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Pathology MSS

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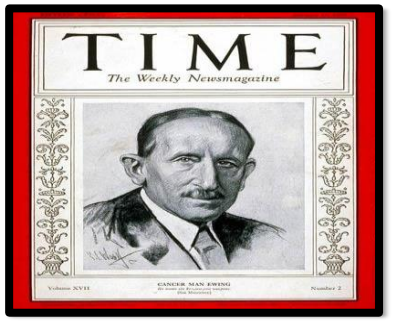
Lecture 6

we talked in lec #5 about bone and cartilaginous tumor, we mentioned that there are certain bone tumors in which we **don't know their cell of origin** .
Example, EWING SARCOMA

EWING SARCOMA:



- **Dr. James Ewing (1866-1943). Described this tumor 1920 Small blue cell tumor (PNET)** [high grade primitive tumor]

Histologically , we see sheets of small sized tumor cells with large nucleus and little cytoplasm .

They are called Blue because when we stain those tumors using routine H&E stain they appear blue due to the blue color of the nucleus which occupies 98% probably of the cell volume.

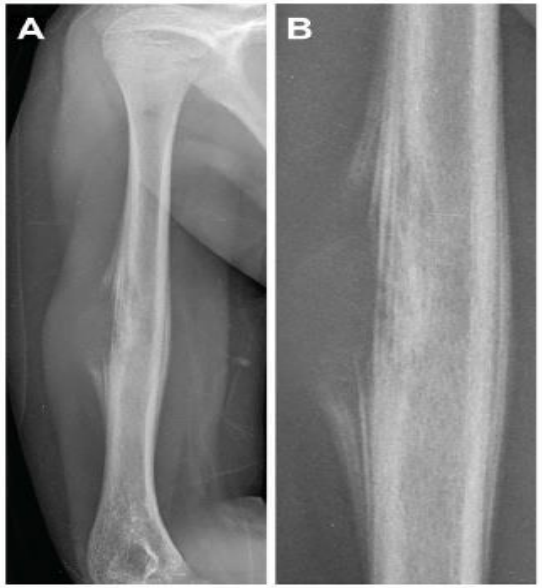
PNET: it is primitive neuroectodermal tumour.

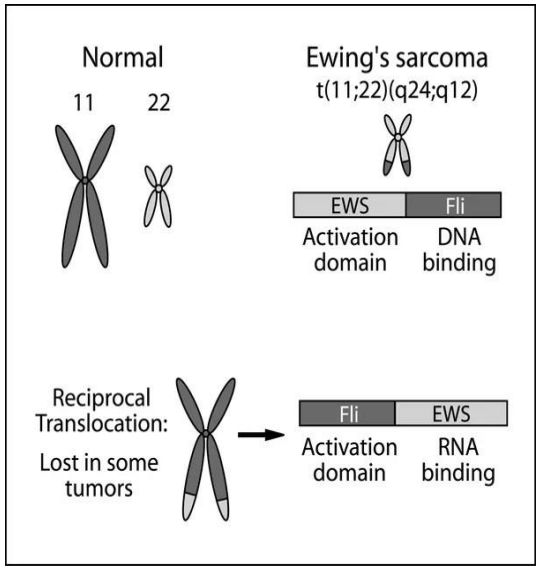
They have general characteristics , they are Primitive , they have neuroectodermal differentiation .

- **2nd most common sarcoma of bone after osteosarcoma** (osteosarcoma is number one)
- **< 20 years, diaphysis of long bones usually you don't see it below the age of 10 (so between 10 and 20)**
- **The most common translocation, 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.**
- **Trx: neoadjuvant CT** (chemotherapy) **followed by surgery; long term survival now reaches 75%**

ES FEATURES:

This is the **diaphysis** of the humerus, notice that this tumor infiltrates the soft tissue and elevates the periosteum causing codman triangle which helps you understand that codman triangle isn't specific for osteosarcoma only



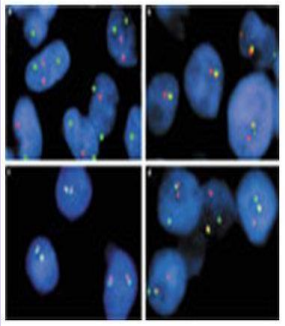


this is the old method by classic cytogenetic analysis, where the translocation occurs between the chromosome 11 & chromosome 22 (11 is a **bigger** chromosome compared to 22)
And the fusion protein product from this translocation.

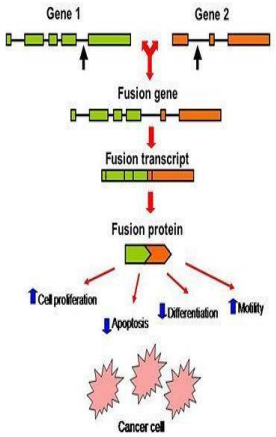
This is translocation t (11,22), there is 2 of them actually (EWS FLI1), (EWS FLI2).
this is a picture of fish analysis, so this is probably the most sensitive test for Ewing sarcoma using florescent In Situ Hybridization (FISH).

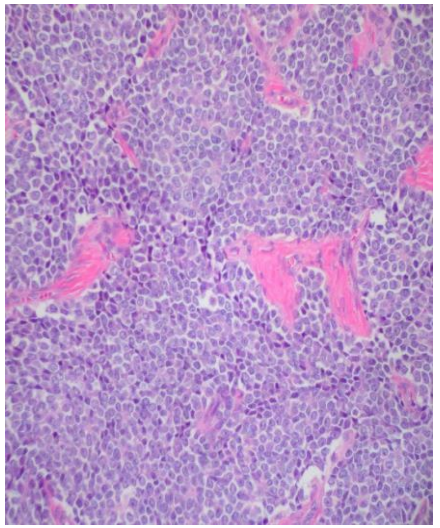
Positive translocation of EWS gene:

EWS FLI1	t(11;22)(q24;q12)
EWS FLI2	t(21;22)(q22;q12)



Pozit. EWS/FLI1 - FISH





a lot of blue cell tumor destroying the bone shown in this histological section

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

GIANT CELL TUMOR OF BONE

we don't know the cell of origin

the location and the age are important to help you narrow your diagnosis

- Locally aggressive neoplasm of **adults** you don't see it in children and you don't see it at the age of 15 or even 20
- **Epiphyses** of long bones
- Osteoclast-like giant cells
- Rare malignant behavior 95% of the cases it behaves in a benign fashion (you can cure it; you can resect it)
- contain high levels of RANKL (which stimulates the differentiation of osteoclasts)
- Trx: curetting and put a bone cement or resection

Giant cell tumors often destroy the overlying cortex, producing a bulging soft tissue mass delineated by a thin shell of reactive bone (Fig. 21.25). Grossly, they are red-brown masses that frequently undergo cystic degeneration. Microscopically, the tumor conspicuously lacks bone or cartilage, consisting of numerous osteoclast-type giant cells with 100 or more nuclei with uniform, oval mononuclear tumor cells in between (Fig. 21.26).

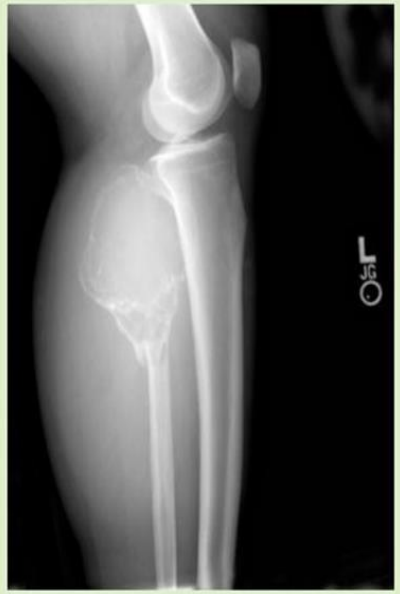


FIG. 21.25 Radiographically, giant cell tumor of the proximal fibula is predomi...

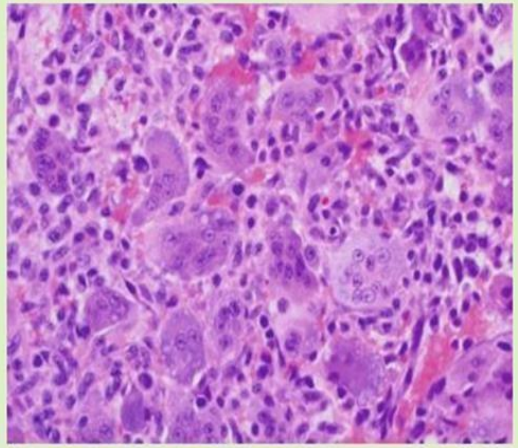


FIG. 21.26 Giant cell tumor illustrating an abundance of multinucleated giant c...

histological appearance of benign tumor: bubble appearance expanding the cortex of the bone without infiltration to the extra cortical space

and if the patient is 45 years 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 Resect it.

histologically you see sheets , wall to wall multi nucleated giant cells or osteoclast-like giant cells

so the tumor cells are the giant cells and the one in between (single mononuclear cells)

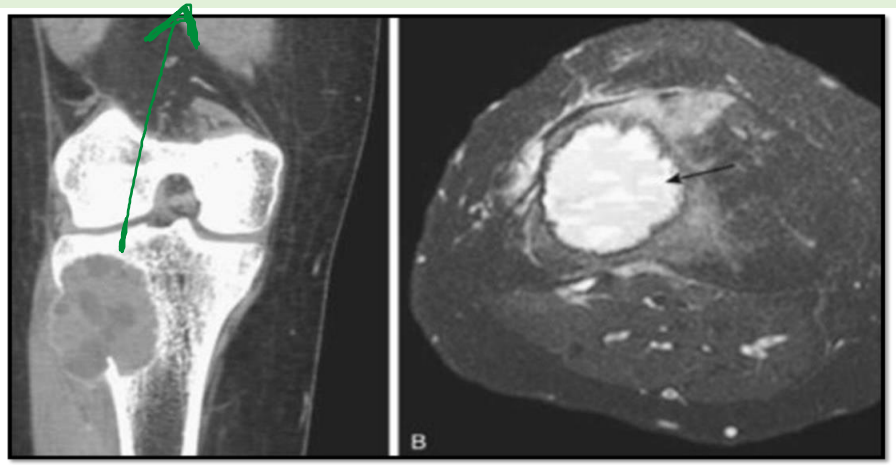
sometimes it is called osteoclastoma because the primary histology is composed of numerous wall to wall osteoclast like multi-nucleated giant cells

ANEURYSMAL BONE CYST (ABC):

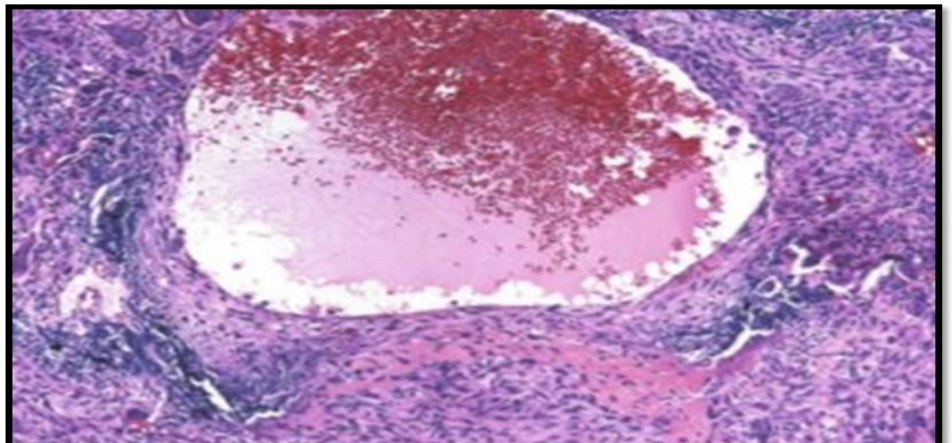
- **Benign tumor**
- **Blood filled cyst**
- **Metaphysis of long bones; adults**

Trx: curetting , bone cementing

If it's 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



by imaging the **metaphysis** of the bone
it could be ABC or giant cell tumor but if you look at it histologically you see a lot of blood coming out with fibrous septa



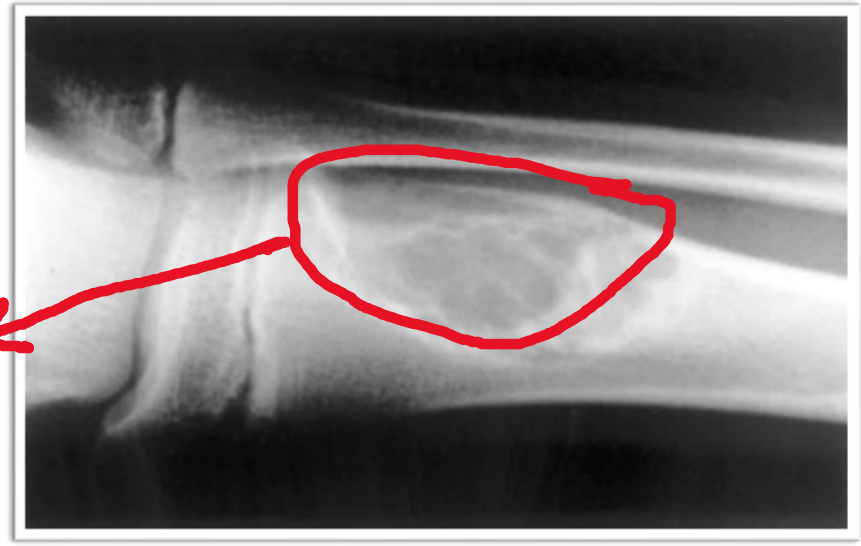
Also, we don't know the pathogenesis exactly, there are multiple theories .
And whether ABC is a tumor or a reactive process is still a debate. some scientists and investigators believe it's probably a reactive condition to a previous trauma.

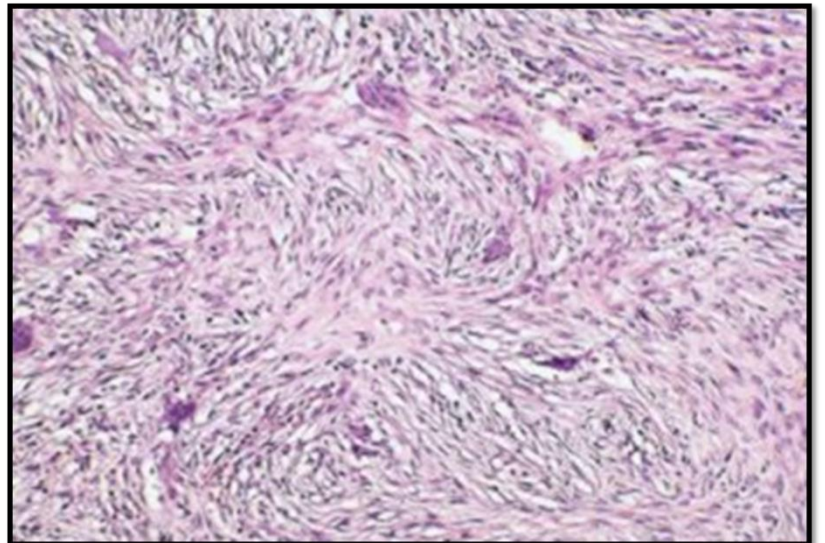
Others believe that there's monoclonal cells in those tumors , meaning that this is probably a neoplasm which is **characterized by a cystic space filled with blood and fibrous reaction around it.**

NONOSSIFYING FIBROMA: fibroma in the bone

- **Benign lesion, maybe reactive not a true neoplasm (other names: FCD, MFD**
- **Metaphysis**
- **Histology: bland fibroblastic proliferation**
- **May resolve spontaneously**

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





looks like a benign fibroma or a fibroblast .
There are some multi nucleated giant cells but they're not common (there is just five or six in here)

FIBROUS DYSPLASIA (FD):

- **Not a real tumor; rather a developmental abnormality of bone genesis due to mutations in GNAS1 gene (cAMP mediated osteoblast differentiation)** **and this will lead to abnormal bone formation.** So some people believe this is a tumor or a neoplasm, others believe this is rather a developmental dysplastic abnormal disease.
- **Forms of FD:** FD is actually a group of diseases or syndromes
  - **Monostotic: affecting one bone** (common bones affected by this FD are the maxillary & mandibular bones of the face causing what we call cherubism in children
  - **Polystotic: multiple bones**
  - **Mazabraud syndrome: FD** (monostotic or polyostotic) **+ soft tissue myxoma** (which is not a common tumor of soft tissue)
  - **McCune-Albright syndrome: polystotic FD + café- au-lait skin pigmentation** (multiple brownish pigmentation of the skin) **+ endocrine abnormalities (precocious puberty)** important

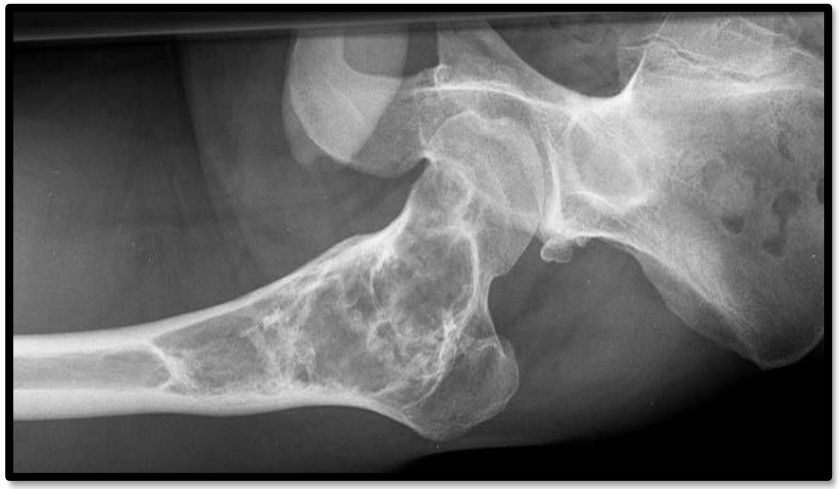
McCUNE-ALBRIGHT SYNDROME:

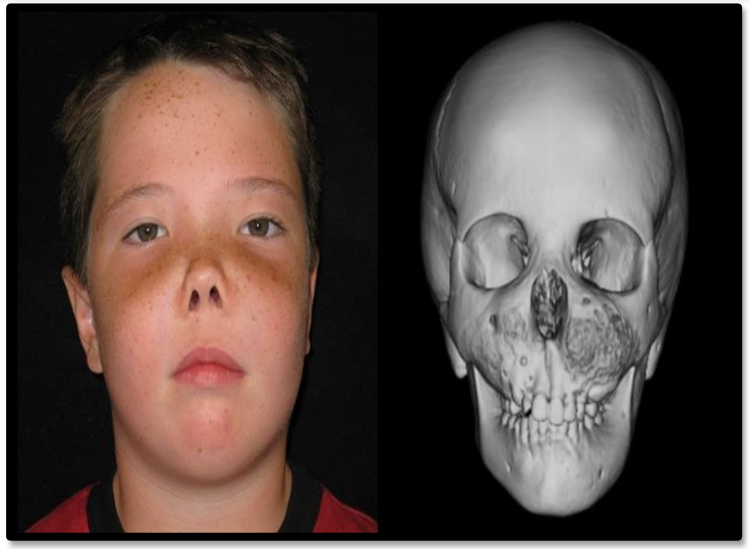
This is an abnormal bone feature . If you look at it , paget disease should also be considered

The **radiology** is slightly similar to paget disease , **biopsy** shows the appearance of Chinese letter

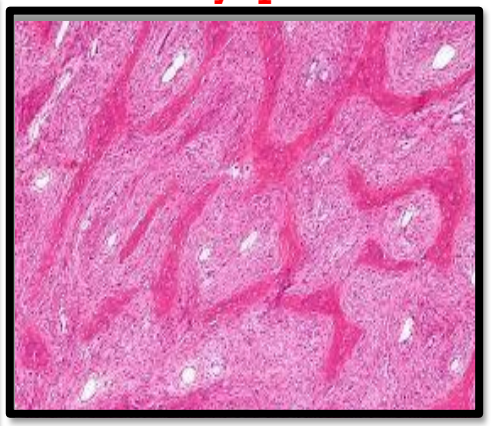
And this is cherubism in children , this patient has dysplasia of the maxillary bone

The femur, endocrine abnormality

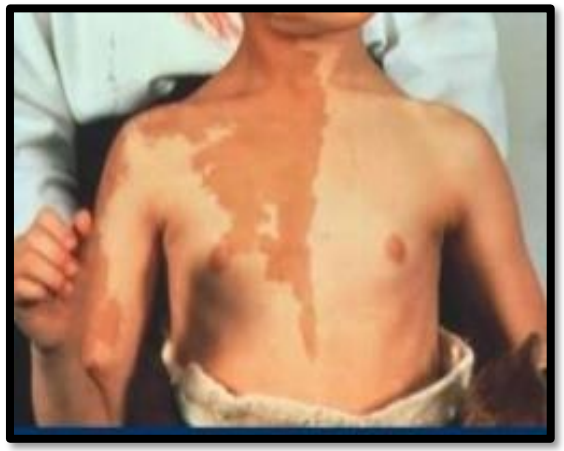




Biopsy, polyostotic fibrous dysplasia



café- au-lait skin pigmentation



if you take a **biopsy** and look at the abnormal trabeculae , you'll notice This appearance of **haphazard** arrangement of bone trabeculae & the fibrous matrix in between , it reminds us with the Chinese letter , so this appearance is called **Chinese letter appearance** in histology
So the classic characteristic microscopic feature of fibrous dysplasia is **Chinese letter appearance** with abnormal development of the bone trabeculae and matrix
So, you can differentiate histologically between Paget disease & McCune Albright syndrome

McCune Albright syndrome patient is a patient with polyostotic FD + **café-au-lait skin pigmentation** (and this is how it diffuse) **+ endocrine abnormalities (precocious puberty)**

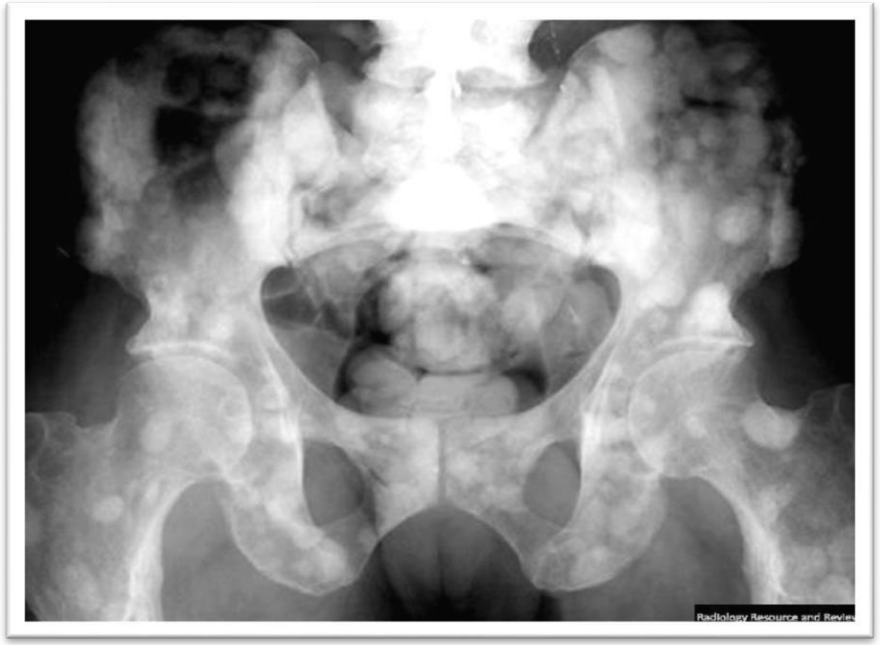
METASTATIC TUMORS TO BONE:

Five major characteristics or concepts you have to understand

- **Much more common than primary bone tumors** (so having tumors going to the bone from carcinoma or hematopoietic malignancies is much more common than seeing osteosarcoma , Ewing sarcoma and chondrosarcoma)
- **In adults: most** metastasis to the bone **are carcinomas** and the most common type of carcinoma which goes to the bone is adenocarcinoma (gland forming carcinoma); the most common primary source of carcinomas to the bone in adult are (those are the bonophilic carcinomas) :lung (lungs are the major cause of bone metastatic both in females and maless because we have a lot of females who are smokers now), **prostate, breast, kidney, thyroid & liver**
- **In children: Neuroblastoma, Wilms tumor and rhabdomyosarcoma** (you don't see carcinoma in children ,very rare)
- **Usually multiple and axial** (vertebral bodies, shoulder bones and pelvic bones); **mostly hematogenous spread to the bone** **(most common source of metastatic)**
- Radiologically when you look at these & make a diagnosis , you can have those by simple X-ray : **Lytic, blastic or mixed** metastasis **(via mediators secretions)**

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

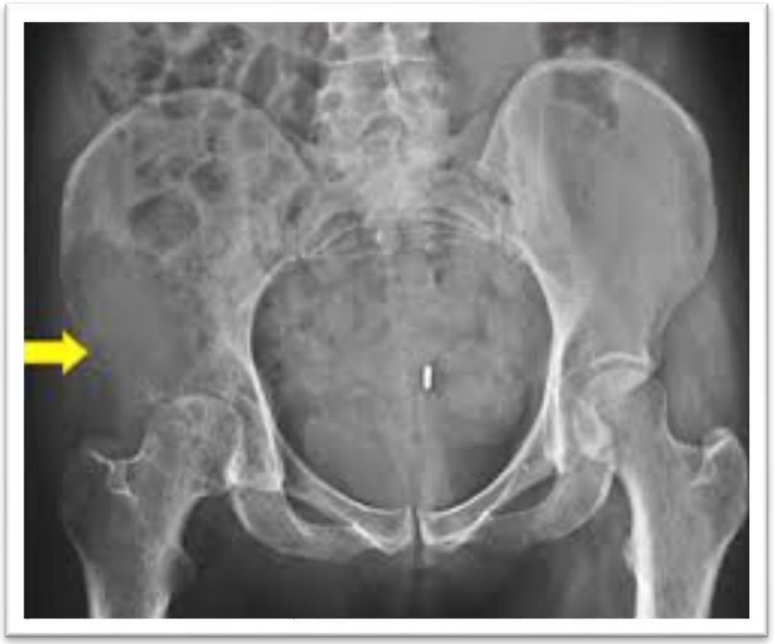
BLASTIC METASTASIS



This is how it look in x-ray

This is a patient with hundreds of blastic metastasis . The primary source here was the prostate, the prostate is commonly associated with blastic metastasis.
When a Prostate tumor goes to the bone , it can cause blastic metastasis & it can also cause lytic, but the blastic is much more common than lytic in prostate malignancies

LYTIC METASTASIS



This is another patient were the bone is eaten in multiple areas (vertebral body, pelvic bone and the femur), this is bad prognosis so this is lytic metastasis . the most common primary of those is probably carcinoma (adenocarcinoma in lungs) this is stage 4 (bad prognosis), after this appearance most of patient don't survive beyond 6-12 months.

Summary

This summary is really helpful

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.