Pathology #1

مجموعة التفريغ السريع

MSS

Subject: *Inflammatory Bone Disease- 1*

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PATHOLOGY of MUSCULOSKELETAL SYSTEM

We are going to talk about the pathology of the musculoskeletal system, and I need you to know the basic principles about it.

Bone cells:
1- The bone forming cells *** osteoblasts *osteoclasts**

2- The bone digesting cells
* **Osteoclast precursors** (which mature into the functioning osteoclasts)
* **Functioning osteoclasts**

Due to the combinations of these types, we **have continuous remodeling of the bone**
This is regulated by the **RANK-RANKL** pathway.-

Congenital and developmental conditions

They are of two types:

I. **Inherited syndromes** affecting the bones: (part of a generalized situation –not selective for bones, but they are affected)

- *Hurler's syndrome (Mucopolysaccharidosis) **Lysosomal storage disease** which causes bone weakness and fracture.

- Marfan's syndrome: mutation in **fibrillin gene** required for structural integrity of connective tissue. It also causes many changes in the **heart**.

A- dysostosis:

Localized developmental abnormalities of migration of mesenchymal cells.
-May be *sporadic* or part of *inherited* syndromes

- **Aplasia** In which there is a missing part of the skeleton (a missing rib or digit)
- **Supernumerary digits** (6 or 4)
- **Abnormal fusion of digits-**(usually accompanied with a congenital abnormalities elsewhere)

B- Skeletal dysplasia

-Abnormalities in bone or cartilage growth or maintenance.
-Due to mutations in signal transduction or in components of extracellular matrix.

1. **Achondroplasia**: defective cartilage (Achondro : no chondro)

- *Autosomal Dominant* disease inhibit proliferation & function of growth plate → **dwarfism** (very common)
- Point mutation in the fibroblast growth factor receptor 3 → inhibits cartilage proliferation → suppression of growth.
- Shortened proximal extremities, trunk of relatively normal length, enlarged head.

- Normal life span, intellect & reproduction (no mental abnormalities)

These two children are of the same age, the dwarf's head is large, and his limbs are shorter while his trunk is similar to that of the normal child.

In addition, if you look at his nose, this one here, is depressed (the bridge of the nose is depressed), but he will grow up to be an adult and he can have children and so on.

Dwarfism can also be due to pituitary.-

(The word pituitary is in reference to the pituitary gland in the body. This gland regulates certain chemicals (hormones) in the body. Therefore, pituitary dwarfism is decreased bodily growth due to hormonal problems)

Dwarfism can also occur in case of hypothyroidism

- (it's called cretinism in this case), unlike achondroplasia it is associated with mental abnormalities.

2-Osteogenesis Imperfecta

The other one, which is **Osteogenesis Imperfecta** or is called **(Brittle Bone Disease),** now what is "Brittle"? . Brittle in English means it's very fragile ,it breaks very easily , these patients have defective synthesis of type 1 collagen, and this is present in bones ,joints,eyes,ears,skin and teeth .

Again it's *Autosomal Dominant* , it has several subtypes(four types) with different outcomes, some children don't finish a few years of life ,some may grow into teenagers ,but as I said they are of different severity (these four types) ,in general ,

- The bones are fragile, with multiple bone fractures, hearing defects, thin skull , dental abnormalities ,and the sclera; instead of being white, it is blue !

-Why?

Because the sclera will be very thin, and the underlying choroid will show through, so usually they have blue sclera (not clear white), not blue eyes!

They have hearing defects, thin skull and dental abnormalities.

Because they have multiple fractures, that their bones are very fragile, they start getting fractures in utero! when they are inside the uterus and that is why they can diagnosed during pregnancy of the mother and if it is early they abort the mother, actually , they should abort the mother, because it's really a life of suffering .

Here (slide 10) you can see a fracture, a fracture of a rib here, multiple fractures here and so on.

Therefore, this starts when the skeleton is starting to be formed in utero and goes on for life!

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3- **Osteopetrosis**

- ☐ Which is **marble bone** disease. What is marble? Indicates that the bone is very hard (تصخر العظم). it is a genetic disease which could be dominant or recessive → reduced **bone resorption** (Excessive bone is formed) due to **Impaired osteoclast function or formation**.
- ☐ Therefore, bone becomes → dense stone-like structure, liable to fracture**.**

Results:

1- Individual will suffer from **Cranial nerve problems** because it affects the skull bones and these are very hard they press on some nerves so patients will have hearing defects and headache for example

2-decresed haematopoiesis: because there is no room for the osteoclast to function and the no bone marrow to be formed properly. That is why the patient may benefit from a bone marrow transplant.

II. Acquired diseases of bone development

1-Osteoporosis

This is very common problem (هشاشة العظام) and it is a progressive loss of bone mass. Bone mass: bone matrix and minerals and so on meaning that the whole bone becomes smaller but the structure is fine this is different from rickets, as we shall see later on.

- ☐ Normally osteoblast & osteoclast activity are in equilibrium
- ☐ Maximum bone mass is in young adults up to 30years
- ☐ Later, osteoclast activity exceeds osteoblast activity
- ☐ Result :Bone loss of 0.7%/year which is normal
- ☐ Governed by several factors e.g. vit.D,

  Parathyroid hormone, level of estrogen….etc.

Commonest Disorder of bone, which could be Localized (immobilized because of bone fracture) or Generalized. And could be

1-primary: (physiological)

- **Post-menopausal in women**
- **Senile in both sexes as an aging process**

2-Secondary (pathological)

- **Endocrine disorders**
- **Carcinomatosis , multiple myeloma**
- **GIT disorders: malnutrition, malabsorption, obesity…etc.**
- **Drugs: corticosteroids, chemotherapy...**
- **Others: immobilization, pulmonary disease…etc.**

*Factors affecting bone resorption

- **Age related changes**
- **Hormonal factors**
- **Physical activity**
- **Genetic factors**
- **Nutritional factors** (low vitamin or low protein diet)

Now, I mentioned the **RANK-RANKL at** the begging of the lecture I said that there are inactive osteoclast and active osteoclast, to change the precursors into the active ones we need this link together with the **M-CSF** "macrophage colony stimulating factor ", now this one "Receptor Activator Nuclear Factor κB", and this one

"Receptor Activator Nuclear Factor Ligand", now the Osteoprotegerin **OPG** works against them ,again these are balanced.

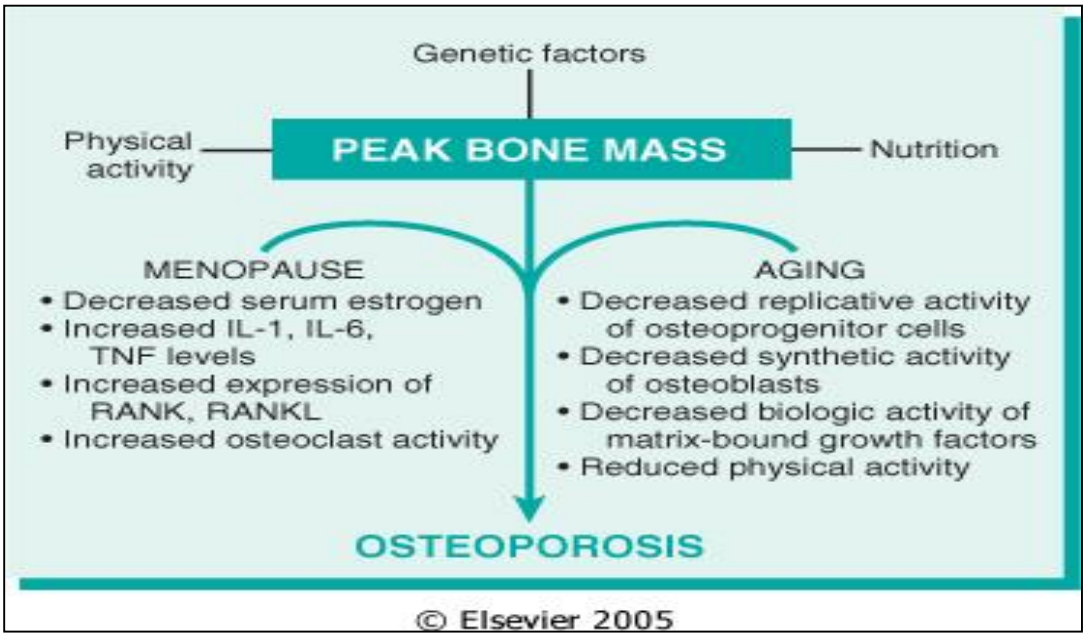
Wiki: Osteoprotegerin is a decoy receptor for the receptor activator of nuclear factor kappa B ligand (RANKL). By binding RANKL, OPG inhibits nuclear kappa B (NF-κB) .

And estrogen play a very important role here because when you have low estrogen, you have continuous activation of this pathway because when you have a normal one it can bind with it preventing this from happening in the normal female.

In the primary post-menopausal: several factors including; cytokines hormones, stimulate the expression of RANK-Ligand and it will bind with it instead of the RANK.

Estrogen deficiency is a significant cause of accelerated bone loss through the RANKL-RANK pathway because it will be activated. (Otherwise, the estrogen will block it)

- Binding of RANKL to RANK promotes osteoclast formation, function, and survival.



This is the genetic factor the physical activity, nutrition, menopause and ageing.

Menopause:

1- Decrease serum estrogen

2- Increased IL-1, IL-6, TNF levels

3- Increase expression of RANK, RANKL

4- Increased osteoclast activity

Ageing:

1-decrease replicating activity of osteoprogenitor cells

2-decrease synthetic activity of osteoblasts

3-decrease biologic activity of matrix-bound growth factor

4- Reduce physical activity

The morphology:

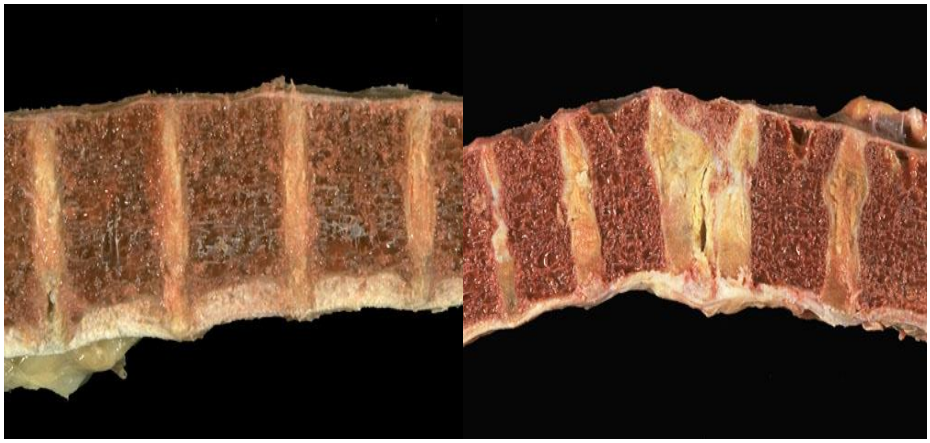
1-Thin bone trabeculae

2- Widely separated

3- Notable osteoclast activity

4- Normal mineral bone content

5- Most changes in weight bearing areas in vertebral bodies & femoral neck



If you compare the normal and osteoporosis of spine you can see the normal one is straight and the other one which represent osteoporosis is thickened where one of the vertebra is collapsed so there will be hunch bag and the bone is very thin and that's why the bone mass is decreased .

there was a question but sorry the voice was not clear, but the answer was: In males as they grow older the activity of estrogen sometimes increases but this is more complicated you have to ask the physiology dr.

The clinical picture:

- **1-Post-menopausal or senile**
- **2-Often missed until fractures occur**

And nowadays they screen the females especially of the bone density to prevent excessive osteoporosis, and many people taking preventing measures to prevent it.

- 3-Lumbar & Thoracic fractures

  Head of femur

- 4-Diminished height (they are shorter than they used to be)
- 5-Kyphoscoliosis → Respiratory function

Typical comments from people with osteoporosis the loss of height and weak bone cause the spin to collapse.

Diagnosis:

1-Plain X-ray but it shows up only after 30-40% bone loss

2-Radiographic measurement **bone density (the most reliable one)**

3-Laboratory biochemical markers of bone:

Formation (alkaline phosphatase)

Resorption (urinary calcium)

(Not very reliable)

4-Rarely, bone biopsy

Treatment:

1-Estrogen replacement therapy

2-Excercise (to build up the bone)

3-Calcium and Vitamin D dietary intake & supplements

4-Biphosphonate

2- RICKETS (in children) / OSTEOMALACIA (in adults):

They had similar mechanism:

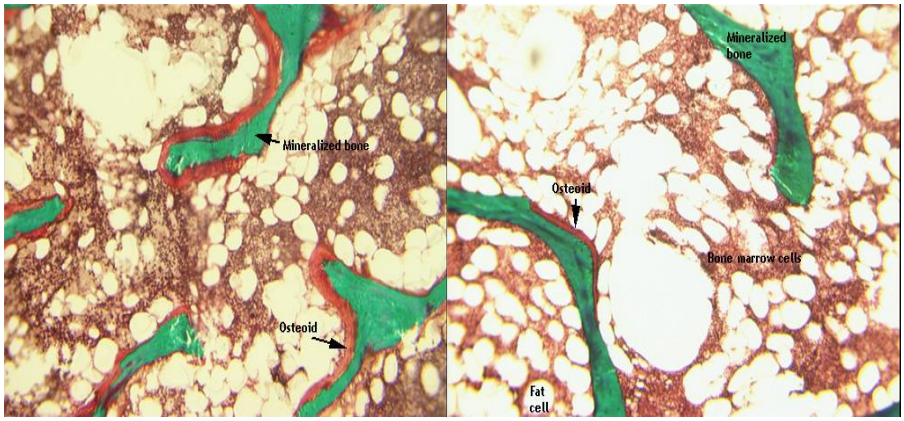
It caused be Decrease in **vitamin D** intake or metabolism

→ Excess of **unmineralized** matrix

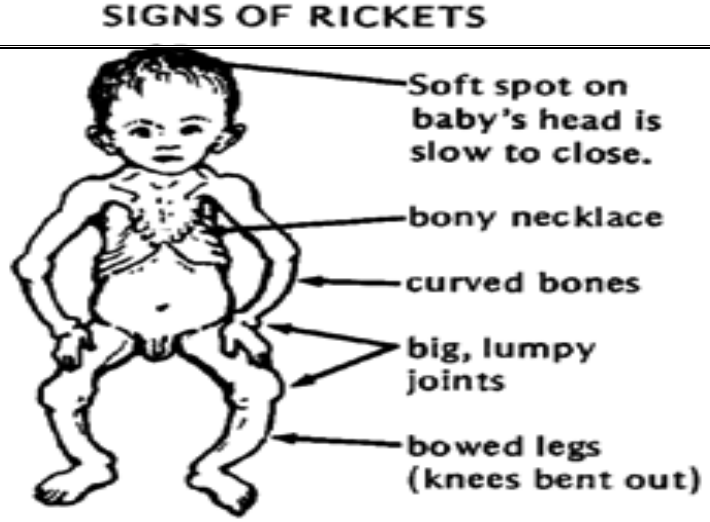
Normally almost 100% of bone is mineralized, whereas in these conditions, mineralization may be < 20%

Histology: thick unmineralized osteoid around more mineralized bone trabeculae

Weak bones → Bone deformities and Fractures



This is not NHD stain this is special method were the biopsy is taken from the iliac crest , here are the bone trabeculae ,the fat and there is rim which is Unmineralized in the left and if you compare the two pic (the left one in not mineralized) .



Now in children, the rickets deformity is much more in children because of no closure of the limiting plats and you can see the bone is not closed in the head and it will be large and they have a soft spot on the baby's head, which is very slow to close.

The rib is very bony and it is like the necklace (bony necklace).

The bones are carved, the joints are very big and lumpy, the legs because they cannot stand the presser of the body they will be bowed and the knees bent.

3- HYPERPARATHYROIDISM:

Is another condition that will affect bone again it can be:

-Primary or Secondary

(In primary the change in parathyroid itself, while the secondary many causes hyperthyroidism you will get it in endocrine section)

When you have increase in parathyroid hormone (this will trigger osteoclast activation and bone resorption)

Therefore, those patients will have a high serum calcium, and in fact, many of them are missed until they go to the doctor and see that serum calcium is high silent hyperparathyroidism.

When there is osteoclast activity, there will be continuing destruction in the bone bone cyst in any site.

You should remember that in <u>HYPERPARATHYROIDISM:</u>

These regions contain a lot of osteoclast and giant cell and these cells are common in many conditions in the bone especially giant cell tumor.

Now not every region with giant cell called giant cell tumor.

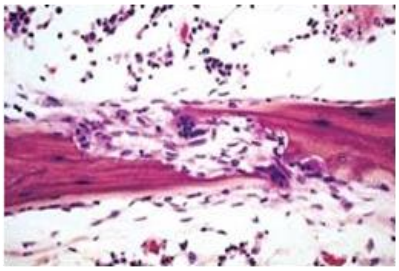
Pic 1

This is one of them it is not it is called brown tumor why?

Because from its name: OSTEITIS FIBROSA CYSTICA in which there are osteoclasts giant cells, hemosiderin & fibro vascular background.

In addition, its occur in any bone such example: ribs, skull. Anywhere which is completely different from giant cell tumors of bone.

So it is very important when we have a biopsy of lesion from bone which probably containing giant cell and osteoclast we should ask about the history and the location of the patient because each one completely different.



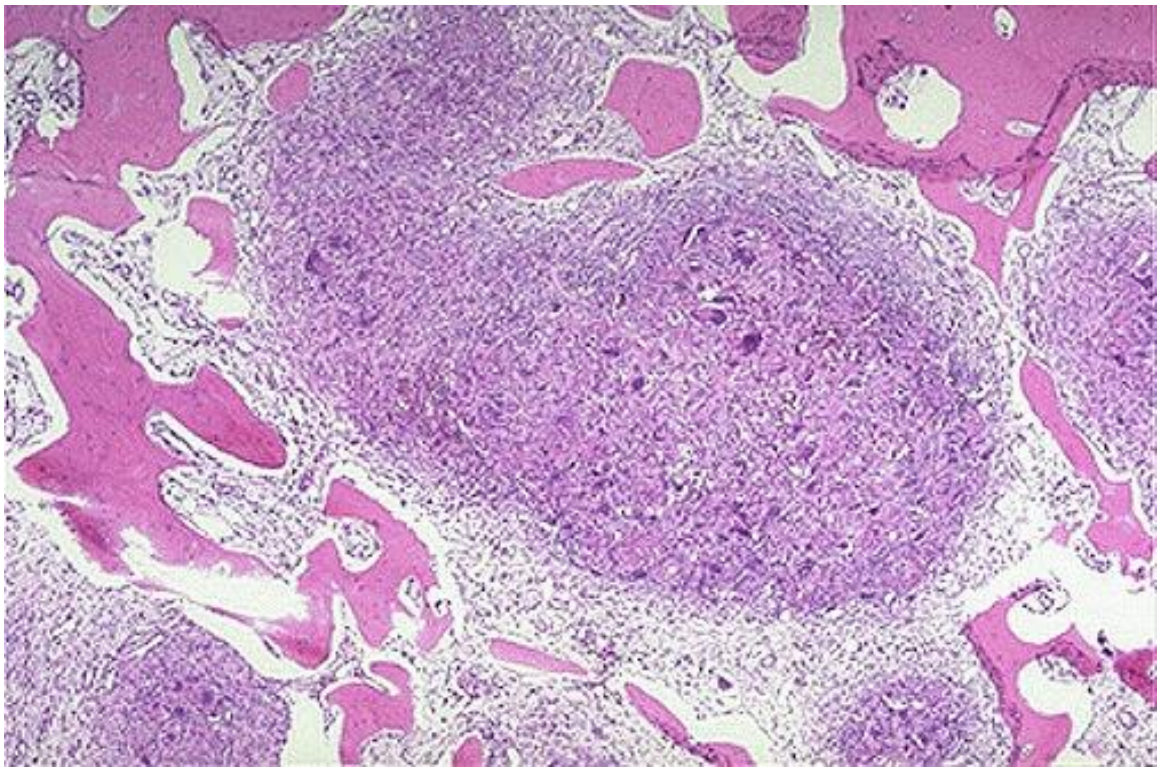
You can see here this is bone and its being eating up by cells

Dissecting into the bone destroy it because of osteoclast activity.

Back to pic 1:

Here is the rib containing this lesion and you can see its quit brown because of the old hemorrhage.

And this is the histology of the lesion:



And the last topic for this lecture is:

4- PAGET'S DISEASE of BONE:

is a very old disease remember that Paget disease also occurs in the breast it has nothing to do with this, both of them are Paget , but we should always say Paget of bone and Paget of breast (Paget of breast is carcinoma).

Paget disease is a localized disorder of bone remodeling usually in the middle age probably much more in males.

Disordered osteoclast hyperactivity with osteoblast activity now those go together irregularly and end $\rightarrow$ by increase bone mass m this bone mass will disorganized mosaic. The bone again is weaker, less compact, longer, and vascular.

And ,the cause is unknown but some believe that it could be viral, genetic, inflammatory disorder.

☐ Three phases of development:

1-Primary phase of osteoclastic activity, bone loss & hyper vascularity.

2-Phase of mixed osteoclastic & osteoblastic activity.

3-Late osteosclerotic phase with formation of dense mineralized bone.

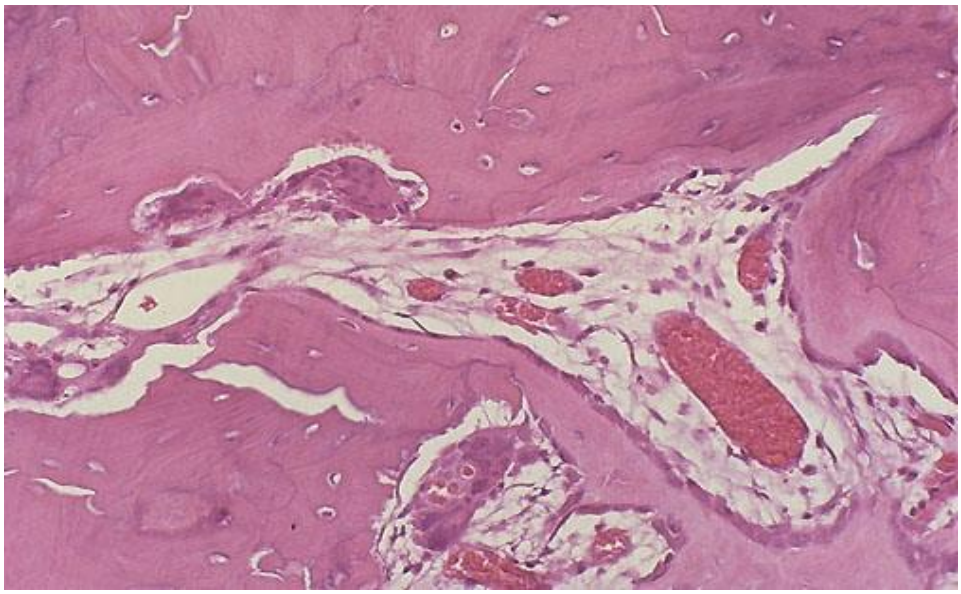
Now each part of the bone will have a mixture (#3 may exist with #1) and that why it gives a very irregular bone.

-the bone marrow is replaced by loose vascular connective tissue

-Bone trabeculae are lined by huge osteoclasts.

-Osteoblastic proliferation with concomitant bone resorption & new bone formation.

-Irregular woven bone deposition with bone thickening (mosaic pattern).



Clinically:

-it is often asymptomatic and discovered incidentally.

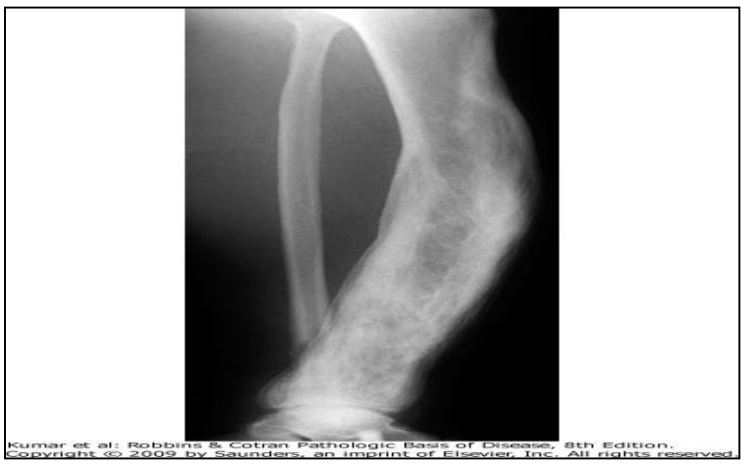
The patient may just notice that incidentally, for example he had enlargement of his head and for those whom wears hat they found that this size of hat does not fit him because his head is large because of the thickened bone.

- ↑Alkaline phosphatase, serum calcium & phosphate normal

- End by Deformities:

- Lower limbs → Bowing of the legs.
- Skull deformed & enlarged → headache

And this is how the bone will look like:



It is very thick

And the complication:

1-Nerve compression → deafness, visual disturbances

2-Increased vascularity in bone marrow leads to arteriovenous shunting → may leads to high output heart failure.

3-Osteosarcoma may develop (1 %)(because there is turnover of bone formation this will trigger abnormalities and mutations, osteosarcoma its a disease of children but when happen in adult you should think of Paget as underlying cause.

#Prognosis good unless complications occur.

The End ☺

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Notes: