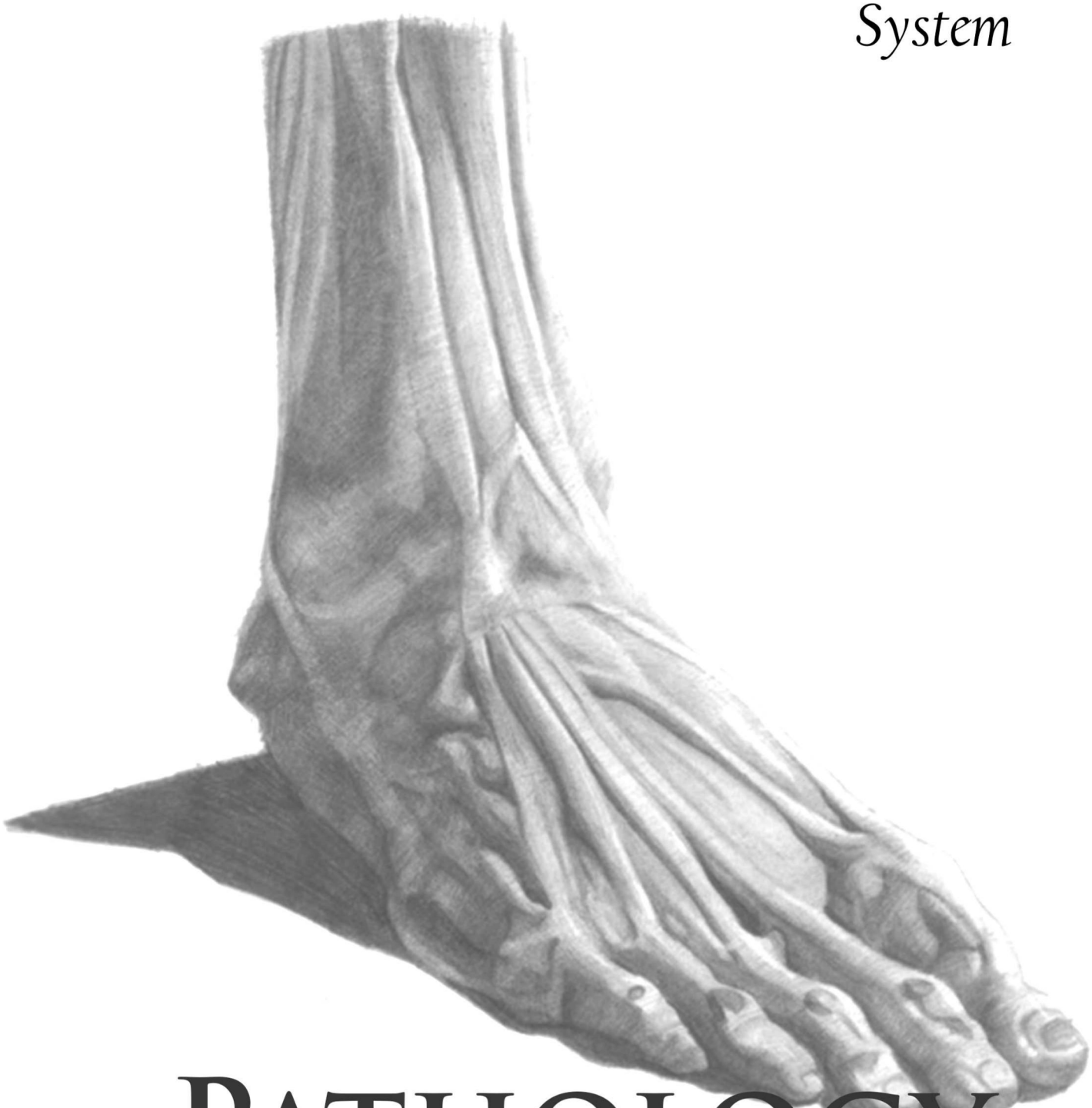
Medical Committee
The University of Jordan

The Skin and MUSCULOSKELETAL System



PATHOLOGY

SLIDES ☐
SHEET ■
LECTURE # 2

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Bone Related Diseases (2)

Vitamin D deficiency:

Vitamin D mainly functions in calcium metabolism in bone. As a result, if there was any deficiency in vitamin D there would be calcium deficiency, and mineralization of bone is decreased. A fundamental change in bone results from this deficiency which is decreased osteoid matrix, osteoid matrix itself becomes deficient, but cells themselves are not affected. It's different from osteoporosis. In osteoporosis both are decreased, the matrix and cells, and the result would be a decrease in the mass of bone, whereas in vitamin D deficiency, there is only a decrease in the matrix. So in osteoporosis all components are deficient, but in vitamin D deficiency the matrix only is decreased.

Clinical course: there are 2 clinical courses in relation to vitamin D deficiency. If it started in children (newborns), it's called **Rickets** (كُساح in Arabic). It occurs early in life (young children), and there is a generalized deformity and it appears in lower limbs as bowing (mainly in long bones), it appears in radiographs. This is the first clinical point.

The second one happens if the deficiency occurs in adults, it's called **Osteomalacia** (mal means bad, the bone becomes bad and thin). There's under-mineralization of osteoid, there's osteoid but it's weak and does not have enough content of minerals. This results in osteopenia (decreased bone mass) and the bone is predisposed to fractures.

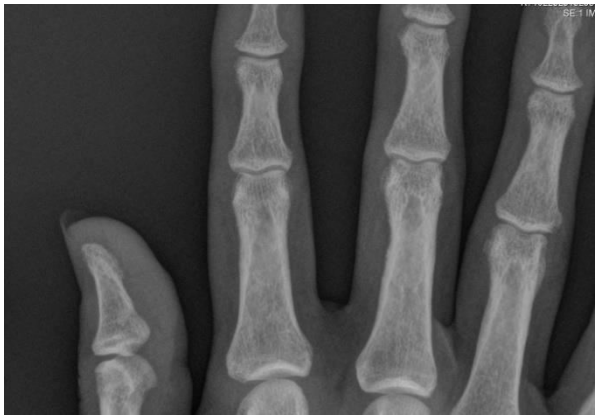
In children this deficiency is very rare, as we have supplements and good nutrition so it's rare these days. In adults it(vitamin D deficiency) is common but usually it does not reach the level of osteomalacia. In adults it can be recognized from other systemic manifestations before it reaches the level of osteomalacia.

Hyperparathyroidism:

It's one of the acquired bone diseases. PTH (parathyroid hormone) maintains the level of calcium in the serum, the main source of calcium is in the gut and the bone. If there was an increase in the level of PTH for a long time, it affects the bone as PTH is a strong stimulant for the bone, it mobilizes (moves) calcium from matrix to blood, and increases calcium uptake from the gut and intestines, in addition to increasing the reABsorption of calcium from tubules. As a result the level of calcium in blood is high. PTH increases the RANK ligand activity, so this activates osteoclasts and bone resorption increases. It's a long-lasting disease and its effect on bone is great and enormous; as it causes persistent stimulation.

PTH increases the excretion of phosphate from the kidney and the reABsorption of calcium from tubules {unlike vitamin D ,which takes them both }. So PTH does the following: it increases calcium levels in blood, decreases phosphate levels in blood, affects bone, increases the synthesis of vitamin D in its active form.

As it's mentioned above, PTH increases RANKL expression and activity, which results in increased osteoclast activation and as expected increased bone resorption. The main focus is in the periosteum (outside of the bone, not in medulla). This helps us in X-ray examination, when you x-ray the hand, you can notice bone resorption in phalanges (phalanex is a tubular bone, its periosteum is affected). So for, examination of hyperparathyroidism is by doing x-ray to the hand and notice the bone resorption of the phalanges.



As you remember Paget disease is an active disease; it needs energy, and the same happens in hyperparathyroidism, osteocalsts need energy and blood flow and with time there would be increased connective tissue in bone (inside the bone itself; bone marrow or medulla) and connective tissue consists of fibroblasts and blood vessels to supply them with blood. This results in fibrovascular core, you can

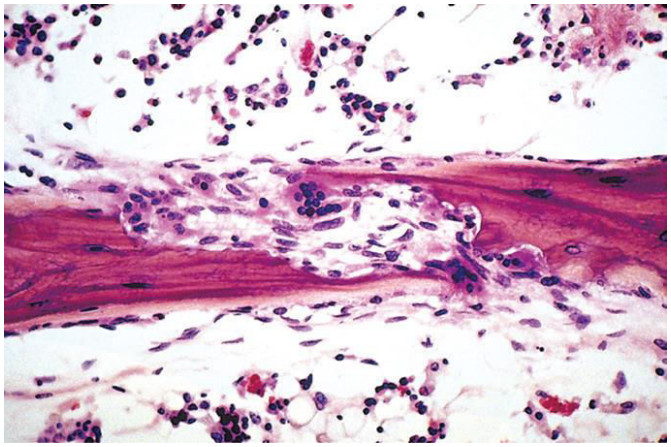
recognize it under microscope, and it's prominent. Under microscope you can see osteoclasts and fibrovascular core which supplies blood to the site of the disease, so with time there would be repeated hemorrhage (by inflammation) and it's an active state. All of these together (osteolcalsts, fibrovascular core and repeated hemorrhage) at the end result in a mass, bone becomes filled up with these components and in this case we call it brown tumor. Brown tumor occurs only in hyperparathyroidism, and any tumor can have many gaps, we call them cysts.

As a result, it ends up in a disease called osteitis fibrosa cystica (osteitis because it's a bone disease, fibrosa because we have fibrous tissue and with hemorrhage there is repair so there would be fibrosis, and cystica refers to cysts formation).

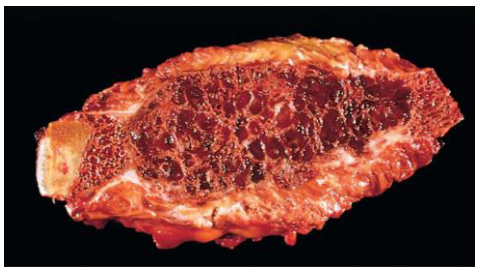
To sum up:

Hyperparathyroidism, increased osteocalsts, increased connective tissue, brown tumor and finally cyst formation which is called osteitis fibrosa cystic.

In early stages you see increased osteoclasts that dissect bone trabucle to bring the calcium. Under microscope you see connective tissue and blood components (hematopoietic cells), what you see here is scattered vessels and fibrous tissue.



In its late stages, it appears grossly as a tumor in bone, brown in color, forming cysts.



Infections:

*Pyogenic Osteomyelitis:

It's caused by bacteria (pus forming bacteria) and if you think about bone it's away from external environment, so for bacteria to reach bone the easiest way is through blood {hematogenous dissemination(spread)} and patient with Pyogenic Osteomyelitis usually has bacterial infection in other places which then moves to the bone (blood borne infection). Bacteria reach bone indirectly.

Most common organism that causes pyogenic osteomyelitis is staphylococcus aureus, but there's an exception in neonates, they take the bacteria from their mothers (lower genital tract), so we see other groups of bacteria such as Group B streptococcus and E.coli, these types of bacteria only appear in neonates infections (not in children or adults).

The patients have tendency to have infections by Salmonella for unknown reasons, and the infection caused by salmonella is not only in bone but in other systems in the body, but staphylococcus aureus is the most common one, in sickle cell disease, they have tendency for salmonella infection but it's not common, staphylococcus aureus is more common, but if we recognize salmonella this occurs typically in sickle cell patients.

In trauma bacteria enters directly into bone, like opened fractures, and in this condition there will be mixed bacterial infection (and commonly there will be anaerobes), if it was a single type of bacteria that means there is an infection aslan (Hasan Hammo style) in other areas.

In clinical practice in around half of patients (50%) you are not able to isolate the bacteria (this doesn't mean that there is no bacteria), it's difficult to isolate it and know which type of bacteria is causing the infection (maybe because it's deep), so in general treatment is empirical treatment (you give a wide spectrum antibiotics to cover these types of bacteria).

Morphology:

Bacterial infection is an acute infection, it starts as acute, so you see sheets of neutrophils in bone, dead cells (either from the host or bacteria), and nectoric bone (both matrix and cells), we call these components sequestrum, it means acute infection of the bone. In acute phase you see liquifactive necrosis (it's like a liquid).

As it's mentioned above bacteria reaches bone by blood, and bone concentrates blood within medulla (bone marrow), so infection starts in the medulla of the bone then it moves outside (bacteria and inflammation move outside and reach the periosteum through the haversian system).

In kids, periosteum (or bone in general) is weak and not solid, it's loosely attached to the cortex, so this periosteum can be easily torn and pulled away from the bone itself, abscess can be formed there (between the periosteum and the bone itself). Abscess (pus) is formed when there's a mass, and this abscess has a tumor effect, it presses the periosteum outside and the cortex inside, it forms a mass there and causes destruction to all these structures. In tumors (cancer of the bone, osteosarcoma) it stars from medulla and goes outside but causes destruction to everything, but here the abscess tends to be localized between both of them. Abscess acts as a tumor, it presses on both direction and on vessels causing ischemia, and liquifactive necrosis starts then it causes ischemic necrosis (secondary ischemic infraction) and it's called segmental bone necrosis
#Note: { ischemia + liquifactive necrosis =gangrene}

When abscess goes out seeding may occur, and may cause secondary abscess in another place, so it ends up like dead region then viable then dead and this is what we mean by segmental bone necrosis.

In advanced stages rapture of periosteum occurs and it goes to the surrounding structures like soft tissues and fascia. In long bones it may go to joints (articular space) especially in children and in causes serious disease, it destroys the cartilage and causes permanent deformity and the child stays short.

In soft tissue, bacteria and inflammation cause destruction to the tract in which they go in, this tract is called sinus (sinus is a tract between two points in body and bacteria causes destruction to that tract, it occurs secondary to an infection).

In children and infants not in the adults, growth is not completed yet, so if this infection spreads outside and reaches joints (cartilage) ,it can cause destruction and impairs further growth (causes permanent disability in bones and joints . ex: patient can't move his\her knee).
#Note: In adults bone growth is completed because growth plates are not there, there are no further growth .

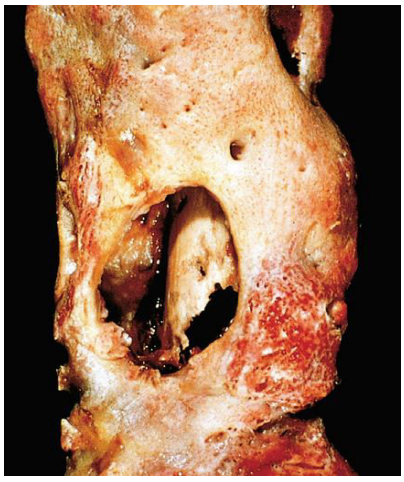
If osteomyelitis happens in vertebrae, it follows the same process (medulla, periosteum, then it spreads outside) and if it reaches the discs between vertebrae and causes destruction again it causes disability (the patient cannot move his back).

That was about the early stages. Now after the first week of infection chronic inflammatory cells (mainly lymphocytes & plasma cells) concentrate in the area of infection. Leukocytes secrete cytokines and this activates new bone synthesis, so you have dead area surrounded by new bone, this new bone is called **involucrum**, it surrounds the dead part of the bone .

Treatment:

Osteomyelitis is difficult to treat; bacteria can reside in that part for years. It's mainly treated by surgical excision. Treatment in clinical takes around 6 months of aggressive antibiotic treatment and it's IV to reach the bone.

You can see the dead part (sequestrum) and the new bone (involucrum). There's destruction to the periosteum and you can see a cavity.



*Tuberculos Osteomyelitis (Mycobacterium):

Mycobacterial infection can reach the bone and in 1-3% (TB is usually pulmonary and then it's systemic). Bone is rarely affected (only in 1-3% of patients of pulmonary TB).

The organism reaches the bone through blood stream (mainly).Sometimes ,in case of pulmonary infection, bacteria can go and infect the bones of the rib cage directly but it's rare. Long bones and vertebrae are the most affected bones of TB infection. Most commonly they are solitary but if the patient has an immune deficiency that means he is more liable to have multiple sites of infection.

Mycobacterial osteomyelitis is rare, just 1-3% of pulmonary TB, hematogenous spread is more common in the spine and long bones, most commonly solitary.

Mycobacteria likes Oxygen, the infection starts outside then goes inside, it likes to start at joints where you have articular space and there's more oxygen than other sites, it tends to start at the synovium (the outer layer of the bone in the joint space between two bones) it starts there then goes inside the bone. In long bones it starts in the epiphysis (the tip of the bone, where two bones attach to each other).

Mycobacteria under the microscope it causes granuloma (multinucleated giant cells reaction) and it has special type of necrosis which is called caseous (caseating) necrosis.

Tuberculosis in vertebral bodies has a name, which is **pott disease** (it means TB of the spine). In the past before the treatment of TB it was common, it can cause significant deformity, it can also spread to the nerves in the spine causing neurologic defects.

In lung bones (abdomen) it can spread forming abscess in the cavities (in abdomen), it can cause abscess around psoas muscle in abdomen.

It's mostly solitary and spreads by hematogenous spread.

Bone Tumors:

They are mostly from metastasis (from outside), it's more common than primary bone tumors. Primary bone tumors are less common, they can be either benign or malignant; benign usually occurs at younger age, and there's matrix (bone or cartilage) and it's obvious (like the original tissue).

Tumors are classified according to the cell of differentiation; osteoid or chondroid. For example **osteochondroma** has both types, bone & cartilage but mainly it's cartilage.

Osteochondroma is the most common benign tumor of the bone. Osteosarcoma is the most common malignant tumor of the bone. In general long bones are more affected by tumors.

Table 20–2 Tumors of Bone

Tumor Type	Common Locations	Age (yr)	Morphology
Bone-Forming			
Benign			
Osteoma	Facial bones, skull	40–50	Exophytic growths attached to bone surface; histologically similar to normal bone
Osteoid osteoma	Metaphysis of femur and tibia	10–20	Cortical tumors, characterized by pain; histologic pattern consisting of interlacing trabeculae of woven bone
Osteoblastoma	Vertebral column	10–20	Arise in vertebral transverse and spinous processes; histologically similar to osteoid osteoma
Malignant			
Primary osteosarcoma	Metaphysis of distal femur, proximal tibia, and humerus	10–20	Grow outward, lifting periosteum, and inward to the medullary cavity; microscopy shows malignant cells forming osteoid; cartilage also may be present
Secondary osteosarcoma	Femur, humerus, pelvis	>40	Complications of polyostotic Paget disease; histologically similar to primary osteosarcoma
Cartilaginous			
Benign			
Osteochondroma	Metaphysis of long tubular bones	10–30	Bony excrescences with a cartilaginous cap; may be solitary or multiple and hereditary
Enchondroma	Small bones of hands and feet	30–50	Well-circumscribed single tumors resembling normal cartilage; arise within medullary cavity of bone; uncommonly multiple and hereditary
Malignant			
Chondrosarcoma	Bones of shoulder, pelvis, proximal femur, and ribs	40–60	Arise within medullary cavity and erode cortex; microscopy shows well-differentiated cartilage-like or anaplastic features
Miscellaneous			
Giant cell tumor (usually benign)	Epiphysis of long bone	20–40	Lytic lesions that erode cortex; microscopy shows osteoclast-like giant cells and round to spindle-shaped mononuclear cells; most are benign
Ewing sarcoma	Diaphysis and metaphysis	10–20	Arise in medullary cavity; microscopy shows sheets of small round cells that contain glycogen; aggressive neoplasm

The doctor said that this table summaries everything about bone tumors and you must know everything about it. You should be familiar with the location , morphology which is the pathology under the microscope and the age is also important.

Bone tumors could be osteoid or chondroid, benign or malignant or mixed .So you end up with different types of tumors.

Osteoma: bone-forming tumor, it's not a tumor or neoplasm, it's mostly a malformation, there's a mass but it's not proliferating.

If you remember we studied hamrtoma, and osteoma is close to hamartoma, it's malformation and disorganization and it ends up with a mass. Osteoma is a developmental abnormality (the structure itself is not normal and there's a mass).

Osteoma occurs only in the skull & face and typically present in middle age.

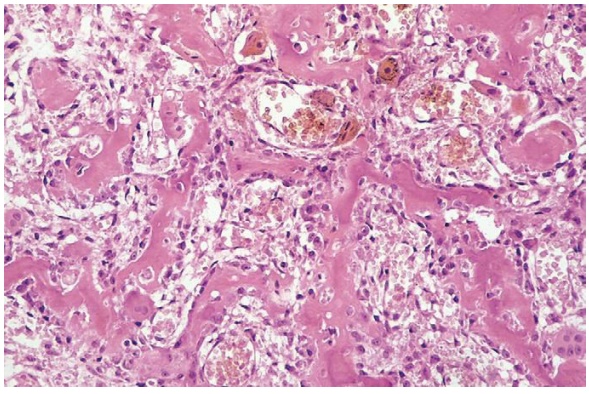
It's most commonly solitary.

It's common and you can recognize it as a mass on the forehead for example of a patient. In some cases it can be syndromic; **Gardener syndrome** is an example, where you have multiple osteomas in the head.

Under microscope it has a normal morphology, you see mixture of normal bone (woven & lamellar bone), but it's obvious clinically (grossly).

Osteoma does not transform into malignant tumor.

Osteoid Osteoma: it's the same thing but this one is neoplasm, there's osteoid formation but in a neoplastic process, and there's proliferation of cells but they're benign and they form structures like the normal tissue (well-differentiated)



Osteoid Osteoma is usually small. If it was big we call it osteoblastoma (they are the same but osteoblastoma is larger and occurs in different locations).

Under microscope you can see mixture of woven and lamellar bone with normal cells.

They arise in the cortex not in medulla (important point).

They both have similar histological and radiological aspects but osteoblastoma is larger in size and it arises in the spine.

In radiology, you can recognize a tumor in the cortex and in the middle it's translucent (it does not reflect the light, it's black in color), this is called central nidus.

Osteoid Osteoma arises mainly in the proximal femur & tibia (long bones).

It's less than 2cm and very painful (these tumors have high concentrations of prostaglandins, it responds well to aspirin{non steroidal anti inflammatory drugs})

Osteoblastoma is the same but it's large and arises in the spine (vertebrae), it's painful but this one does not respond to aspirin, it's treated by surgical excision, it should not be treated by radiology, it will be converted into osteosarcoma if it was treated with radiotherapy (radiation causes more mutations).

So Osteoid Osteoma & Osteoblastoma are different in many aspects; the size, the site, and clinically (one responds to aspirin but the other does not).

Under microscope you can see mixture of woven and lamellar bone and in between there's fibrous tissue.

Ta7eyyeh la Mohammad Al-Zghoul, mnawwer garabah.. w ta7eyyeh la Mohammad Nawaiseh for correcting this sheet, kaman had garabti.