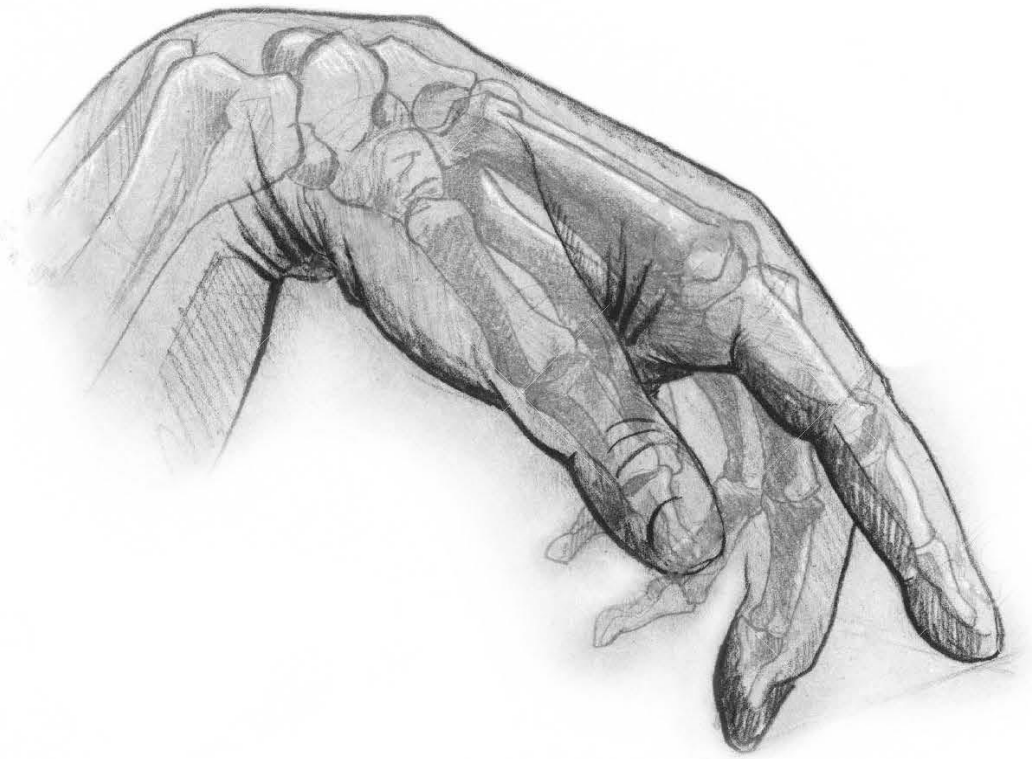
The

Musculoskeletal

System



Pathology

☑ Sheet ☐ Slide ☐ Handout

Number:	3
Subject:	Bone Tumors
Done By:	Raghad Bataineh & Dana Rida
Doctor:	Tareq Al- Adily

Date: 23/2/2016

Price: 0/00/0000

Bone tumors:

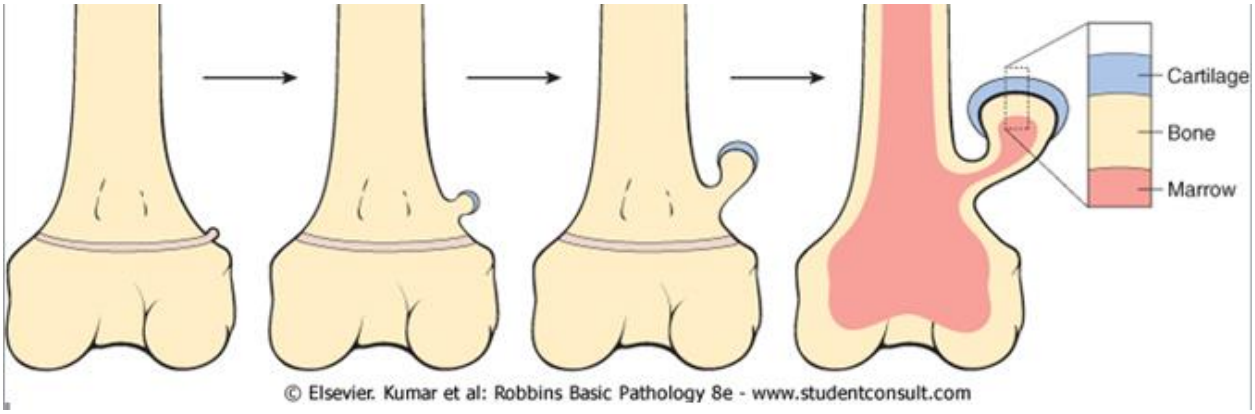
In today's lecture we're going to continue talking about bone tumors. Bone tumors can be categorized into 3 groups:

- Osteoid tumors.
- Chondroid tumors (ex: chondroma, chondrosarcoma , osteochondroma).
- Fibrous tumors.

We've already started talking about the first group and now we continue.

1) **Osteochondroma**: it's the most common benign tumor of the bone, and as the name implies, it has two components: osteoid (bone) and chondroid (cartilage). It has another name which is **Exostosis**, it's clinically used.

   This tumor is attached to the bone by a stalk, so there's a stalk then comes the tumor (see the picture below). As other benign tumors it occurs at young age, mostly in adolescence. Mostly it's a single tumor.
   The common site for osteochondroma is the metaphysis of long bones especially around the knee (femur), but also can occur in any part of the body .
   It's slightly more common in males (the ratio is 3:1).
   Multiple tumors exist in syndromes mainly, so if there are multiple tumors then the syndrome is called **Multiple Hereditary Exostosis**. In syndromes the manifestations are rare and they appear early during childhood. So this syndrome happens in children with multiple tumors.
   The mutated gene in this tumor is the **EXT gene**, and the mutation is mainly in chondrocytes, this is why it's called osteochondroma not chondrosteoma, because the mutation that causes the neoplasm is in the chondroid part.
   In physical examination, it's palpated as an outgrowth around the bone, and it has the normal components (cartilage, bone and bone marrow inside the stalk).



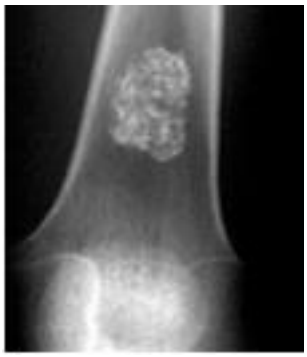
2) **Chondroma**: a benign tumor of pure cartilage.
It can arise within the bone marrow (the medulla), in this case it's called Enchondroma –inside the bone itself.
Sometimes it appears outside the bone (around the bone), in this case it's called Juxtacortical Chondroma –outside the cortex.
Both are benign tumors of course, they only differ in the location.

It occurs in young age groups, between 20-50 years of age. The most common site for chondromas is the long bones of fingers and toes (occur in hands and feet not around the knee as other tumors).
In most cases it's solitary and sporadic, and if there happens to be multiple tumors then it's a syndrome. We have two syndromes which can be associated with chondroma:
-**Ollier syndrome**: multiple tumors, they commonly occur unilaterally (one hand only not both).

-**Maffucci syndrome**: multiple tumors, but here we have other tumors in the body especially in soft tissues and joints.
In order to differentiate between the two syndromes we have to look for other tumors in the body –in soft tissues more specifically-, if they're present for example in the skin or inside the abdomen, and they look like hemangiomas in radiology, and are confirmed by a biopsy then it's a Maffucci syndrome.

?How does it appear in radiography?

Its appearance is called the **O-ring sign**, it appears as a radiolucent region (black, because the x-ray can penetrate the tumor) and in the middle there's a calcification and this calcification appears white in color.
Under the microscope it looks completely normal, normal cartilaginous tissue.
* remember that chondromas are benign tumors so they are well differentiated .



Remember: whenever you see this O-ring sign it's a chondroma, but osteosarcoma appears triangular in shape (Codman triangle).

3) **Chondrosarcoma**: this is the 2nd malignant tumor we've taken so far (the 1st was osteosarcoma).

It's a pure cartilage producing cancer, and like chondroma, it can occur within the medulla or Juxtacortical.
It's a disease of the elderly >40 years of age.

We're going to illustrate the differences between chondrosarcoma and osteosarcoma.

Osteosarcoma	**Chondrosarcoma**
Involves the osteoid and sometimes the chondroid.	Pure chondroid only.
Occurs at young age.	Occurs in the elderly.
Most common site: around the knee, in 60% of the cases.	Most common sites: the pelvis and shoulders.
Most tumors are of a high grade, poorly differentiated and aggressive.	Could be of a low grade, intermediate grade, or high grade.

The grade of the tumor in chondrosarcoma differs among patients and in 10% of them it's a mixture, which means if you take a biopsy from one site of the body and you find it of a low grade, then you take a biopsy from another site of the

body it can be of a high grade! That's why you have to take more than one biopsy since the treatment is different for high-grade tumors. How do we determine the grade of the tumor in chondrosarcoma?

We examine three important features of malignancy:

1- Cellularity: the number of chondrocytes inside the lacunae.
Normally, each lacuna contains a single chondrocyte. In cases of malignancy, a single lacuna can contain multiple chondrocytes (for example 4 chondrocytes).
2- Mitosis: the number of mitotic figures.
3- Pleomorphic cells: different shapes and sizes.

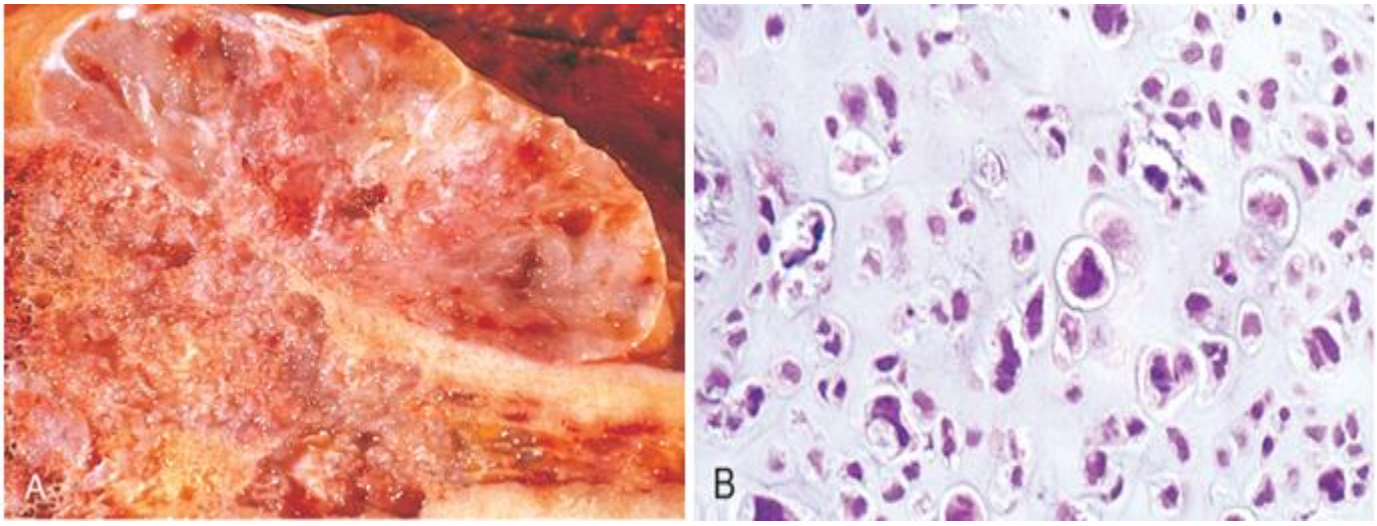
So if you see large cellularity, mitotic figures and marked pleomorphism then it's a high-grade tumor.

If the tumor resembles normal cartilage and the increase in cell's number and mitotic figures is minimal, then it's a low-grade tumor.

Pathologic features:

Grossly: the cartilage has a bluish color, although there is a hemorrhage but there is still a slightly blue color, so it's a chondrosarcoma. (A)

Microscopically: pleomorphic cells with abnormal size and shape, plus mitotic figures. (B)

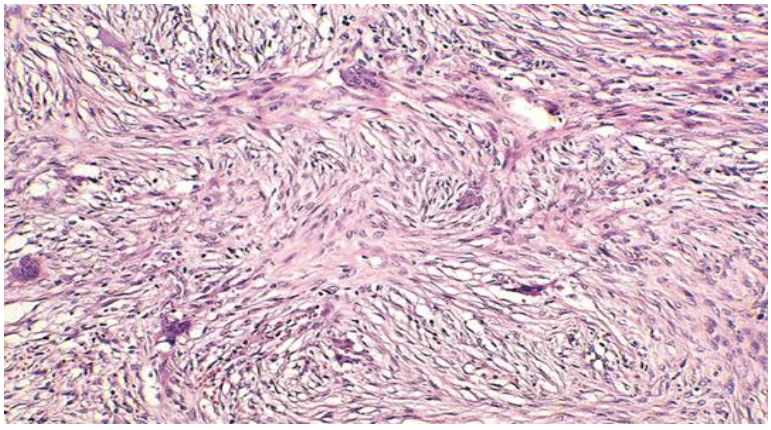


4) **Fibrous cortical defect / non-ossifying fibroma**:

As the name implies, it's mostly a developmental defect rather than a true neoplasm. It's an abnormality in cell maturation, which causes problems in the bone.
It's very common in children >2 years (30%-50%), which means one out of two children has fibrous cortical defect. It resolves by itself as the child grows older.
The fibrous cortical defect is very small in size <0.5cm.
If they become bigger they're called non-ossifying fibromas, and these cause more problems.

50% of cases are multiple and bilateral (affect both sides of the body).
They appear as radiolucent regions. They're asymptomatic, and they are discoveredincidentally, if a child (for some reason)gets an x-ray, then they appear.
In case of non-ossifying fibroma, fractures happen sometimes because the bones are very weak in that area, and this is the only complaint the patient has.
Microscopically: it appears like a response to a local trauma, which means activation and proliferation of fibroblasts.
Fibroblasts are spindle in shape, and they form a network which is called a **storiform pattern** (like a carpet الحصيرة), and in the middle you can see scattered osteoclasts (multinucleated giant cells).

➔ The storiform pattern.



5) Fibrous dysplasia (FD)

Again from the name there is no definite tumor, it is a common one ,and it's benign in most cases. If we compare FD with the previous type "fibrous cortical defect", the chance of problems in FD is higher than fibrous cortical defect *higher chance in developing tumors*.

Flash back> *fibrous cortical defect(FCD): we said in most cases they would be small incidental findings and they resolve, or in some cases get bigger.

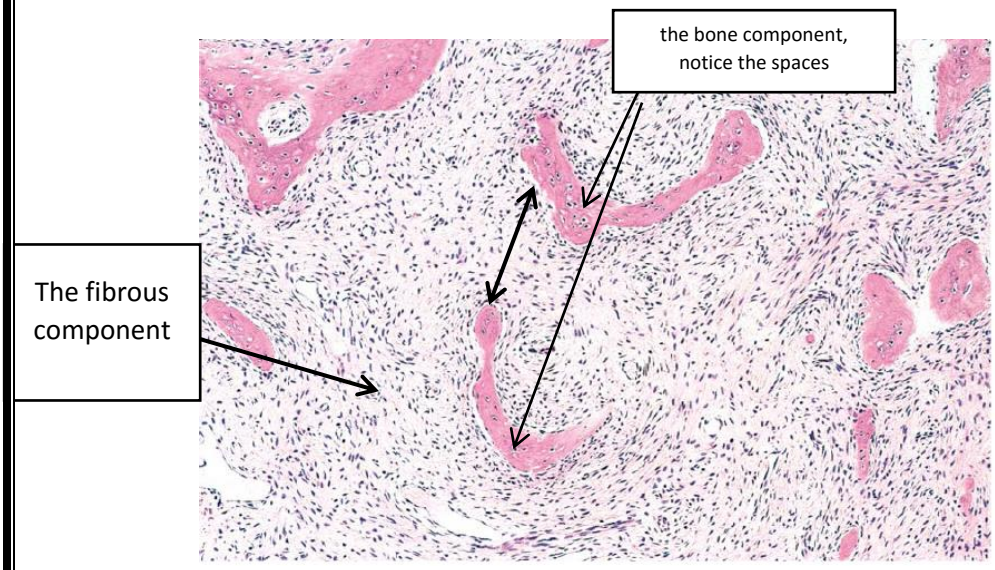
Another difference between these two diseases is that , FD has a fibrous tissue component but also we have bone component, under the microscope we can see immature bone. Whereas in FCD it's purely fibrous.

The theory is that there is a mutation in the bone(the bone cells), that makes them more active and they cannot mature normally.

Clinically most cases are monostotic; single bone effected with lesions, solitarily. Happens within 70% of the cases, it is incidental finding(patient gets an X-ray for something else, and FD appears there), most common sites where FD is found in the ribs, then femur, then scalp.(memorize the order).

The second type is polyostotic, happens if we have FD in multiple bones or sites. Most common site is the femur not the ribs. In this type of FD it appears earlier in life, it's really progressive , lesions become enlarged and cause abnormalities for patients, to say for example the patient has the disease in the right femur, it will grow abnormally but the left will be normal, eventually the patient will end up with one leg longer than the other. So in polyostotic dysplasia the patient will have deformities where ever the lesions occurs, if it occurs in the skull or face on one side, the second side will be normal, but the affected side will show deformity and shorter growth. Polyostotic occurs in 30% of cases, within these 30% we have a 1% case that has FD along with it endocrine diseases, called McCune-Albright syndrome (it happens early in life ;with kids, and the most important endocrine problem is precocious puberty; refers to the appearance of physical and hormonal signs of pubertal development at an earlier age than is considered normal) . in all FD we have a mutation in the G-protein that constitutively activates adenylyl cyclase with resultant cyclic adenosine monophosphate (cAMP) overproduction, which is responsible for proliferation, so that leads to making all bone cells more active than usual and they don’t have time for maturation, at the end we have

like a tumor. Under the microscope we have both components fibers ; we said it is a fibrous tumor so fibroblasts they are splendid and they don't have a storiform pattern like in the previous diseases , it is more single space, we also have the bone component, notice the trabeculae , they are not like the normal bone, here they are far from each other , single spaced, thin and small, they also look like Chinese letters, very curved and have abnormal shapes, so when we see both components and the bone looks like Chinese letters we figure that this is FD.



Since FD is benign , on X-rays they are well demarcated,well-circumscribed, and sometimes they give small shatters, we call them ground-glass appearance, like glass when it's broken.

There is an important information about Polyostotic disease, some patients develop osteosarcoma with it, so FD can really behave like a tumor, move from benign to malignant. Polyostotic FD is a second disease that gives rise to osteosarcoma, the first one was Paget disease.

6) Ewing sarcoma(primitive neuroectodermal tumors (PNETs))

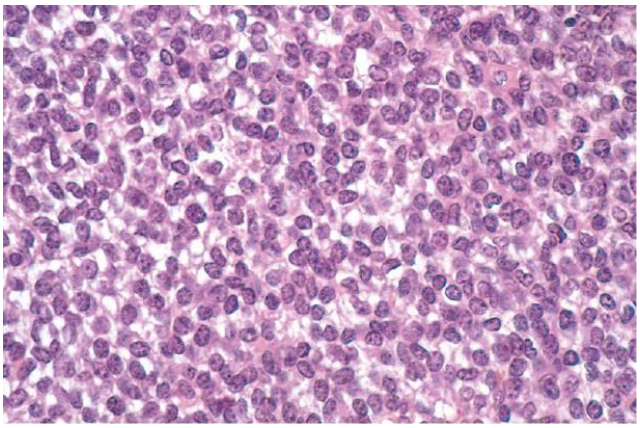
It is not classified, not osteoid, nor chondroid, nor fibrous, just named according to the scientist that discovered it and it wasn't known by that time what was the origin of these malignant cells. Now we know that they originate from a very primitive cell, that is responsible to give rise to the ectoderm in the embryonic

stage, this cell becomes malignant in Ewing sarcoma. So this Ewing sarcoma is a primitive tumor, not differentiated at all because it comes from a very immature cell, and if it has slight maturation it goes to the neuronal tissue(neuroectodermal). the tumor is very primitive it tends to be very aggressive, which makes it the worst bone tumor between all bone tumors. This tumor is second most common malignant bone tumor after osteosarcoma. It is a disease mostly common in children(10-15 years old), mostly 80%of cases are below the age of 20 , boys are slightly more affected with this disease, in general bone tumors are more common in boys.

It has also racial predilection, in black people it rarely occurs for unknown reasons, it's more common as a white people disease.

We have multiple translocation but they share a common feature, EWS gene on chromosome 22, it becomes fused with other genes, most common Fly 1 and ERG. So we have a translocation mutation and a fusion , two genes are fused to create a new gene and a new function that wasn't there. So we end up from this mutation a protein that keeps the cells proliferating.

Since they are highly primitive and not differentiated; so they appear really small and you can only see the nucleus. They appear like the lymphocytes, but slightly larger. Ewing sarcoma looks like lymphoma(a lot of lymphocytes) they appear alike under the microscope.



As we said if they take one step in maturation they will go to neuronal tissue and form something we call a rosette, it is called Homer-Wright rosettes, like a flower which means that the nuclei are arranged into a circle and in the middle there is an empty space. This occurs normally in the neuronal genesis , the neurons take this figure then they mature more into neurons. So the Homer-Wright rosette

occurs in Ewing sarcoma it is the same disease, it is just a morphology period were we see the primitive cells take a shape of a flower.

Ewing sarcoma arises in the medulla of the bone, most common site is the femur, also it can appears in the appendix but the most common site is the femur, and again it's highly aggressive and invasive. When the cells destroy the bone, like in Pyogenic Osteomyelitis they activate new bone formation (in Pyogenic Osteomyelitis we said that cytokines produced by the inflammatory cells, they activate the osteoblasts to create new bone) here we have the same thing, we have the destruction of the bone causes an inflammation, inflammatory cells secret cytokines, and they produce a new bone, this new bone it is like layers, thin layers next to each other and in the X-ray it appears as onionskin, looking like the onion , this occurs in Ewing sarcoma, because the destruction is severe and there is a new bone formation around the tumor.

7) **Metastasis**

More common than primary bone tumors, since bone is very rich in blood, circulation almost goes there and it is slow, which makes it a favorite place for metastases, so metastatic tumors tend to go to the bone. Mostly metastasis occur in the spine(axial skeleton). Most tumors when they get there they don't cause direct physical injury to the bone, instead they reside there and secret materials which causes bone erosion, like PTHRp (parathyroid hormone related peptides) that are similar to parathyroid hormones , the difference is that parathyroid hormones are secreted by parathyroid glands, and if they are secreted by something else other than the parathyroid gland we call them PTHRp, here they are secreted by the malignant cells in the bone that activate osteoclasts causing bone resorption. So patients with this, have pain and fractures in the bone, secreted prostaglandins cause pain , Some cancers they activate osteoclasts.

In prostatic carcinoma when it goes to the bone it activates bone synthesis, so on the X-ray we will see very thick bone in that area, this is called osteoblastic or osteosclerotic causes sclerotic lesions (very thick). So prostate cancer is the most famous one in this type, it goes to the bone but doesn’t destroy it, it actually activates bone synthesis ending with very thickened bone. If I want to know if a patient with prostate cancer has metastasis or not, just do an X-ray, if there is a thickening that means there is a metastasis there.

Sometime we have mixtures, since cancer cells don’t follow rules and do what they like, so patients might have sclerosis with the presence of osteolytic together at the same side.

Sorry for any mistake

"Don’t sugar coat everything.. You’ll get diabetes”