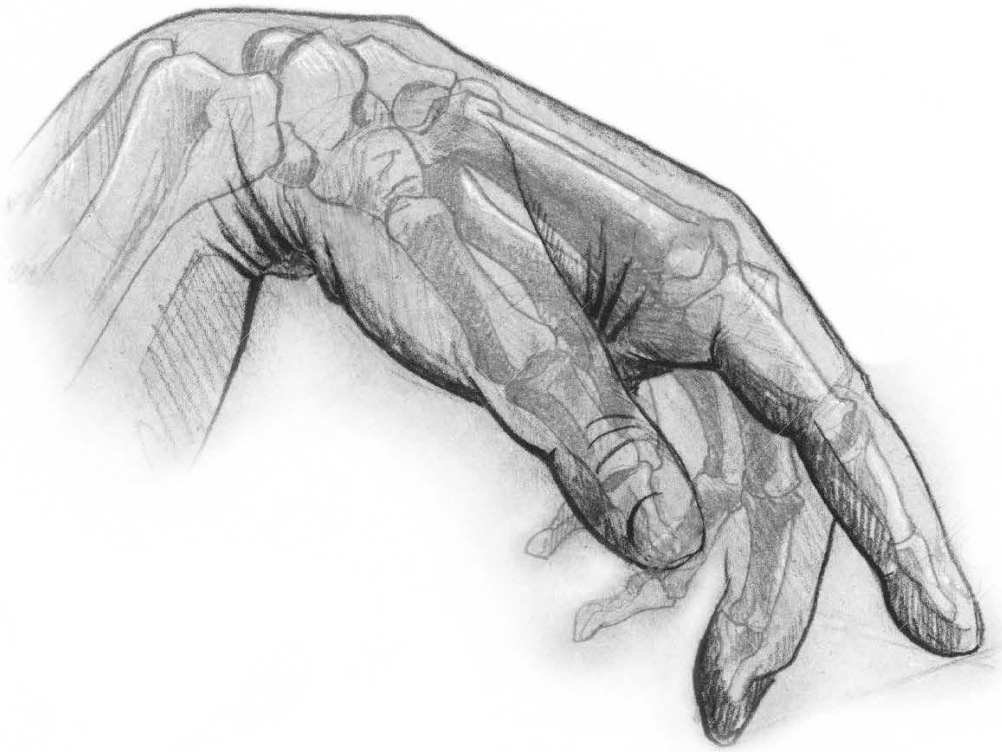
The

Musculoskeletal

System



Pathology

☑ Sheet ☐ Slide ☐ Handout

Number:	2
Subject:	Osteomyelitis + bone tumors
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Price:

In the first lecture , We have talked about some congenital and acquired metabolic bone disease , in this lecture we will continue our topic about metabolic bone disease and start talking about bone tumors ..

1-Vitamin D deficiency

Is a metabolic disease, and a systemic one (effects the body as a whole). Vitamin D normally is responsible for **calcium metabolism in bone**. So, if there is a vitamin D deficiency there , we will have a deficiency in calcium as well, and the fundamental change or impact will be on bones. The mineralization of the bone will decrease and there will be a deficiency in osteoid matrix.

Make sure to differentiate between osteoporosis and vitamin D deficiency. In **OSTEOPOROSIS** all elements are decreased. That means, both cells and matrix will be deficient.**In vitamin D DEFICIENCY** the matrix only is decreased or deficient.

Clinically, we have two settings or clinical courses regarding this disease:

1- If it started in **children or new borns**, its called **rickets**. And it is a childhood disorder (occurs early in life) in which there will be a distinctive skeletal deformities .
2- If it started in **adults**, it's called **osteomalacia**. The osteoid will be underminerlized and weak and it doesn't have enough content minerals resulting in what's called osteopenia and Accordingly the bone becomes weak.

Note: osteopenia (bone mineral density is lower than normal. So that the bone will be prone to fractures). This is diagnosed usually **By radiology**, sometimes clinical presentation is beneficial, bones will appear curved "children" since it can't grow in normal way. However, in **rickets it will be more prominent** (bone is still developing), Whereas in osteomalacia it's already formed.

2-hyperparathyroidism

Parathyroid hormone is essential for calcium metabolism and homeostasis in the body. It **increases calcium** level in the blood, and **lowers that of the phosphate**.

At cell level, **PTH activate RANKL** production. Which will cause recruitment of osteoclast. So, if there is an increase in PTH hormone for any reason there will be an **increase in the function of osteoclas**t→more reabsorption of the bone→ bone become weak→ calcium will be mobilized from bone to blood→ that will cause hypercalcemia.

Another function of parathyroid hormone is **activating vitamin D**. which in turn will increase the calcium absorption from gut and decrease its excretion, so again it is hypercalcemia.

Quick revision

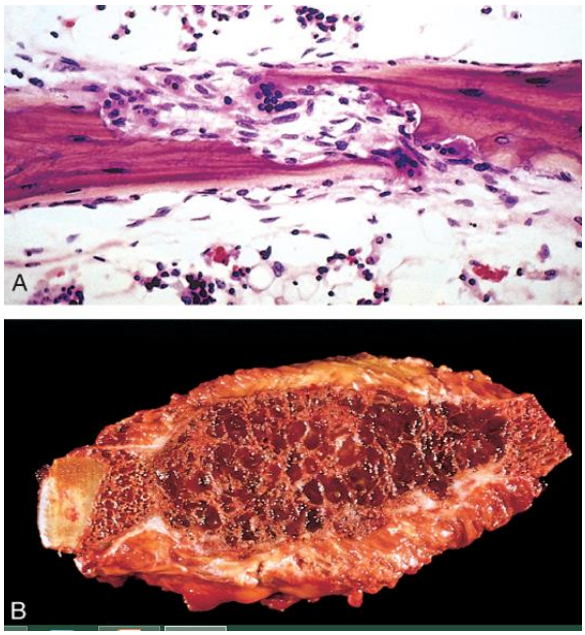
PTH hormone causes:

i. hypercalcemia
ii. Hypophosphatemia
iii. Activation of vitamin D

For **diagnosis** we observe the effect of this disease in small bones like fingers(phalanges). Unlike other diseases (osteoporosis or paget) where we look for it in long bones.So we can do x-ray to see changes which are obvious in fingers and toes.

under microscope→ we will see osteoclasts and a **fibrovascular** core(fibroblasts and blood vessels) which supply blood to site of disease .

With time there will be a hemorrhage, that will result in the formation of a MASS that is Called **brown tumor**"**osteitis fibrosa cyctica**". (benign lesion. Consist of osteoclast,fibrovasculture core and hemorrhage).



First image →Here we can see osteoclasts interrupting bone trabeculae.
Second image→ it is a brown tumor (cystic mass) so osteoclasts are there as well as fibroasculare core and hemorrhage.

3-Pyogenic osteomyelitis

Whenever you see pyogenic it's bacteria since viruses can't cause pus . So that disease is caused by bacteria.But how bacteria gain access to the bone? MOST commonly through blood (haematogenous spread) however in some cases we may have fractures or trauma that will lead to the entrance of bacteria (less common).

the most common microorganism is *STAPH AURUES*. and there are exceptions:

1- in **neonates it's E.COLI and STERP B** (taken from female genital tract).
2-in **sickle cell anemia patients its salmonella** (unknown reason).
3-in traumatic osteomyelitis , we will have mixed bacteria , including anaerobes .

Since its difficult to isolate bacteria, we don't depend on bacterial culture for diagnosis.in 50 % of clinical cases no bacteria is isolated. So we treat patients empirically (through wide spectrum antibiotics).

- **Morphology**
  - Acute phase→ we have sheets of neutrophils along with necrotic bone that is damaged by bacteria. ALL together called **sequestrum.**

  - the inflammation starts at the medulla then goes outward toward periosteum through Haversian system.In children the periosteum is still immature means its NOT fused with the bone so when there is infection there it will push the periosteum outside causing **subperiosteal abscesses**. as abscess is formed it will push the periosteum outside then it may spread to connective tissue around it (skin- joints-fascia).

    Quick info

    Abscess is a special form of infection when dead material and inflammatory cells form a MASS not a tumor and the treatment is surgical drainage.

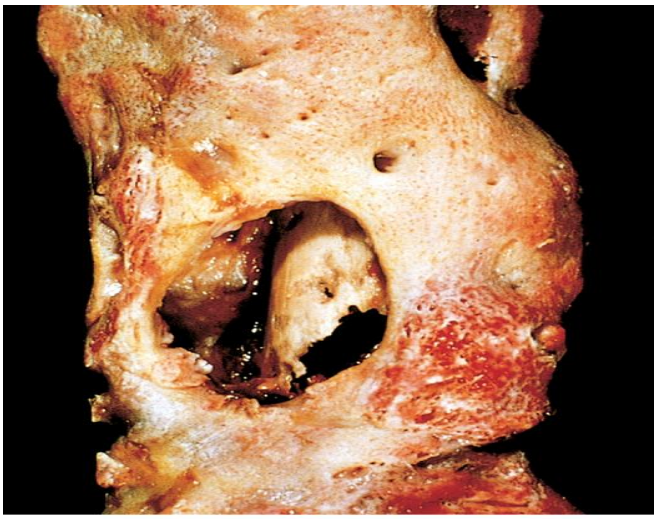
  - the movement of periosteum further may impair blood supply to the effected region.Ischemic injury may develop and when there is ischemia, segmental bone necrosis take place.

  - And if there is more damage, periosteum may be damaged it may reach distal regions like skin forming a tract called **draining sinus.**

  - In children the disease is more severe that it **may reach joints causing deformities**.
    Usually osteomyelitis stays for long time in acute phase but it may develop into chronic one and we will notice the following:
    1- neutrophlis disappear.
    2-accumulation of lymphocytes and macrophages.
    3-activation of bone synthesis .

Note: bone synthesis here is activated by cytokine released by the WBC's. The new bone that is formed named **involucrum**.osteomyelitis is a chronic disease, take long time to be treated → at least 6 months of intravenous antibiotics.

In this picture we can see destruction in the bone. And also the sequestrum (necrotic + inflammatory cells). And finally involucrum (new bone synthesized around necrotic one).



4-Mycobacterial osteomyelitis

Mycobacterial osteomyelitis complicates around 3% of pulmonary tuberculosis cases. In other words, if you have 100 patients with TB then three of them will have bone infection by mycobacteria. Again the most common route is through blood.

Mycobacteria is an aerobic bacteria (needs oxygen) in order to grow, so it reaches the bone through blood. But the main site of infection is Joints synovium (it has higher concentration of oxygen there). And from there it spread outside and cause destruction to the surrounding tissue and bone.

Pott disease(tuberculosis of vertebral bodies)causes deformity.Once this bacterium infects the spine it goes outside and reach adjacent muscle which is psoas muscle in pelvis. And result in abscesses formation.

Bone tumors

Bones are one of systems in the body that have a lot of tumors. We will mention the most important ones.

bone is a favorite site for metastasis. So that metastatic tumors are more common than primary ones. **Bone marrow neoplasms are more common than primary ones .** primary bone tumor is classified into benign and malignant, benign is common among young people**.**

Malignant is also common in young but can develop in old ages. So benign tumors are commonly seen in paients before 40 .

-the most common benign tumor of bone is osteochondroma.
-the most common malignant tumor of bone is osteosarcoma.
-long bones are more common to develop tumor.

➢ Osteoma

It's **not a true neoplasm**, it's a developmental abnormality. It occurs in middle aged people. And most common site is skull and face. Mostly it's solitary. If it occurs multiple, then it's called **gardener syndrome** .Under microscope it looks completely normal. And we have a mixture of woven (immature) and lamellar bone (organized).Since it's not a true neoplasm, it does not transform.

➢ Osteoid osteoma and Osteoblastoma

Osteoid osteoma is a true benign neoplasm occurs in long bones , especially around knees.
Osteoblastoma is like osteoid osteoma but its large.develops in vertebra.both **osteoid osteoma** and **osteoblastoma are benign tumors occur in teenage and middle age**. Both arise in the cortex as well. They have similar histology and radiology.**osteoid osteoma** arises in long bones (femur and tibia) , it

produces a lot of prostaglandins , Therefore it's Painful but respond to aspirin .Osteoblastoma arise in vertebra , it's Painful (doesn't respond to aspirin).

treatment for both is **surgical excision ,** radiotherapy is contraindicated , due to the fact that it may lead to a malignant transformation .

➢ Osteosarcoma

The most common malignant bone tumor, It's a bone producing tumor. It effects all age groups but most commonly among children (75%).It occurs anywhere in the body but most commonly around knee (active part of the Skeleton).

-Mostly is primary, solitary, poorly differentiated.
-Around 1% of Paget disease patient will develop osteosarcoma.
-starts in medulla itself.

Osteosarcomas can occur at all sites, but occur mostly in fast-growing areas, such as long bones, especially around the knee joint. osteosarcomas are solitary tumors, which means they occur alone. There are intra-medullary.

osteomas occur in thecortex, but osteosarcomas, on the other hand, occur in the medulla of thebone. They are poorly differentiated and produce osteoid,for the mostpart, but can also produce cartilage and fibroid tissue.

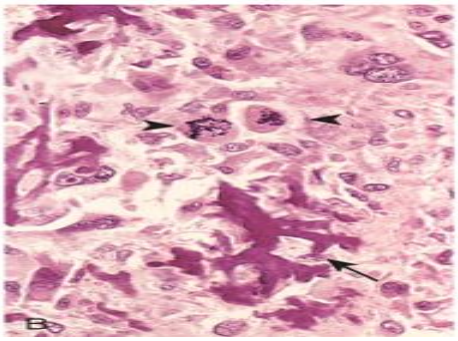
Like any malignant tumor , Most cases of osteosarcomas have unknown causes , Even the predisposing factors are unknown. There are, however, genes which become mutated and contribute to these tumors.In the case of osteosarcoma, **this gene is RB(retinoblastoma) which is a potent tumor suppressor.** When this gene is mutated, it becomes inactive, leading to the cell becoming more mitotically active.

The RB gene is mutated in 70% of osteosarcoma cases. This is in sporadic cases. In hereditary cases, the RB gene mutation leads to retinoblastoma(tumor in the eye), as well as osteosarcoma,

Usually in cancer, there will not be only one gene that is mutated in a cancer. There are thousands of mutated genes for example **p53**, which is “the guardian of the genome” is commonly mutated in osteosarcomas. **Cyclins** are the “breaks” of the cell cycle. Without them, the cell cycle will be uncontrolled. So, mutations in the cyclins, cyclin-dependent kinases, and cyclin dependentkinase inhibitors will lead to uncontrolled cell proliferation. The most Important mutation, ultimately, is that in the RB gene.

Morphology

This tumor is **cystic** and hemorrhagic. This type of tumor displays cystic degeneration. Remember it is intramedullary, then it moves outside, destroying the cortex, periosteum, and the soft tissue. So, tumors frequently destroy the surrounding cortex, reach the muscles, and they can move within the medulla and replace the bone marrow . However , this tumor infrequently penetrates the epiphyseal plate and entering the joint space . (While in pyogenic osteomyelitis , it reaches the joint)



Microscopically , cells vary in size and shape (pleomorphism) , prominent mitotic figures and hyperchromatic nuclei .
Some transformed cells may also produce cartilage and fibrous tissue , cartilage forming osteosarcoma is called **chodroblastic osteosarcoma**

Clinical

Osteosarcomas typically manifest as a painful enlarged masses , although a spontaneous fracture can be the first sine . A triangular shadow on the X-ray film between cortex and raised periosteum (Codman triangle) is a characteristic of osteosarcomas

Osteosarcomas typically spread hematogenously , at the time of diagnosis , 20% of patients have pulmonary metastases .

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Note : you should know the most common site as well as the age group.

- **Review Questions**

1- A 17-year-old boy presents with pain and swelling about the left knee for the past month. He thought that this condition resulted from an old football injury and that it would resolve without incident. The pain, however, has persisted and is severe enough to cause him to limp. Radiographs of the knee demonstrate a lifting of the periosteum and a speculated “sunburst” pattern in the distal femur. Which of the following is the most likely diagnosis?

(a) Osteosarcoma **(B)** Chondrosarcoma
(c) Ewing sarcoma **(D)** Giant cell tumor
(e) Knee sprain

2- A 2-year-old boy presents with his third bone fracture within the past several months. There is no history or evidence of trauma. Several close family members have been similarly affected. The child is small for his age, and the sclerae are tinged a bluish color. Radiographs reveal generalized osteopenia and evidence of multiple fractures, both old and new. Which of the following is the true about this disorder ?

(A)most cases represent new acquired mutations
(B)it’s due to gene mutation in alpha 1 , 2 or 3 collagen chains .

(c) the patients may become deaf due to cranial nerve nerves compression
(D)people with variant 1 of this disease have normal life expectancy .
(E) B+D

3- what bone disease can occur due to prolonged immobilization(disuse atrophy), aging, estrogen deficiency after menopause. Can cause Back Pain, and fracture of femur neck ?

(A)Osteopetrosis (B)Paget disease
(C)Osteoporosis (D)osteoma
(E)non of the above

Answers :

1- (A) osteosarcoma
2- (D)people with variant 1 of this disease have normal life expectancy
3- (C)Osteoporosis

The end

Sorry for any mistake…..please refer to slides.