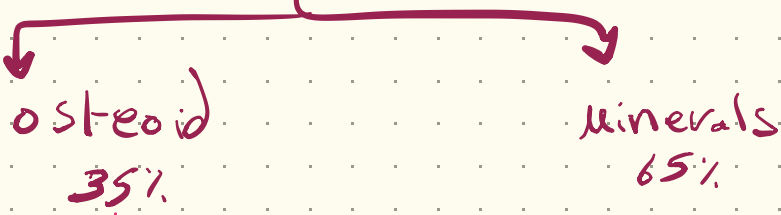


Bone structure

① Matrix →

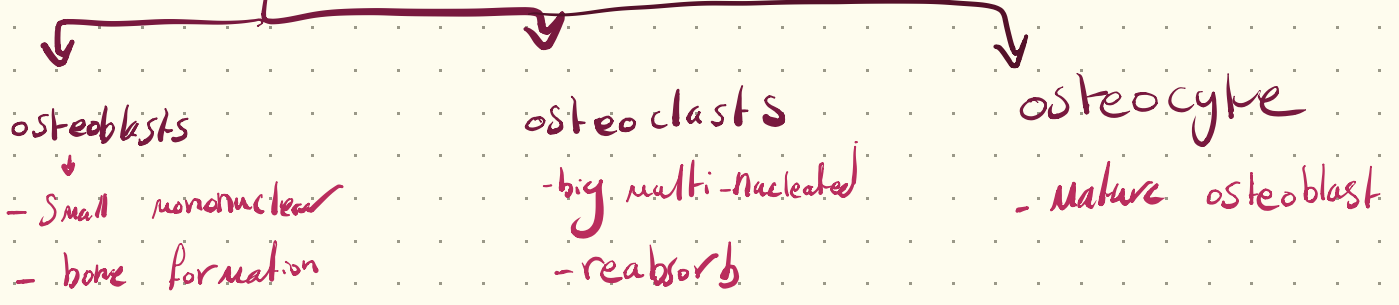


Lecture

1

Done by : farah hasanah

② Cell →



(Lamellar vs Woven)

- ① Mature
- ② linear
- ③ organized
- ④ equal distribution of osteocyte & osteoid

- immature bone
- in embryos and new baby
- in adult → mean there is wrong
- ↓
- fracture → cancer

(development of bone)

endochondral

- long bones are formed
- (cartilage \rightarrow bone)
- first start in diaph. and the last place where the ossification is happen in epiphysed.

intramembranous

- flat bones are formed
- Membrane $\xrightarrow{\text{into}}$ bone
- the origin is mesenchymal

Remodeling and homeostasis \rightarrow

+ Osteoclast differentiation	- Osteoclast differentiation
PTH (Parathyroid Hormone)	BMPs (bone morphogenic proteins)
IL-1	Sex hormones (estrogen & test.)
Steroids	

meaning the reabsorb is high and weak bone and less bone density.

meaning less reabsorb and bone strong

كلا سبغ (osteoblast) تحتوي على (RANK - ligand)

(+) bind

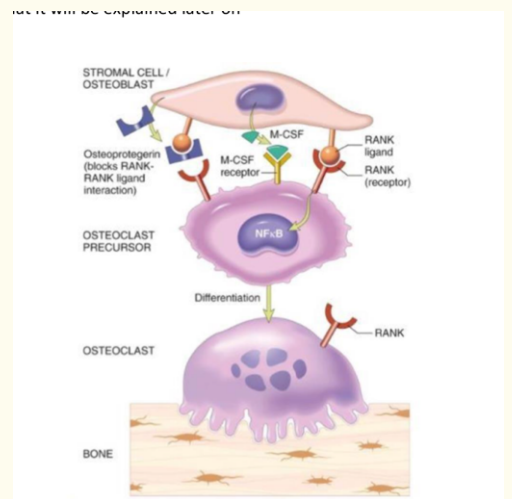
(RANK receptor) (precursor osteoclast) سبغ

يؤدي إلى إفراز (M-CSF) from osteoblast + (cytokin secreted by stromal cell)

(M-CSF) receptor from (precursor osteoclast)

↓
(Mature osteoclast) \rightarrow cytoplasm \uparrow size nucleus

receptor all at surface of (pre cursor - osteoclast)



- Congenital disorders of the bone :-

Dysostosis

abnormal bone

① abnormal condensation and migration of mesenchyme (embryonic)

② genetic abnormalities in certain genes called the "homeobox" genes

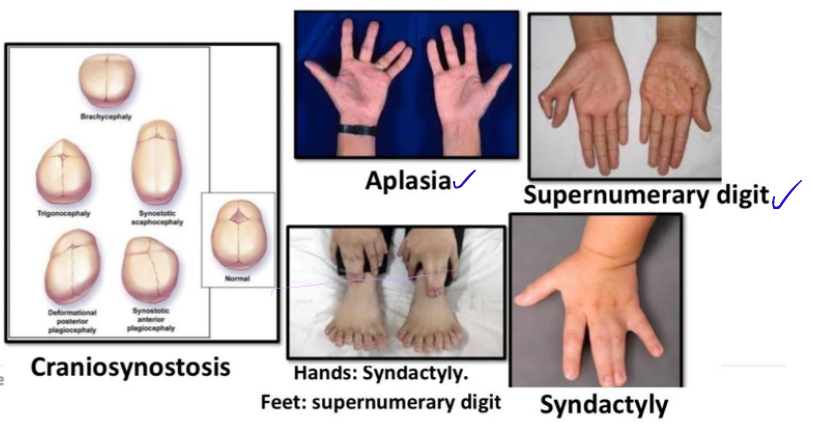
③ abnormal in cytokines and their receptors (have new role in condensation and migration of mesenchyme)

Example :-

① Aplasia: no formation (4 fingers) \rightarrow apoptosis

② Syndactyly and craniosynostosis:-
 fusion of fingers
 problem in apoptosis
 problem in suture of the skull that effect brain growth

③ Supernumerary digit:
 additional finger or toe



Dysplasia

① "disorganization of the bone and cartilage"
 mutation gene that control the development and remodeling of bone

② Not Preamalignant

③ Autosomal Dominant

Ex \rightarrow

① Achondroplasia \rightarrow the most common case of the dwarfism

\rightarrow the problem in endochondral ossification \rightarrow long bone

\rightarrow the major one is FGFR3 (fibroblast growth factor receptor)

\rightarrow no effect in intelligence or reproductive life normal life

\rightarrow effect on:- big head and frontal bossing
 big chest wall

② Thanatophoric dysplasia

- common lethal of dwarfism

(\downarrow baby die in uterus or at birth or after birth)

\downarrow because there's small chest leading to respiratory insufficiency

- mutation FGFR3 (fibroblast growth factor receptor)

- can diagnosed early by ultrasound

③ Osteogenesis imperfecta (Brittle bone disease)
 (impaired bone formation)

\rightarrow inherited disorders of connective tissue

\rightarrow group of disorders (not single)

classification according to the

Severity of disease \rightarrow Type 1 \rightarrow relative normal life "most benign"
 \rightarrow Type 2 \rightarrow more severe

\rightarrow but it's deficiency by type 1 collagen synthesis

the symptom \rightarrow

① blue sclera ② hearing loss

③ teeth abnormality ④ bone weak easy to break

④ Osteopetrosis →

- very hard bone
- opposite of osteoporosis
- group disorder → rare
- impaired osteoclast function:
 - ↓ resorption bone
 - collagen ↑ متكاثف
- Symptom:-
 - ① fracture → كسر عظام كسر العظام
كسر العظام
 - ② leukopenia → قلة كريات الدم البيضاء
bone also كسر كسر bone marrow
- Dx → x-ray

Lecture

2



Metabolic Disorders:-

osteopenia
(1-2.5) below the mean

osteoporosis
↓
Severe osteopenia

2.5 below the mean

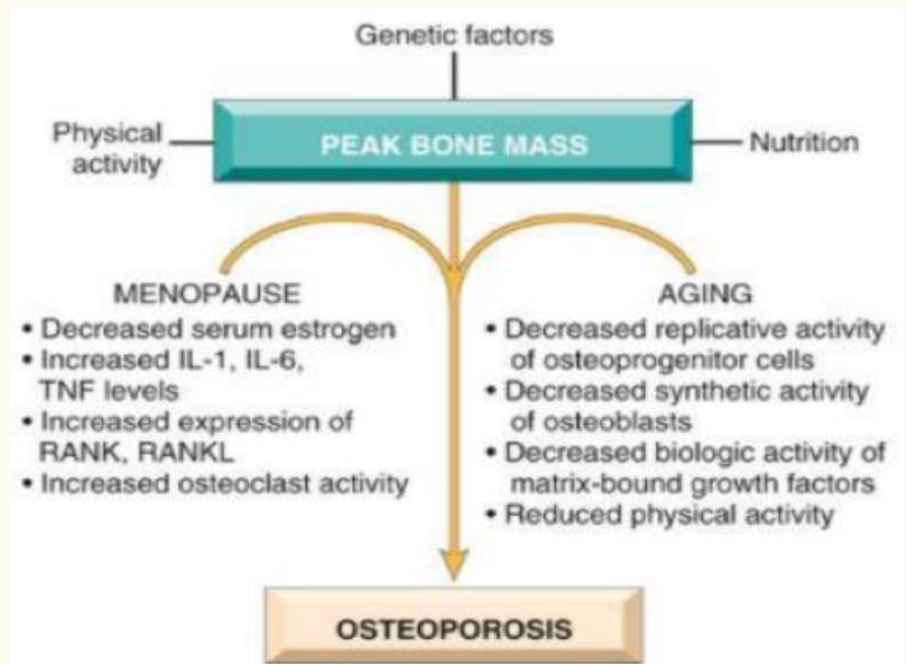
Osteoporosis

Primary

Secondary

More common
Senile (aging)
postmenopausal

- less common
↓ 1.5
- hyperthyroidism
- malnutrition
- steroids



• the treatment of it is:
↳ not easy, so prevention is important

Clinically :-

① Vertebral fractures → ① density low

② Femur and pelvic fractures
(immobility, PEs, pneumonia)
↓
pulmonary embolism
تجلط شرابين
في الرئة

Diagnosis :- Special imaging technique
(bone mineral density) **BMD**

↓
Dual-energy x-ray absorptiometry (DEXA) bone densitometry

Prevention and treatment:-

① Exercise

② Calcium and Vitamin D

③ Bisphosphonates (Medication) → reduce osteoclast that lead apoptosis to it.

④ Denosumab:- drug anti-RANKL (block osteoclast activation)

⑤ Hormones (estrogen)

↳ but have side effect

(HRT)

+ Hormone replacement

therapy: side effect

like → DVT → (deep Venous Thrombosis)

↳ (Stroke + hypertension) →

estrogen is alone

Progesterone

Rickets and osteomalacia (Vitamin D related disease)

↓
in children

↓
in adult

The Symptom →

- ↓ Mineralization of bone → (because the V.D) is responsible to enters cut to bone, So if V.D ↓ the mineralization of bone will ↓
- ↑ Fractures (microfracture)
- Skeletal deformities
- growth isn't normal.

Hyperparathyroidism :-

Primary

Hyperfunction
in the parathyroid
it self

Secondary

chronic renal failure

فتالي الكالسيوم ↓ مما يستج
Parathyroid to secrete (PTH)
that lead to hyperplasia.

Tertiary

Hyperparathyroidism classification

Different causes and features of hyperparathyroidism - raised parathormone (PTH).

	primary	secondary	tertiary
pathology	Hyperfunction of parathyroid cells due to hyperplasia, adenoma or carcinoma.	Physiological stimulation of parathyroid in response to hypocalcaemia.	Following long term physiological stimulation leading to hyperplasia.
associations	May be associated with multiple endocrine neoplasia.	Usually due to chronic renal failure or other causes of Vitamin D deficiency.	Seen in chronic renal failure.
serum calcium	high	low / normal	high
serum phosphate	low / normal	high	high
management	Usually surgery if symptomatic. Cinacalcet can be considered in those not fit for surgery.	Treatment of underlying cause.	Usually cinacalcet or surgery in those that don't respond.

NICE have issued guidance for the use of cinacalcet in what they call refractory secondary hyperparathyroidism which is classified as

Clinically :-

Brown tumor

① -cystic

② weak b and full of blood

Not neoplasm
Just looks like it.

③ look like mass

① osteoporosis: fibrosa cystica:

② osteitis fibrosa cystic

③ von Recklinghausen's
disease of the bone

(3+2+1) = 6
without von.

Recklinghausen's
neurofibromatosis type 1

no inflammation but it's describing

severe untreated hyperparathy.

PAGEt disease of bone (Osteitis Deformans)

Lecture

3

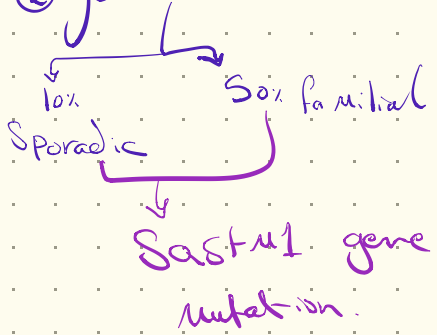
(3 phases)



the cause :-

① 1% in USA (geographic variation)
↳ Northern more than South America

② genetic factors



③ environmental factors :-

④ Viruses (measles and RNA viruses)

Mosaic Pattern

Paget disease have several type :-

- ① breast → 100% cancer
 - ② in Vulva → 25% cancer
- } in skin Epidermis

Clinically →

① 85% → polyostotic "more than one bone"
15% → monoostotic "one bone"

② Axial skeleton more affected (Axial bone) more risk fracture.
 → vertebral body
 → shoulder girdle
 → upper femur
 → pelvic bones
 → spinal cord

③ Most patient are mild and asymptomatic (Pain)

"Vague Pain"
Crisis

- microfracture
- nerve compression

Dignosis :-

↑ Serum alkaline phosph
 ↓ bone ↓ liver

+ normal Ca and P₀₄
 ↳ no v.D deficiency and hyperparath.

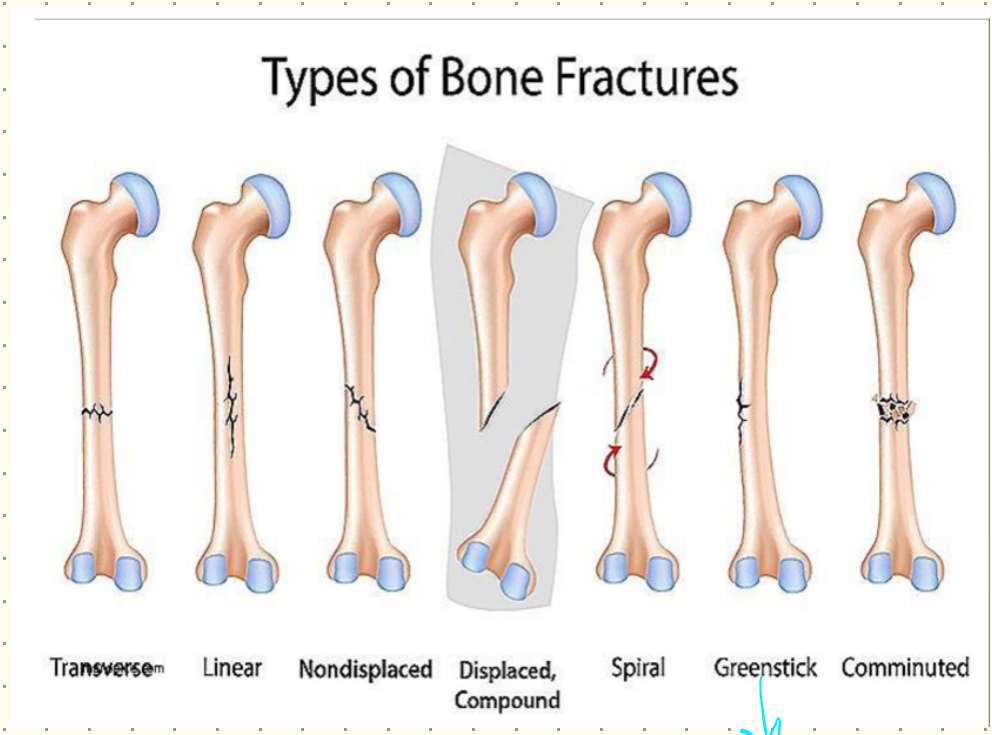
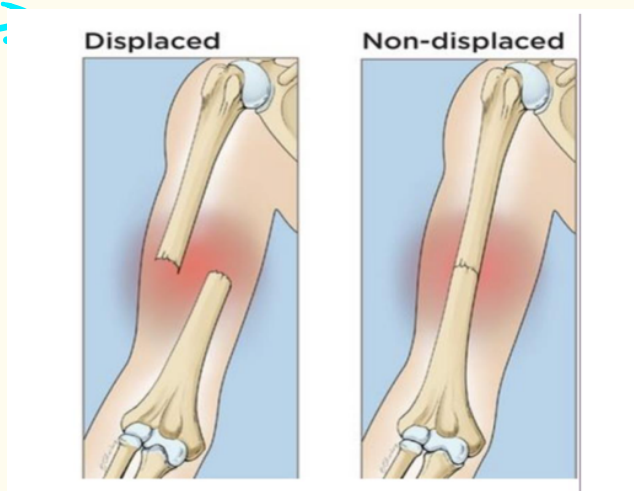
④ Leontiasis ossea (lion face) // Sever Paget "

⑤ Plat basi → invagination of skull base

⑥ osteoarthritis

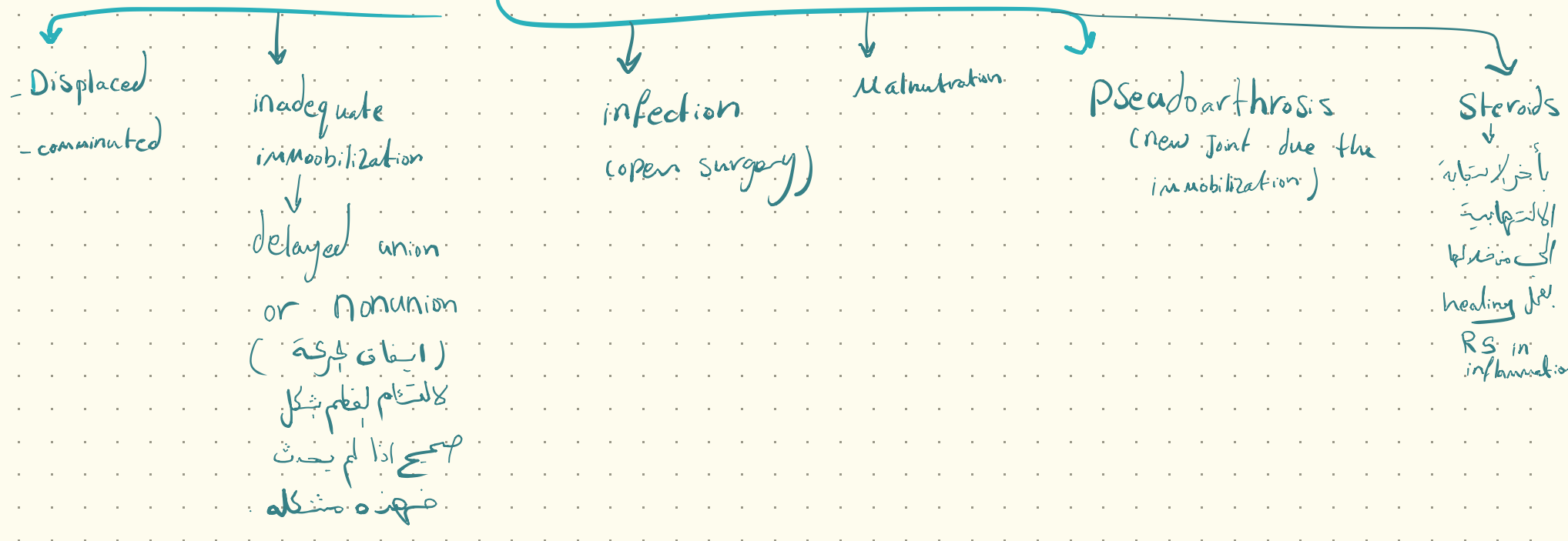
⑦ osteosarcoma

Fracture :-



* in infants
+ after 2 day
there's hematoma

Factor impacting proper healing :-

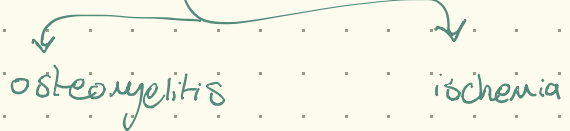


Osteonecrosis (Avascular Necrosis)

→ most bone necrosis is caused by compression of vessels

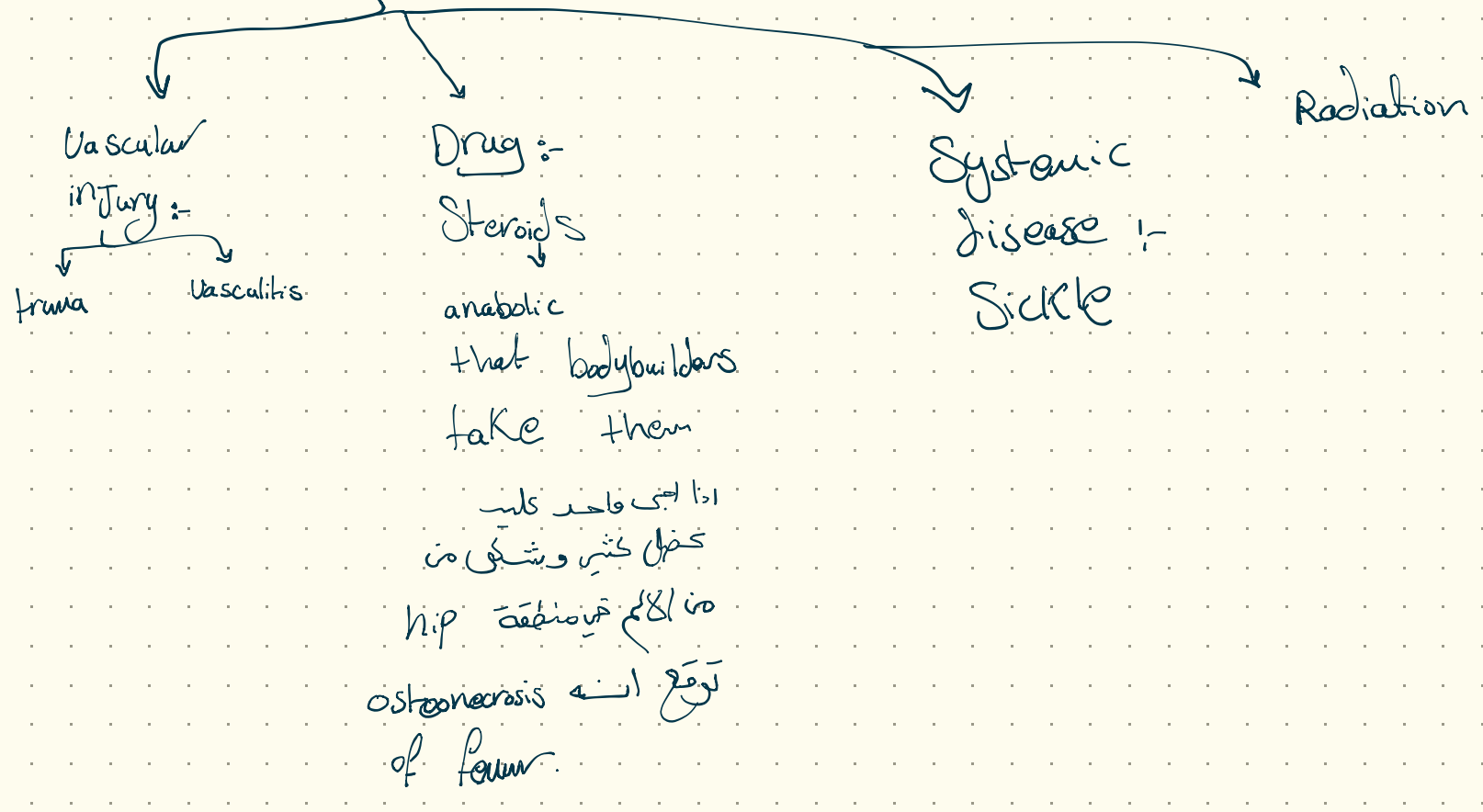
→ infarction (ischemic - cut blood supply - necrosis) of bone and marrow

→ osteonecrosis: death in bone tissue

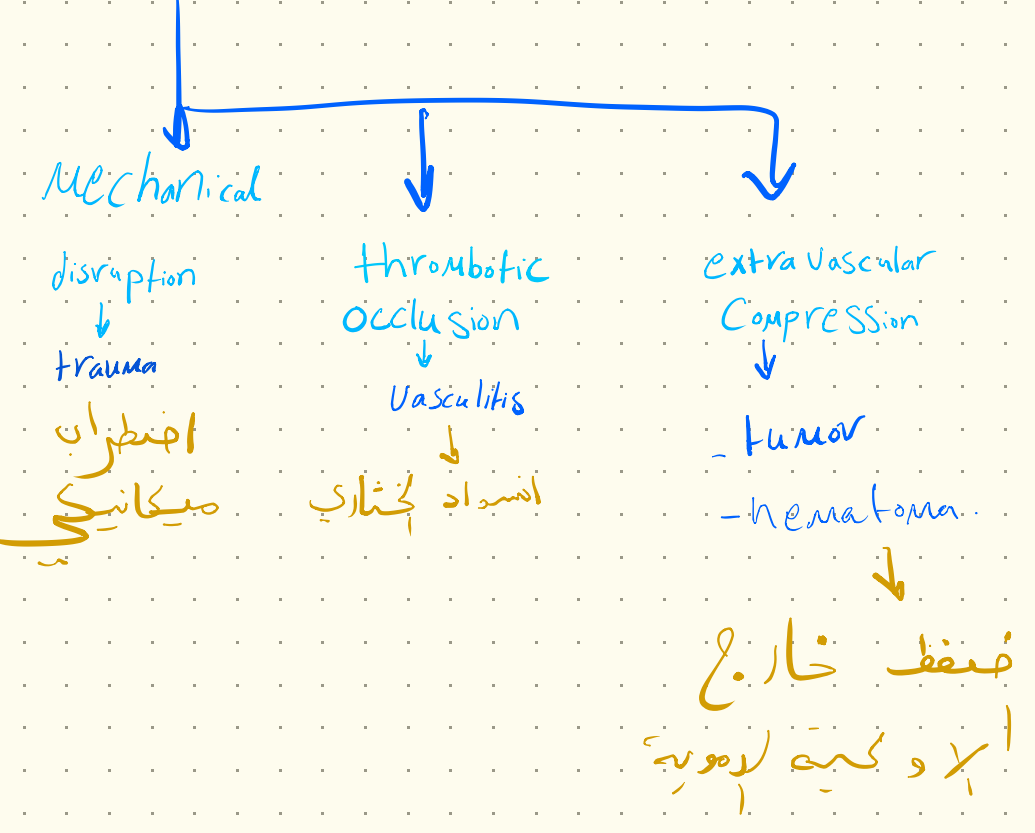


→ most bone infected → head of femur

Associated conditions:-



Mechanism:-



the shape of fraction area is pyramidal triangular

- yellow color
- severe pain of bone

Lecture

4

Osteomyelitis → inflammation of bone marrow

(Case)

Systemic infection:-

- * detectable body
- * die to septicemia
- Such as gram negative
- * *C. albicans*

Primary

Solitary focus: "more common"

- only bone is infected
- from surgical procedure
- + *Staph. aureus*

bacterial is the most common cause of osteomyelitis

Pyogenic osteomyelitis = pus forming inflammation of the bone
Case by (infecting organism)

Staph. aureus

80%/90%
the most common
cause of acute
Pyogenic osteomyelitis

① in patient with recurrent UTI
② IV abusers
مضادات حيوية

Escherichia Coli

Klebsiella

Pseudomonas

Mechanism of spread

Hematogenous spread

most common and occurs mainly in children
Example: Otitis media, Tonsillitis, Impetigo of the skin
بكتيريا يودي الى blood (bacteremia)
acute pyogenic osteomyelitis

Extension from a contiguous site

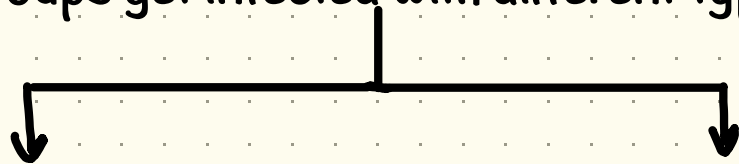
occurs mainly in adults.
Example: A patient with uncontrolled diabetes has a diabetic foot with severe ulcers, infections and gangrenes in the lower limb
→ bacteria goes to underlying bone.

Direct implantation after compound fractures and orthopedic surgeries

Example:

- 1) A patient with a compound fracture in which the fractured bone is communicating with the overlying skin and becomes exposed to environmental bacteria that might enter and cause secondary osteomyelitis.
- 2) A patient with a closed fracture in which the skin was intact needed a surgery, and during the surgery the bone might have got infected.

Different age groups get infected with different type of organisms.



• 1 Neonates :

Haemophilus influenzae & Group B strep.

↓
pyogenes

• 2 Sicklers :

Salmonella, ①

patients with sickle cell disease are more likely to develop Salmonella pyogenic osteomyelitis for some reason.

Gram -ve osteomyelitis

~ Important Note: The most common cause of pyogenic osteomyelitis for patients with sickle cell disease is (Staph. aureus but we should think about Salmonella.

• aureus ←
Salmonella ←

upto

* Note

In 50% of acute osteomyelitis cases, no organisms can be isolated (blood culture is negative) - but that doesn't mean that there is no bacteria Why?, mainly due to previous improper administration of antibiotic, so improper diagnosis and treatment interferes with your blood culture results [patient that was partially treated > False Neative result)

Stages osteomyelitis:

Acute inflammation -> ①

Spread of mediators & neutrophils and signaling molecules -> ②

Recruitment of WBC ->

Pus Formation (exudate) ->

Vascular thrombosis ->

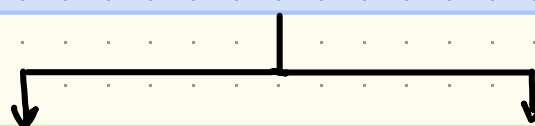
Necrosis of the bone->

Liquefactive necrosis ->

Lifting of periosteum late sign of acute Pyogenic osteomyelitis)

any bone can effect

Long bones get infected more often .



□ in adults :
Metaphysis & epiphysis

□ in children :
Metaphysis Or epiphysis (not both)

↓
according to blood supply

ACUTE

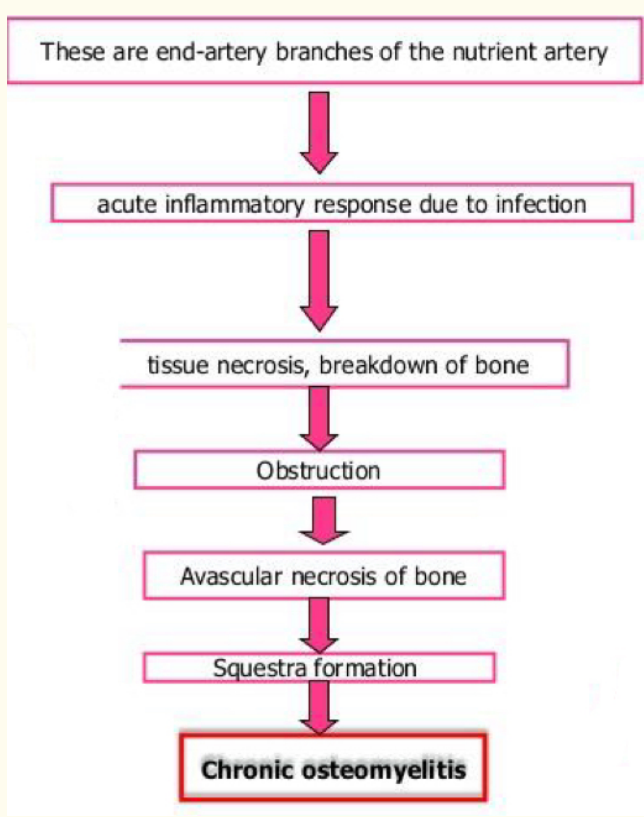
الحاد

PUS & NEUTROPHILS

CHRONIC

LYMPHOCYTES AND PLASMA CELLS

And Macrophages



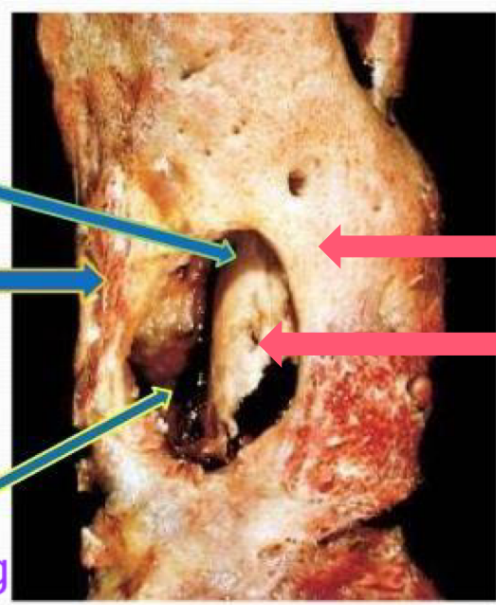
Important terms regarding to Osteomyelitis

1. ^{dead} **Sequestrum**: is the necrotic (dead) bone that is embedded in the pus / infected granulation tissue.

2. ^{reactive bone} **Involucrum**: is the new bone laid down by the periosteum that surrounds the sequestra. (Involucrum: active bone forming region) / (the area of the active bone that surrounds the dead bone).

3. ^{near (open)} **Cloaca**: is the opening in the involucrum through which Pus & sequestra make their way out.

- **Sequestrum** is the necrotic bone that is embedded in the pus/infected granulation tissue. **Dead necrotic bone**
- **Involucrum** is the new bone laid down by the periosteum that surrounds the sequestra. **Viable bone (reactive)**
- **Cloaca** is the opening in the involucrum through which pus & sequestra make their way out. **Pus (sinus draining from periosteum)**



Reactive (viable) bone

Dead bone

-In infants the presentation is subtle, with only unexpected fever.

-In adults it appears as a local pain.

نیزد افغ

- عرضة ضعف جسمي، خفقان

- الالم موضعي جسمي لكبار

Manifestations of Hematogenous Osteomyelitis :

Fever ,

malaise (loss of appetite) ,

chills

Leukocytosis (increased WBC count)

(Throbbing) pain locally (helpful for differential diagnosis) it is a characteristic of presence of pus .

تنص

Diagnosis

You should have a high index of suspicion

لك ما تشاهد وتصل بالان
ومعرفة صحتها

X-ray is done, though, X-ray maybe normal in early phases -> however we shouldn't wait till we see the X-ray lytic changes

Biopsy and bone cultures are required to identify the pathogen in most instances.

-Important note :

-normal X-ray does not rule out the presence of osteomyelitis ,
-actually if we see changes in the X-ray scan due to pyogenic osteomyelitis , that means the patient is in a late phase of the disease.

Treatment

Admission, →

دخول مستشفى

IV antibiotics

surgical drainage of pus.

Just we make
surgical if there
pus.

Proper IV antibiotics for Staph. aureus are given to patients in 80-90% of cases , unless the patient suffers from UTIs or is a drug abuser , then you should think of more broad spectrum antibiotics.

سلاحي فالتس
صناعة
تاخر

Causes of Chronic Osteomyelitis

Delay in diagnosis

Extensive necrosis (unlucky patients will have huge amount of necrotic bone in acute osteomyelitis which is very hard to clear with antibiotics due to the presence of an extremely virulent organism)

Inadequate therapy: Inappropriate antibiotic or incomplete treatment with an antibiotic

Weakened Host Immunity: the patient is taking immunosuppressive drugs or steroids

COMPLICATIONS OF CHRONIC OSTEOMYELITIS:

Pathologic fractures (abnormal bone)

Secondary amyloidosis: deposition of a protein called amyloid; amyloidosis is associated with chronic diseases including chronic

Endocarditis: a rare condition that involves inflammation of the heart lining, it can be lethal

Sepsis: the bacteria and bacterial toxins in the blood stream.

Squamous cell carcinoma of draining sinus: the draining sinus around the skin can cause Squamous cell carcinoma and it is very rare.

Sarcoma of the bone: similar to paget disease of bone.

Mycobacterial Osteomyelitis

- 1) Caused by mycobacterium tuberculosis.
- 2) It is a chronic type of inflammation
- 3) Used to be a disease of developing countries.

Now: there are more cases in developed countries like the USA due to immigration, but the main reason is immunocompromised patients.

1-3% of patients with pulmonary or extrapulmonary TB can have bone involvement

Carcinoma / Sarcoma

Hematogenous (spreads through the blood) or direct spread

Examples :

I. TB in the lung can spread to the ribs or the humerus through the blood.

II. TB in the skin (diabetic foot), the bacteria goes to the underlying bone.

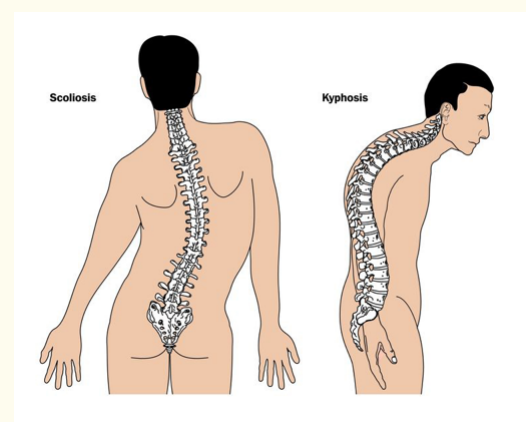
Clinically: it is very hard to diagnose maybe subtle and chronic course, so you should have an **index of suspicion**

معرفة مسبقة

TB SPONDYLITIS (POTT DISEASE)

Pott disease: is a disease caused by TB infecting the vertebral body (destructive spine TB)

- 1) Can be referred to as chronic osteomyelitis of the vertebral body
- 2) After taking a biopsy and staining it with H&E, we can see necrotizing granuloma.
- 3) Patients start to get better like magic after starting the regimen of anti TB drugs
- 4) Difficult to treat
- 5) May lead to pathologic fractures (compression fractures) that may compress the nerves leading to neurologic deficit, scoliosis, kyphosis



BONE TUMORS AND TUMOR LIKE CONDITIONS:

Primary bone tumors are rare: That is, secondary bone tumors arising from metastasis are much common than those originating primarily from bone

Benign is much more common than malignant tumors

Most tumors in the First 3 decades (benign); adults more to be malignant

Treatment: aims to optimize survival while maintaining function.

BONE-FORMING TUMORS

benign

Malignant

OSTEOID OSTEOMA

OSTEOBLASTOMA

OSTEOSARCOMA

- more common than osteoblastoma
- Less than 2 cm
- Young men
- Metaphysis of long bones: Femur & tibia; nidus with surrounding bone reaction
- Severe nocturnal (night) pain (mediated by PGE2), relieved by aspirin & NSAIDS (non-steroid anti-inflammatory drugs).
- Treated by radiofrequency ablation (Removal of tumor by using strong radiation) or surgery

- More than :2 cm
- Posterior vertebrae;
- ~~no rim~~ of bone reaction by radiology
- Pain unresponsive to aspirin
- Treated by curetting (clean or scrape)

- malignant osteogenic tumor (forming abnormal bone- woven bone).
- Excluding hematopoietic tumors (myeloma and lymphoma), osteosarcoma
- is the most common primary malignant tumor of bone.
- Osteosarcoma has a bimodal age distribution; 75% of osteosarcomas occur in adolescents (between 10-15).
- The smaller second peak occurs in older adults (between 55-65) who frequently suffer from conditions known to predispose to osteosarcoma, such as Paget disease, TB of bone and previous radiation. These are referred to as secondary osteosarcomas.
- The most common sites are the metaphyseal regions of long bone (distal femur and proximal tibia) around the knee, but it can happen in another location.
- Patients present with Progressive pain or pathologic fracture.
- Imaging: large destructive and infiltrative lesions with Codman triangle
- Approximately 70% of osteosarcomas have acquired genetic abnormalities:

ⓧ Histologically, both look like reactive bone with some hemorrhage and reactive giant cells, you don't see atypia. At our level, they look the same histologically

The tumor frequently starts in the bone, and they go deep into the medulla and outside into the periosteum followed by infiltration of the periosteum and the surrounding soft tissue, they elevate the periosteum, and they start producing abnormal woven bone leading to the appearance of an angle, known radiographically as Codman triangle .

presence of mets (metastases) at diagnosis is a bad prognostic factor.

the molecular genetic changes of osteosarcoma are actually complex and we don't use them routinely for diagnosis or for prognosis, the histology imaging is more than enough and it is not really a difficult diagnosis.

OSTEOSARCOMA FEATURES

simple x-ray morphology,

MRI morphology

histological section,

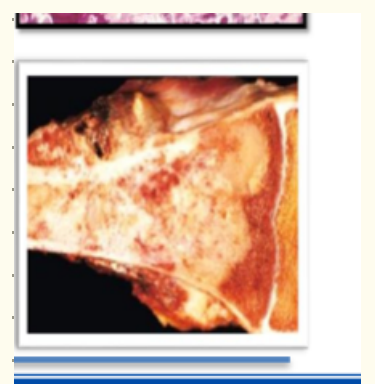
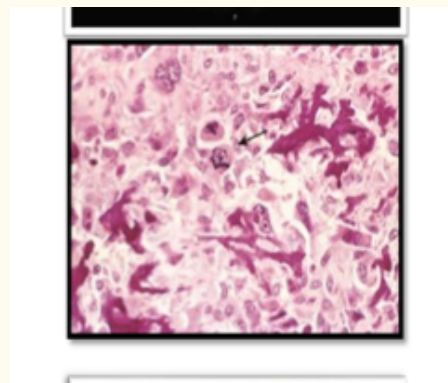
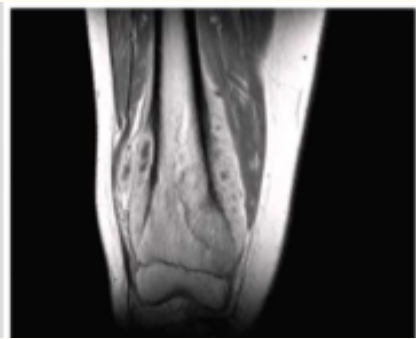
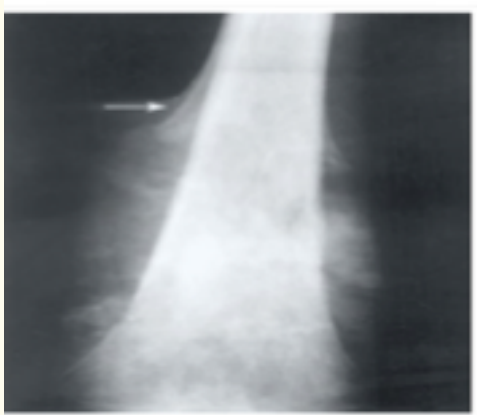
gross examination of the specimen

distal femur showing a process which started in medulla of the bone and infiltrates the surrounding tissue elevating the periosteum and this angle between actual bone and the periosteum is called Codman's triangle

shows the processes, tumor arises at the metaphysis and extends to the soft tissue, the skeletal muscle infiltrated by this tumor, and this is the periosteal elevation causing Codman triangle.

contains malignant osteoid by malignant osteoblast with haphazard patterns of frequent abnormal mitosis, it's all woven bone.

if we cut the distal head of femur longitudinally, we see an excess articular cartilage arises from it.



OSTEOSARCOMA TREATMENT

treated with a multimodality approach (MDTeam) that consists of

(1) neoadjuvant chemotherapy

using chemotherapy before the main treatment which is surgery)

2) surgery

to remove the tumor

(3) chemotherapy

to prevent or to kill any metastatic possibility.

Radiation

to control the local diseases.

These aggressive neoplasms spread hematogenously to the lungs. There are some exceptions, they don't usually go to the lymph nodes.

CARTILAGE-FORMING TUMORS

Osteochondroma

-known clinically as **benign exostosis**, is a benign cartilage

capped tumor that is attached to the underlying skeleton by a bony stalk (composed of benign bone covered by benign cartilage)

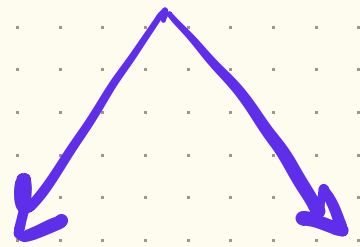
Osteochondromas develop in bones of **enchondral** origin and arise from the metaphysis near the growth plate of **long tubular bones**

-About 85% are solitary (in a specific area).

-The remainder are seen as part of the **multiple hereditary exostoses (MHE)** syndrome .

-It is rarely transformed to chondrosarcoma (<3-5%), if they do, usually they do in cases when they are **MHE (More Common in MHE)**.

If you diagnose a patient with **MHE**, you have to follow up closely to watch those osteochondromas to avoid transforming to malignant **chondrosarcoma**

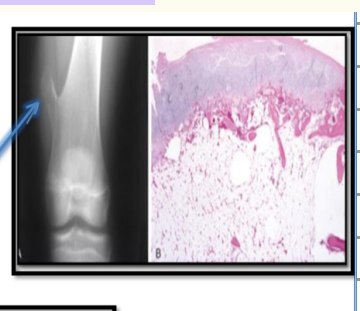


∅ X-Ray of the distal femur:

osteochondroma, notice the tumor with normal bone and cartilage. very classic appearing of a mass with normal cartilaginous cap, you don't see destruction of the tissue around it ((no infiltration or Codman triangle))

Microscopic histology:

if you cut this tumor and you look at it, you will see normal cartilage, normal subchondral bone and bone marrow .



normal

CHONDROMA (ENCHONDROMA)

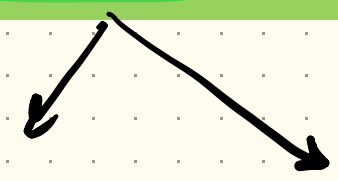
1)They arise within the medullary cavity (medullary enchondroma) or on the cortical surface (cortical chondroma

2)Enchondromas are usually diagnosed in individuals **20 to 50 years of age**.

3)Typically, they appear as solitary metaphyseal lesions of the tubular bones of the **hands and feet**

4)**Ollier disease**: Multiple enchondromas.

5)**Maffucci syndrome**: multiple enchondromas + skin



Microscopic histology:

normal benign cartilage & No atypia

X-ray Radiology:

Cartilaginous appearance on x-ray, no destruction or infiltration, no elevation in the **periosteum (no Codman's triangle)**

normal

Chondrosarcoma

Chondrosarcoma is about half as common as osteosarcoma (50% incidence of osteosarcoma)

∅ chondrosarcoma is less common, if you treat 20 cases of osteosarcoma, you will maybe treat 10 in chondrosarcoma

Prognosis of chondrosarcoma depends on the grade (Grade 1: excellent prognosis / Grade 3: bad prognosis) "شبه"

Grading is determined by cytologic and histologic appearance of the tumor

Chondrosarcomas commonly arise in the axial skeleton, especially in the pelvis, shoulder and the ribs. Usually present as painful, progressively enlarging masses ((large tumors)).

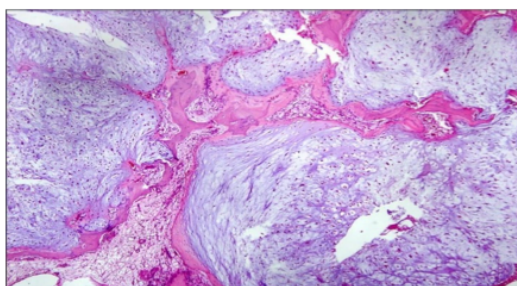
Individuals with conventional chondrosarcoma are usually in their 40-50 years of age.

Tumor stage measures the extent of tumor spread in the body → meta

Treatment: ¹ surgical treatment +/- ² chemotherapy & ³ radiotherapy (to prevent metastasis).

Histologically

abnormal malignant cartilage (it may be grade 1 or 2 but not grade 3 yet because you can still see the cartilaginous differentiation is obvious → low grade tumor



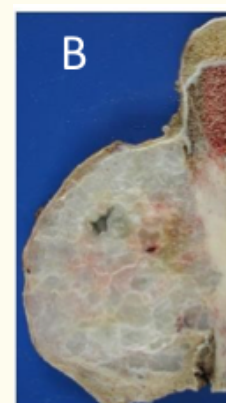
X-ray

Huge chondrosarcoma in the diaphysis of the humerus, there's Codman triangle, the tumor is infiltrating into the bone marrow and outside of the soft tissue elevating the periosteum



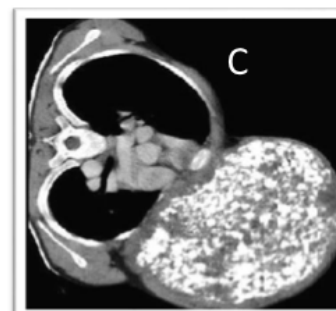
gross specimen

which when it was removed, characteristic cut surface of cartilaginous, it's large and infiltrating the soft tissue and the medulla bone.



CT

scan, where huge mass with a cartilaginous morphology on imaging, this is called bubble soap appearance



Tumors of Unknown Origin Ewing Sarcoma

Ewing sarcoma is a malignant tumor composed of primitive round cells.

second most common sarcoma of bone after osteosarcoma.

Entities previously classified as Primitive neuroectodermal tumor (PNET).

Also called Small blue cell tumor. (Note that small blue cell tumor isn't a specific diagnosis for Ewing Sarcoma, it is also present in lymphoma, neuroblastoma, rhabdomyosarcoma and others). 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

usually it is less than 20 years of age.

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

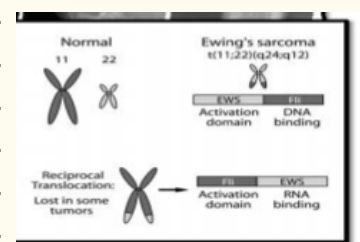
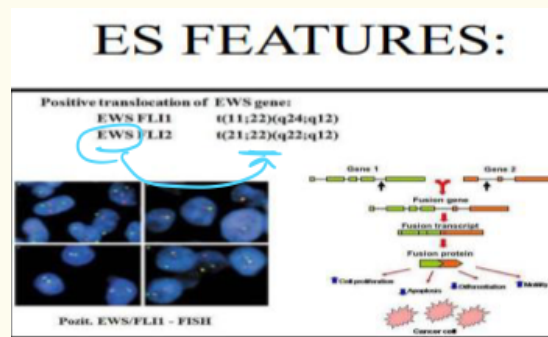
radiologic

this is translocation t (11,22), there is 2 of them actually (EWS FLI1), (EWS FLI2).

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.

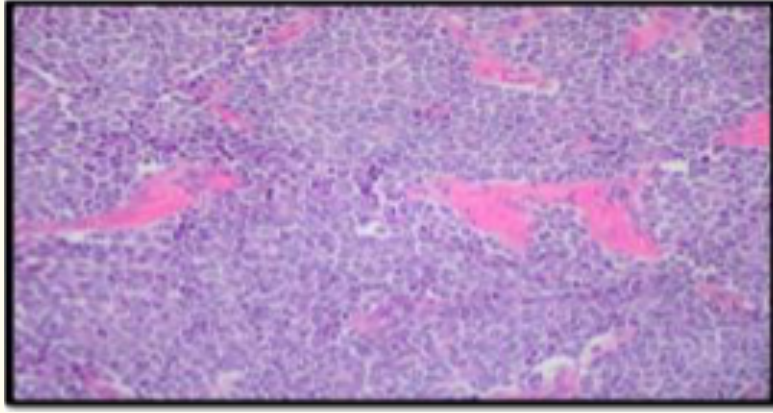
(molecular) this is a picture of fish analysis, so this is probably the most sensitive test for Ewing sarcoma using florescent insitu hybridization (FISH).

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.



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



صبر کا رسول ہے؟

Done by: Farah
hasanat