MSS

Sheet no.

Pathology

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In lecture 5, we talked about bone forming tumors and cartilage forming tumors, and we mentioned that there are certain bone tumors which we don't know the cell of origin for them.

So, in this lecture we will talk about tumors of unknown origin.

Tumors of Unknown Origin

Ewing sarcoma

- Dr. James Ewing (1866-1943), described this tumor in 1920.

- small blue cell tumor (PNET).

This tumor is considered one of the small blue cell tumors , this name is usually given to those high grade primitive tumor histologically after we look at the microscope and see sheets of small size tumor cell with large nucleus , little cytoplasm so this is called small blue cell tumors , and the word (blue) because when we stain those tumors by routine H and E stain , they appear blue because of the blue color of the nucleus which occupies 98% of the cell volume

-PNET: it is primitive neuro ectodermal tumor.

Those tumor in general, they have general characteristics, they are primitive, and they have neuro ectodermal differentiation.

-second most common sarcoma of bone after osteosarcoma.

So, osteosarcoma is number one in terms of frequency followed by Ewing sarcoma

-<20 years, diaphysis.

Again the age distribution here similar to osteosarcoma usually, you don't see Ewing sarcoma below the age of 5 or below the age of 10 and after the age of 20 , so between 10 and 20 , but usually it is less than 20 years of age .

This tumor usually arises in the diaphysis of long bones.

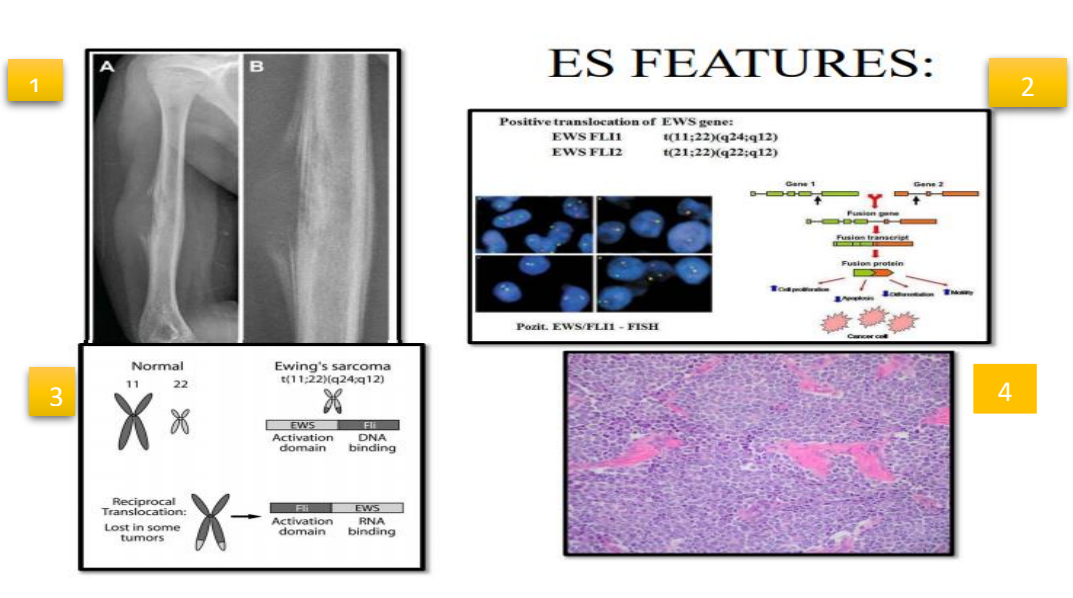
-The most common translocation, which is present in about 90% of Ewing sarcoma cases, is t(11;22) (q24;q12),which generates an aberrant transcription factor through fusion of the EWSR1 gene with the FLI1 gene.

This tumor is characterized by the present of signature translocation.

-Trx: neoadjuvant CT followed by surgery; long term survival now reaches 75%.

after the diagnosis, it is need neoadjuvant chemotherapy followed by surgery .

the current long-term survival now reaches up to 75% which is really good compared to 20 ,30 years old.



انتبه للأرقام يا باشا

1-(radiologic) this is an example of Ewing sarcoma in the diaphysis of the humerus , note that this tumor infiltrating the soft tissue and elevating the periosteum causing Codman triangle , which help you to understand that Codman triangle is not specific characteristic for osteosarcoma only .

2-this is translocation t (11,22), there is 2 of them actually (EWS FLI1), (EWS FLI2).
(molecular) this is a picture of fish analysis, so this is probably the most sensitive test for Ewing sarcoma using florescent insitu hybridization (FISH).

3- this is the old method by classic cytogenetic analysis, where the translocation occurs between the chromosome 11 which is a bigger chromosome than chromosome 22. and this method show the fusion protein produced from this translocation.

4-(histologic) : when patients comes with the pain or pathologic fractures , biopsy is taken and under the microscope , you will see a lot of small blue cell tumors destroying the bone .

So these are radiologic, molecular and histologic features of Ewing sarcoma.

Giant cell tumor of bone :

-locally aggressive neoplasm of adults .

You don't see this tumor in children , you don't see this tumor at the age of 10, 20 or 15 , this is why we have mentioned at the beginning of bone tumor lectures that the location and the age are important to help you narrow your diagnosis .

-epiphses of long bones .

It has a bubble appearance expanding the cortex of the bone without infiltration to the extracortical space.

(this is a classic appearance of a benign tumors)

And if the patient is 45 years of old, this is the most Common differential of giant cell tumor of bone, so They go in and take a biopsy and sometimes they just Resected.

Histologically: it is sheets wall to wall, multi-nucleated Giant cells or osteoclast like giant cell, so the tumor cell Are the giant cells and the one in between (the single mononuclear cell).

-osteoclast like giant cell:

Sometimes they call it **osteoclastoma** because the primary histology is composed of numerous wall to wall osteoclast like multi-nucleated giant cells.

-rare malignant behavior:

95% behaves in the benign forms (you can cure it; you can resect it)

-cells contain high levels of RANKL:

There is a lot of research on this. recently they found that RANKL is present in this tumor at high level, which is the RANKL that stimulates the differentiation of osteoclast in the bone.

-Trx: curetting or resection.

ANEURYSMAL BONE CYST: (cyst inside the bone filled with blood)

-ANEURYSMAL BONE CYST(ABC) is a benign tumor characterized by blood – filled cystic spaces and fibrous reaction around it.

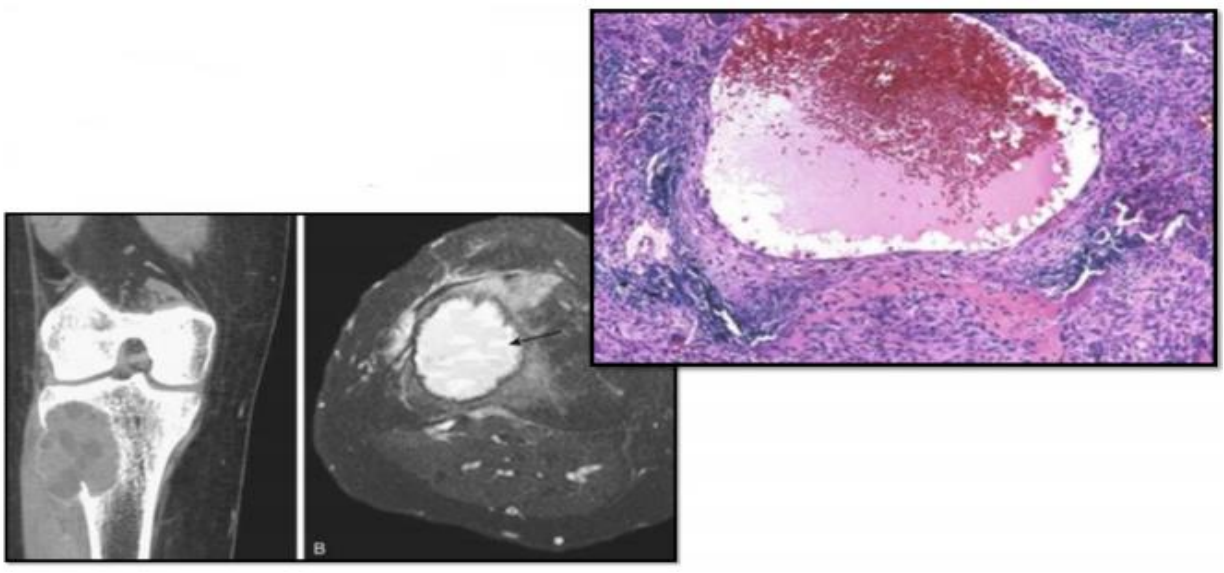
-some argue that (ABC) is not a true neoplasm (probably reactive condition caused by previous trauma or infection)

- It most frequently develops in the metaphysis of long bones.

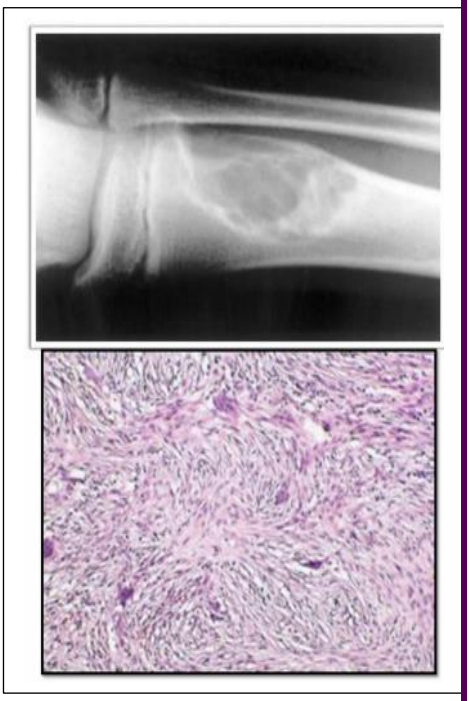
-Affects adults.

-Trx: curetting , resection

If it is localized like this lesion in the upper fibula probably you can remove it without impact on the function of the lower limb in the patient



Non ossifying fibroma. (a fibroma in the bone)



This is the bone (tibia) and there is a lesion here which is not destroying the surrounding structure, it is not elevating the periosteum, it is well circumscribed.

the biopsy looks like benign fibroma

(mostly fibroblast some multinucleated giant cell)

But there are not common

-Benign lesion, maybe reactive not a true neoplasm

- Other names: fibrous cortical defect (FCD) & metaphyseal fibrous defect (MFD).

-Metaphysis in long bone.

- Histology: bland fibroblastic proliferation.

-May resolve spontaneously:

One of the things which has been observed in these non-ossifying fibroma that some times they resolve spontaneously and this is one of the evidence that the people who believed that this reactive process are taken in to consideration that could be viral infection or trauma reaction resolve and go is away .

Giant cell tumor of bone , ANEURYSMAL BONE CYST and Non ossifying fibroma , probably the 3 of them many times they come in to the diagnosis and there is some clues histologically , radiologically and clinically , however the final answer will be among pathologist (take biopsy out and decide)

FIBROUS DYSPLASIA (FD):

- Not a real tumor; rather a developmental abnormality of bone genesis due to mutations in GNAS1 gene (cAMP mediated osteoblast differentiation).

So during bone growth and development something happens based on a mutation in a certain gene which is GNAS1 gene that is responsible for the osteoblast differentiation via cAMP pathway and this will lead to abnormal bone formation.

-fibrous dysplasia is a group of diseases or syndromes. (forms of FD)

– Monostotic: affecting one bone

Common bones which are affected by this FD is in the maxillary and mandibular bone of the face causing what we call cherubism in children

– Polystotic: multiple bone

– Mazabraud syndrome: FD (whether it is monostotic or polystotic) + soft tissue myxoma (not a common tumor of soft tissue).

Target

-McCune-Albright syndrome: polystotic FD + café-au-lait skin pigmentation (multiple brownish pigmentation of the skin) + endocrine abnormalities (precocious puberty) .

EX ⟶

If they give you a scenario of 11 years old female patient , she has precocious puberty ,she has well developed breast , hairy axilla , hairy pubic hair , multiple brownish pigmentation of the skin and abnormal facial bone appearance this is McCune-Albright syndrome.

-Abnormal bone that's somehow similar to Paget disease.

-We can differentiate between McCune-Albright syndrome and Paget histologically. McCune-Albright syndrome has a Chinese letters appearance while in Paget disease the bone appears in a mosaic pattern (pathgnomic).

The following pictures represents features of McCune-Albright syndrome:

The components of McCUNE-ALBRIGHT syndrome:
-endocrine abnormality
-polystatic fibrous displasia
-(cafe) pigmentation of the skin

METASTATIC TUMORS TO BONE:

- Much more common than primary bone tumors.

So having tumors going to the bone from carcinoma, from hematopoietic malignancies is much more common than seeing osteosarcoma , Ewing sarcoma and chondrosarcoma .

-In adults: most are carcinomas; lung, prostate, breast, kidney, thyroid & liver.

In adults the most common metastatic to the bone is carcinoma and the most type of carcinoma which cause to the bone is adenocarcinoma (gland forming carcinoma).

Now, lungs are the major cause of bone metastatic both in female and males because we have a lot of females who are smokers now.

-In children: Neuroblastoma, Wilms tumor(kidney) and rhabdomyosarcoma.

In children, you don't see carcinoma (very rare) .

-Usually multiple and axial (vertebral bodies, shoulders, pelvic) : mostly hematogenous spread.

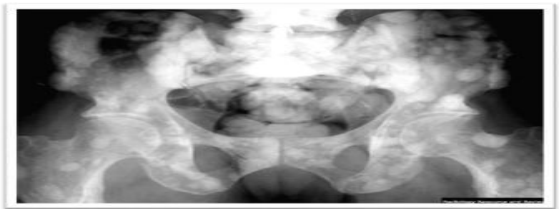
-lytic, blastic or mixed (via mediators)

The radiographic appearance of metastasis may be purely lytic (bone destroying), purely blastic (bone forming), or mixed. These lesions appear as a result of secretion of certain mediators.

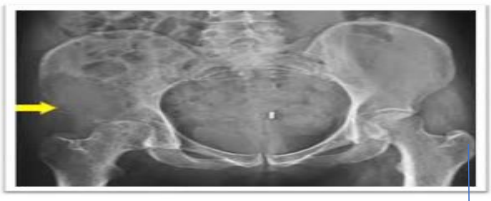
The presence of multiple lytic metastatic is much more common than blastic and mixed metastatic.

Simple X-RAYS

BLASTIC METASTASIS



LYTIC METASTASIS



This is a patient with hundreds of blastic metastatic.

-the primary source here was the prostate.

-the prostate is commonly associated with blastic metastatic.

-this is another patient were the bone

is eaten in multiple areas (vertebral body, pelvic bone, femur)

-the most common primary of those is carcinoma (adeno carcinoma in lungs)

-this is stage 4 (bad prognosis) after this appearance most of patient don't survive beyond 6-12 months.

Summary

Bone Tumors and Tumorlike Lesions

Primary bone tumors are classified according to the cell of origin or the matrix that they produce. The remainder is grouped according to clinicopathologic features. Most primary bone tumors are benign. Metastases, especially from lung, prostate, kidneys, and breast, are far more common than primary bone neoplasms.

Major categories of primary bone tumors include

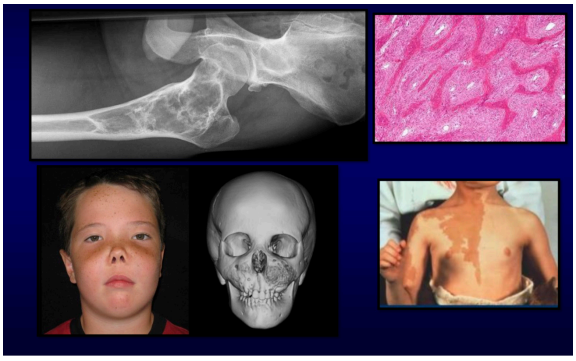
- **Bone forming:** Osteoblastoma and osteoid osteoma consist of benign osteoblasts that synthesize osteoid. Osteosarcoma is an aggressive tumor of malignant osteoblasts, predominantly occurring in adolescents.
- **Cartilage forming:** Osteochondroma is an exostosis with a cartilage cap. Sporadic and syndromic forms arise from mutations in the *EXT* genes. Chondromas are benign tumors producing hyaline cartilage, usually arising in the digits. Chondrosarcomas are malignant tumors of chondroid cells that involve the axial skeleton in adults.
- **Ewing sarcomas** are aggressive, malignant, small round cell tumors most often associated with t(11;22).
- **Fibrous dysplasia** is an example of a disorder caused by gain-of-function mutations that occur during development.

Test yourself

1)A 13-year-old boy was brought by his parents with right forearm pain and swelling. Imaging showed an infiltrative diaphyseal tumor with two Codman triangles one proximal and one distal. The fine needle aspiration smears revealed numerous small tumor cells with high nuclear cytoplasmic
ratio. The molecular signature abnormality of this tumor is:
a. t (11;22)(q24;q12)
b. MDM2 translocation
c. t (x;18)(p12;q15)
d. Point mutation of osteoblast P53 tumor suppressor gene e. Gene mutation in fibroblast growth factor receptor 3

Answer: A

2)The images below belong to a 11-year-old boy who came with precocious puberty and multiple endocrine glands abnormalities. What is the most likely diagnosis?
a. Leontiasis ossea / platybasia
b. McCune-Albright syndrome
c. Multiple hereditary chondromatosis d. Familial Paget disease of bone
e. Mazabraud syndrome



Answer: B