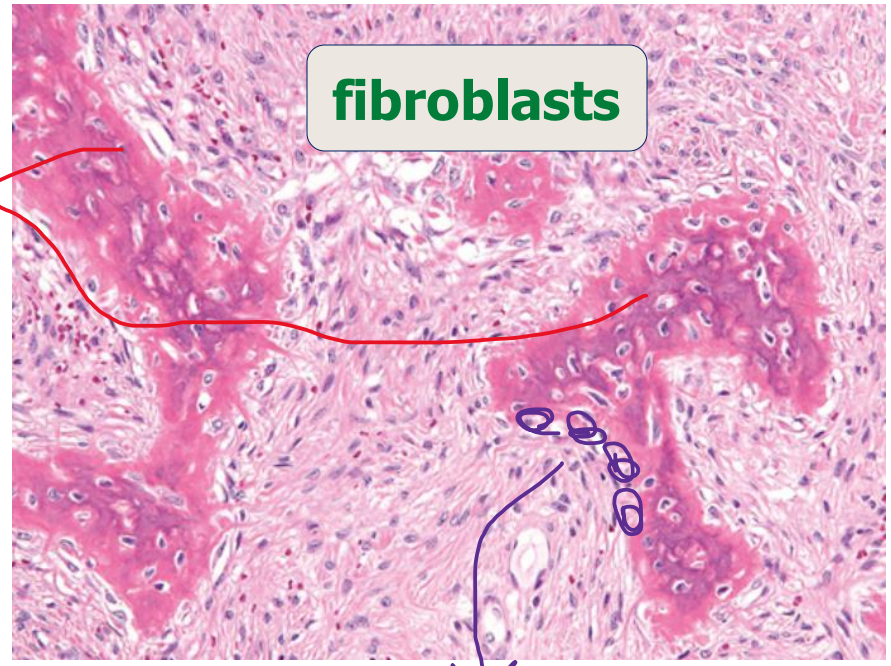


Remember: there is bone formation, but it's incomplete (not mature)

MORPHOLOGY

Those are the **woven bone,** (the pink material) they are curved, separated from each other.

بشبهوها بالحروف الصينية



Normally, it should rimmed by OB. So here I don't see them 😢.

- Small curved woven bone trabeculae (**Chinese letters**), not rimmed by osteoblasts
- Abundant fibroblasts in between

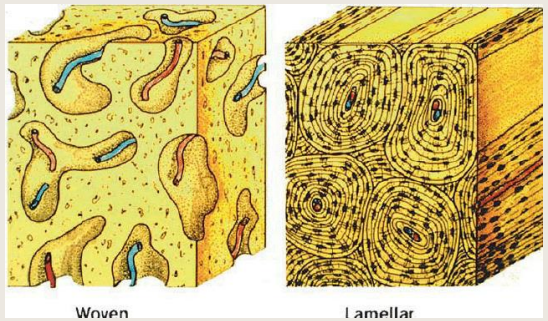
NOTE:

Early bone (woven bone):

- Small
- Separated from each other
- Doesn't show the lamellae of lamellar bone

Lamellar bone: is characterized by the organized arrangement of collagen fibers into layers or lamellae

Woven bone: is characterized by the irregular arrangement of collagen fibers, large cell number, and reduced mineral content



BONE METASTASIS

-Any cancer can spread to bone, because bone is very vascular organ, so we have high chance for metastatic cells to reach bone.

-Direct invasion = from other organ (eg. Lung)

- More common than primary bone tumors
- Any cancer can spread to bone (hematogenous, lymphatic or direct invasion)
- Commonly multifocal (multiple bones)
- Can be **bone destroying** (lytic lesion), **pure blastic** (bone forming) or **mixed**
- Prostate cancer commonly cause osteoblastic lesion
- Malignant cells secreted prostaglandins, cytokines and PTH-like peptide, activating osteoclasts
- WNT proteins are secreted in osteoblastic metastasis

-mixed pattern: destruction and at the same time it synthesises new bone

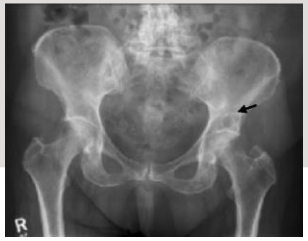
Wnt proteins comprise a major family of signaling molecules that orchestrate and influence a myriad of cell biological and developmental processes

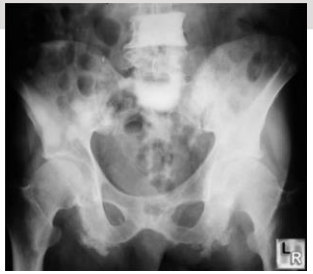
- Prostate cancer commonly cause osteoblastic lesion

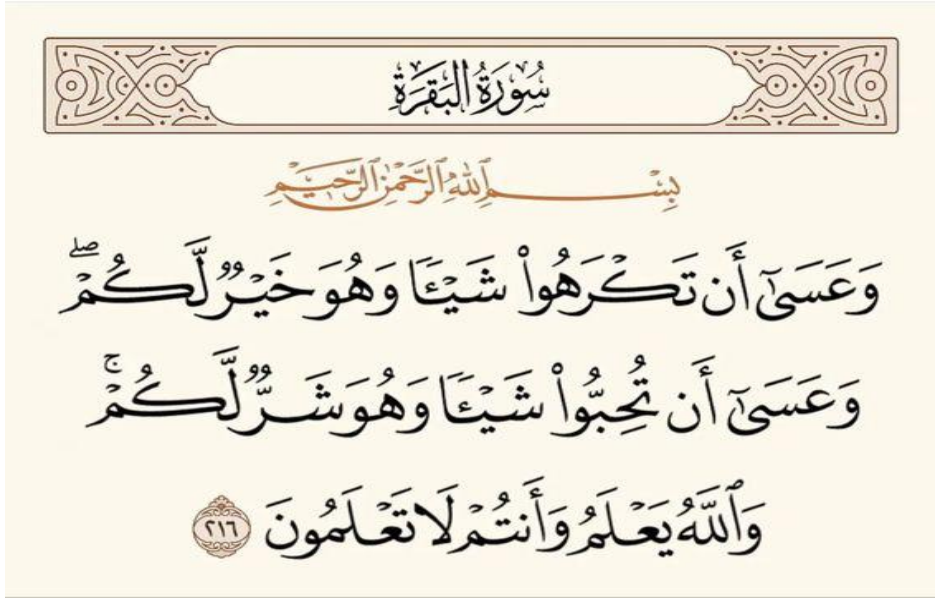
When we take a radiograph for the spine of the patient with prostate cancer, and if we see a very thick bone, we will know that he has metastasis.

Additional:

lytic	mixed	Blastic
• Resorb the bone	• Lytic + blastic	• Forming bones • Prostate cancer





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