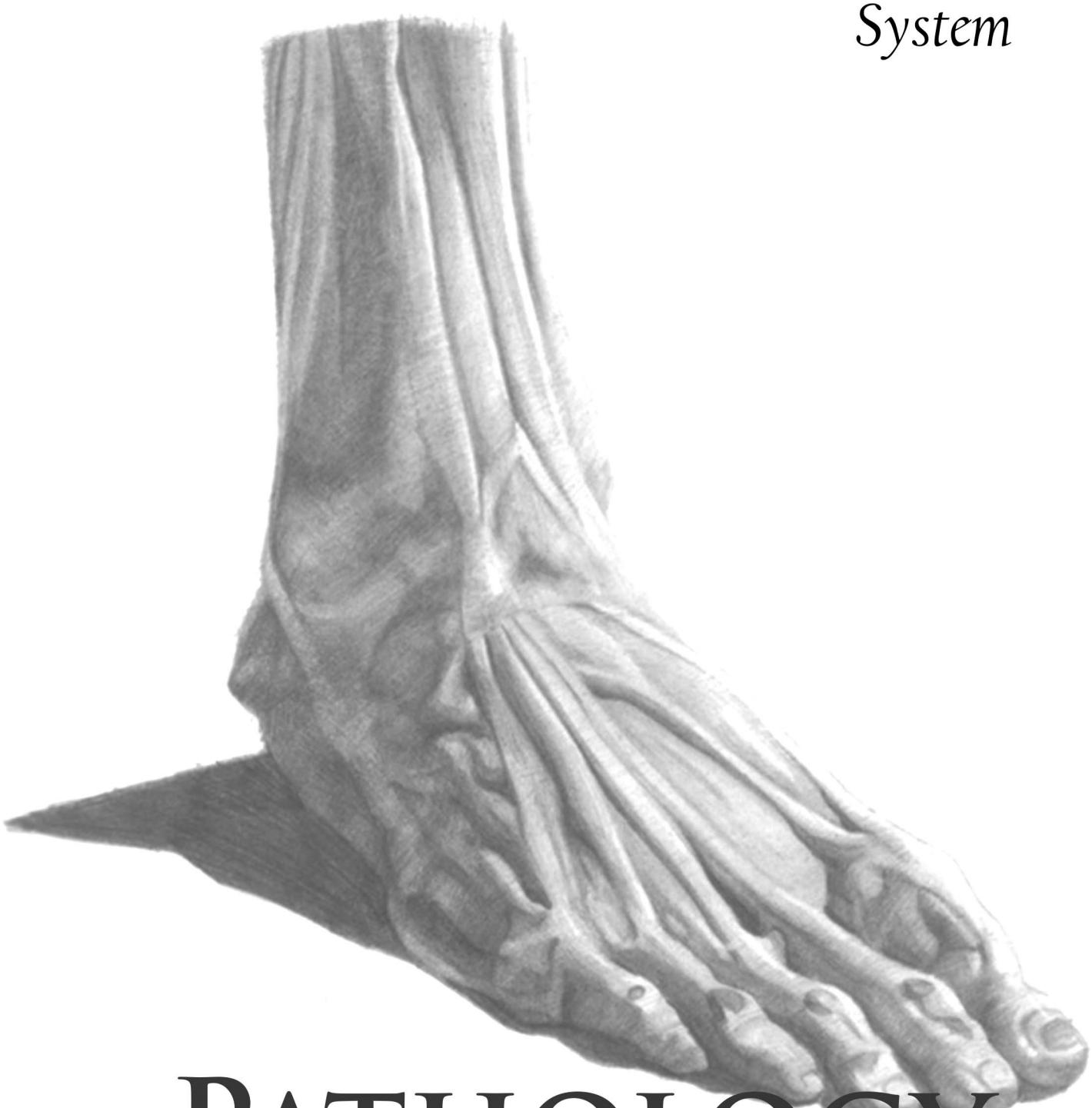
Medical Committee
The University of Jordan

The Skin and
MUSCULOSKELETAL
System



PATHOLOGY

SLIDES ☐
SHEET ■
LECTURE # 3

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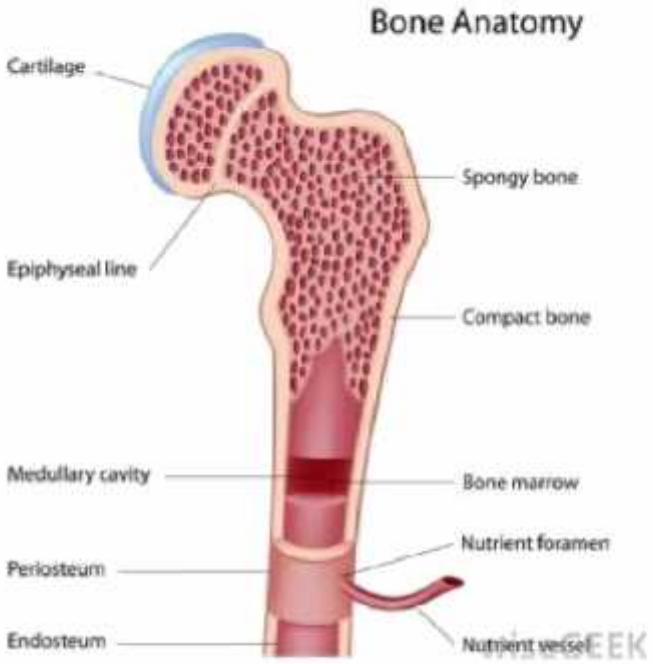
Pathology of the Skin and Musculoskeletal System

Before we start, here's a picture giving you a basic understanding of bone anatomy, just so that the terms mentioned aren't lost on you:



Note: The part of the bone termed cortex, which is repeated several times during this lecture, is the same as the compact bone.

Osteosarcomas

Osteosarcomas are **the most common primary malignant tumors of the bones.**

Secondary malignant tumors refer to metastasis(more common than primary tumors), however primary malignant tumors is a more general term. **The most common benign tumor of the bone is an osteochondroma.**

The definition of an osteosarcoma is a malignant tumor of the bone which produces bone matrix and is made up of malignant cells which synthesize osteoid. It is the most common primary bone tumor after metastasis and hematopoietic leukemia. Osteosarcoma occurs in all age groups, but **occurs predominantly in children and over 75% of cases occur in those less than 20 years old**. This is important for you to understand. A child has still not completed his growth, so it

is logical that their bones would be the most vulnerable. Osteosarcomas, and sarcomas, in general, are more common in children.

It is the opposite with carcinomas, which are predominate in adults. For example, in the case of breast cancers, where breast tissue rests in children and how this cancer only affects adults. Also, in the case of lung cancer where adults have been exposed to much more pollutants than children.

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. **They are intra-medullary**. As we discussed previously, **osteomas occur in the cortex**, but osteosarcomas, on the other hand, occur in the medulla of the bone. They are poorly differentiated and **produce osteoid** ,for the most part, **but can also produce cartilage and fibroid tissue.**

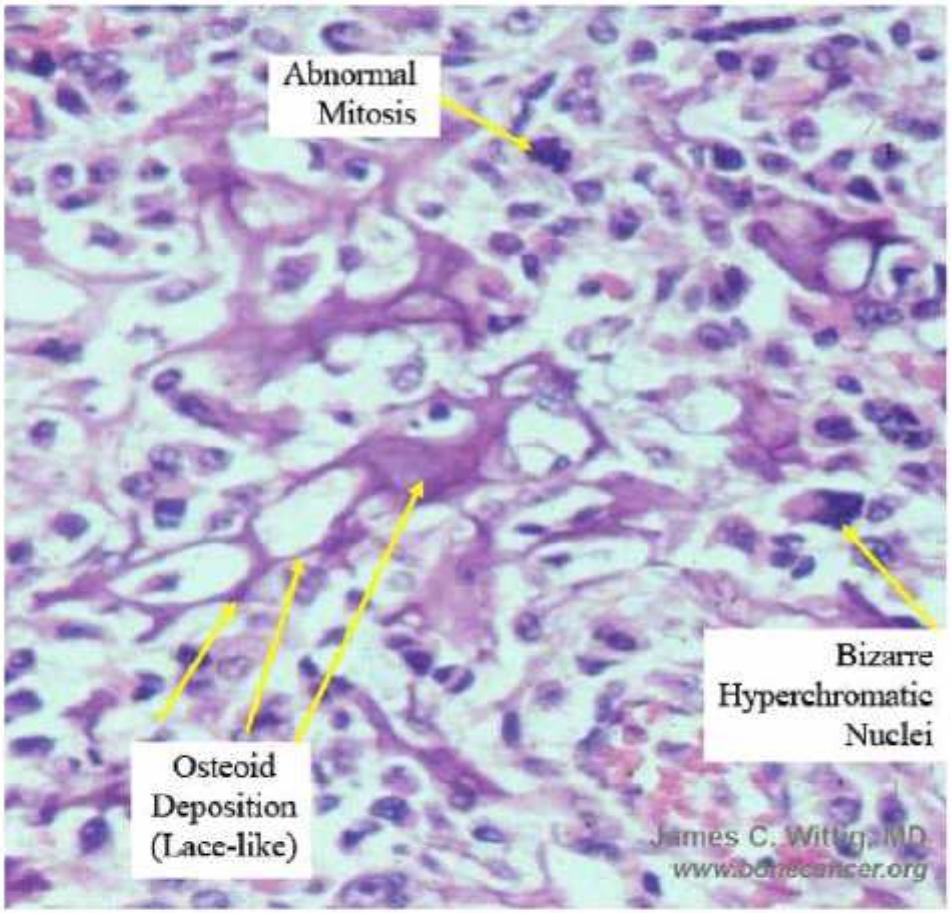
Pathogenesis:

Most cases of osteosarcomas have no known cause. 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 osteosarcomas.

As you all know, in cancer, not only one gene is mutated in a cancer. There are thousands of mutated genes. 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-dependant kinases, and cyclin dependant kinase inhibitors will lead to uncontrolled cell proliferation. The most important mutation, ultimately, is that in the RB gene.

Once again, fast-growing bones are those most vulnerable to osteosarcomas, such as the growth plate around the knee joint, on the metaphysis of the bone. Just like any tumor, you can see a solid mass. **This tumor is cystic and hemorrhagic.** This type of tumor displays cystic degeneration. Remember it is intra-medullary, 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. **Only the epiphysis is usually spared.**



Microscopically, we can see malignant cells, as well as osteoid deposition. We have malignant, bizarre, giant multi-nucleated cells, and mitotic figures. These are all features of malignancy.

The malignant cells produce abnormal bone, which is thick and branched. This bone(osteoid deposition) is referred to as lace(تخريم)-like. The bone branches like the strings of a fishing net. Malignancies can also produce cartilage along with osteoid.

If cartilage is produced in a large amount, we call it chondroblastic osteosarcoma. This is a variant of osteosarcoma. Clinically, it is a tumor, so patients will have swelling and localized symptoms, such as pain and hotness. If you are presented with a painful, enlarging mass and weak bone, which spontaneously fractures, you have the signs of a tumor.

The protruding tumor gives off the shape of a triangle. We call this Codman's triangle, the result of a tumor growing outside of the bone. This is very important for you to know. As in all sarcomas, osteosarcomas do not go to the lymph, but head directly for the blood. So osteosarcomas spread hematogenously.

Now, we will head to the most common benign tumor of the bone.

Osteochondroma

In the last lecture, we discussed that osteochondromas contained both components (bone and cartilage), but is **mainly a chondroid tumor**, which is why we called it osteochondroma. Osteochondromas are **also known as exostosis.** Osteochondromas have a unique structure. They resemble polyps. They have stalks and heads(or caps). **The stalk is the bone, and the head is the cartilage.** This is characteristic of osteochondromas. They grow outside with a stalk, unlike osteosarcomas, which are solid masses. They occur on many sites, but like osteosarcomas, are most common in the knee**. Most are sporadic and solitary.** In the case that they are multiple, this is usually syndromic, such as in **Hereditary multiple exostoses**, which is inherited as autosomal dominant.

The gene which is mutated in this tumor is the EXT gene, which is a tumor suppressor. In the case of its mutation, you're faced with increased growth. **Osteochondromas can also occur in the pelvis, scapula, ribs and fingers**.

Cartilage Tumors:

Chondromas

Chondromas are isolated and produce ONLY cartilage. They produce no bony stalk. Chondromas are **benign tumors** with a symphysis of hyaline

cartilage. The cartilage is identical to normal cartilage, however it is in the form of a mass. This tumor leaves from two sides.

1)If it leaves from the medulla of the bone, we refer to it as an **enchondroma**

2)If it leaves from the soft tissue, we refer to it, as **a juxtacortical chrondroma**

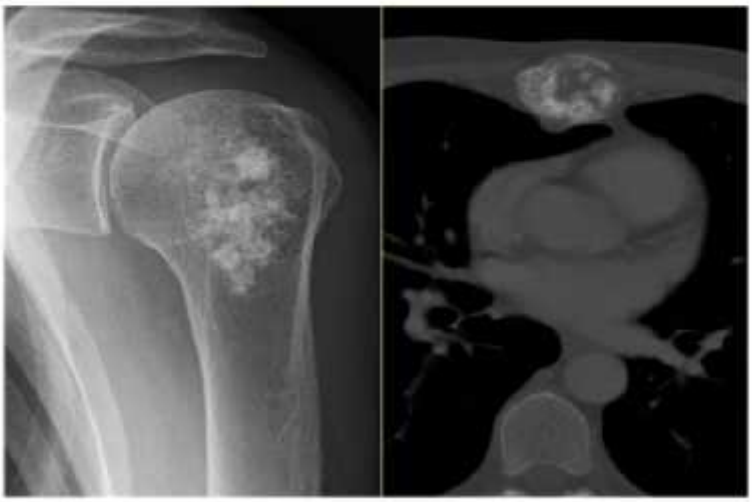
Both of them affect those between the ages of 20-50. All tumors we will discuss are metaphyseal, but differ in terms of whether they are cortical or medullary.

Chondromas are most common in the phalanges, where they are manifested as pink chondromas.

There are syndromes associated with chondromas, just like there are for other tumors. In osteosarcomas, the syndrome was retinoblastoma. In osteochondroma, the syndrome was Hereditary multiple exostoses. For chondroma we have two syndromes

1) **Ollier disease** is a non-hereditary sporadic disease which leads to the formation of enchondromas at the growth plate(specifically, the diaphyseal region in the short tubular bones and the metaphyseal region in the long bones) of certain bones. Ollier disease affects limbs, asymmetrically. It may affect one arm and not the other. It may also affect both limbs, and be more concentrated on one.

2) **Maffucci syndrome**– Characterized by multiple pink chondromas with soft tissue tumors, and hemangiomas(blood vessel tumors).



On x-rays, the enchondroma's growth appears as the letter O. It is translucent, non-reflective and has calcification in the center, which the x-rays reflect off, giving the O shape.

Note on the picture: This is the closest picture I could find to indicate that enchondromas are O-shaped. All the other sources indicate that they are more lobe-shaped.

Note: Syndromes are a manifestation of mutations that one is born with, not something that occurs due to the tumor.

Chondrosarcomas

Chondrosarcomas are malignant tumors which produce cartilage(NOT bone). It is less common than osteosarcoma. It affects a different age group than osteosarcoma. While osteosarcoma affects children, **chondrosarcoma affects older age groups.**

Microscopic examination is necessary to examine chondrosarcomas. Osteosarcomas are poorly differentiated, but chondrosarcomas can be anything from well differentiated-low grade(normal cartilage with scattered cells) to high grade(accompanied by necrosis and high mitosis).

The tumor grade is determined by cellularity, atypia, mitotic activity and the color of the nucleus. Lacunae should carry one cell. If there is more than one, then that's a sign of cancer, and the increasing number, means increased severity. If the nucleus is very dark, then the DNA is active-due to mitosis. There is also atypia, where the cells do not resemble one another. Sometimes, there is a mixture of well differentiated and poorly differentiated areas in the tumor.

10% of patients have low grade chondrosarcoma and a second high grade one

Explanation: De-differentiated chondrosarcoma occurs in less than 10% of cases, and it is usually found in the arm, leg or pelvis bones. This tumor is a very different kind of chondrosarcoma that is especially difficult to treat. A part of the tumor appears to be a low to intermediate grade cartilage tumor, and it is located close to a high grade non-cartilage kind of sarcoma.

The most common site of chondrosarcoma is in the pelvis(most commonly), the shoulders or the ribs. Chondrosarcomas are intra-medullary tumors which extend outside the bone.

Fibrous cortical defect

A fibrous cortical defect is not a pure tumor. The fibrous cortical defect is similar to the osteoma, which is a malformation. The fact that it is common, proves it is not a tumor. **It occurs in 30-50% of children.**

The fibrous cortical defect occurs as a variant of bone development, rather than as a neoplasm. It is a small defect, less than 5cm, which shows up in X-rays. It occurs in the metaphysis of the distal femur or proximal tibia, again around the knee. 15% of these defects are bi-lateral or multiple. **If it is large(larger than 5cm), it is called a non-ossifying fibroma** and becomes similar to a tumor; It causes problems, such as fractures, because the bone is weak.

Microscopically, you can see a cellular region of fibroblasts, which cannot mature into bone and are accompanied by macrophages**. We see 3 cells in fibrous cortical defects, (1) Fibroblasts, with (2) Macrophages running along them, and (3) Osteoclasts.**

Fibrous cortical defects have a very strange morphology, but are nonetheless, not tumors. We call the arrangement of fibroblasts Storiform, and it resembles the arrangement of threads on a rug.

Fibrous dysplasia

Fibrous dysplasia resembles non ossifying fibroma. It is considered a benign tumor. **The most common sites for Fibrous dysplasia are the rib and femur, followed by the jaw**. Fibrous dysplasia can also be regarded as a developmental defect, but causes a large mass in bone. Therefore, there is a debate on whether or not it is a defect or a tumor. We have abnormal osteoid formation and an absence of fibroblasts. This is symptomatic.

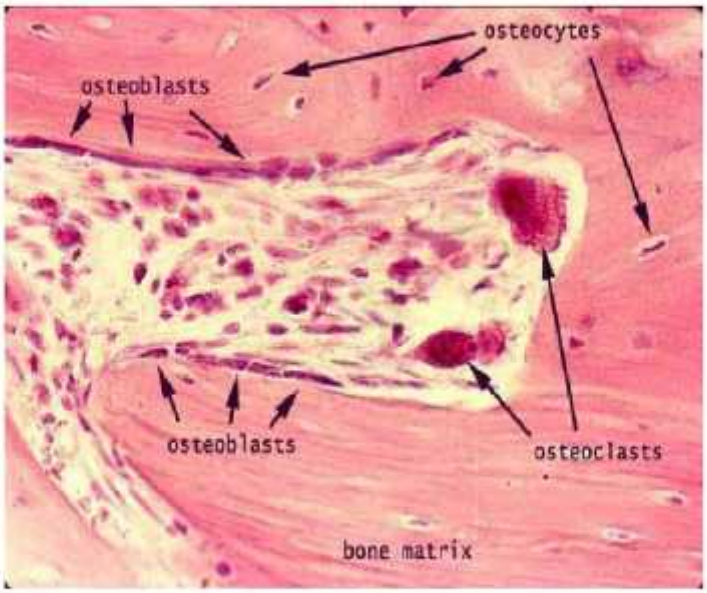
Fibrous dysplasia is categorized into two types:

1) **Monostotic fibrous dysplasia(Jaffe-Lichtenstein syndrome)-** Which makes up 70% of cases. In this case, **the tumor is benign and involves only a single bone.** The benign tumors can cause very painful swellings and bone deformitites. However, it is often asymptotic.

2) **Polystotic fibrous dysplasia(Albright's disease)-** Makes up 29% of cases. **It is more aggressive and occurs in multiple bones.** Sometimes, this symptom can become large and cause disfigurement, unlike the monostatic syndromes.

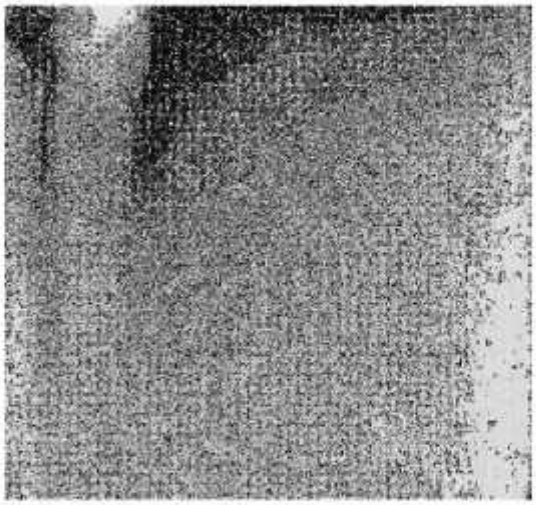
*__McCune-Albright syndrome__(a severe form of polyostotic fibrous dysplasia):- Makes up <1% of all cases. This is accompanied with **endocrine diseases, and bone and skin lesions**. You'll probably never see this type in your practical life. This type is found in children which have reached precocious puberty, which is early onset puberty due to abnormal hormones. It may also be accompanied by skin lesions(brown café au lait spots)

The tumors range from asymptomatic to those which cause significant deformity.



Under the microscope, you can see **thin, curved osteoid cells which resemble Chinese letters**. Osteoblasts are not present in the normal amount or normal morphology. Normally, there is an osteoblast ring around the osteoid.

These tumors are intra-medullary, vary in size, and have a ground glass appearance



Symptomatic regions can be removed by surgical excision. Fibrous dysplasia should not receive radiotherapy, because the tumor is benign. If you give these cells radiotherapy, they will become malignant. Fibrous dysplasia can be progressive and transform to osteosarcoma.

We now have three diseases which can transform to osteosarcoma:

1) **Paget's disease**
2) **Osteoblastoma,**
3) **And fibrous dysplasia,** if the tumor receives radiotherapy

Ewing's sarcoma

Ewing's sarcoma is the worst type of bone tumor. The cells are very primitive and have nearly no differentiation, save for a few dendrites. Under the Ewing family of tumors, Ewing's sarcoma can also be grouped with PNT(primitive neuroectodermal tumor).

Ewing's sarcoma and PNT share the same translocation. The only difference is that Ewing's sarcoma is specifically inside the bone, and PNTs are general, therefore not necessarily in the bone. There is no family history or other predisposition that can elude to this tumor.

Ewing's sarcomas are the 2nd most common primary bone tumors in children. Most cases are in patients aged 10-15 years. **80% of patients are less than 20 years old.** Ewing's sarcoma affects more boys than girls. Ewing's sarcoma has a greater racial predisposition for Caucasians, but is rare in those of African descent, for example.

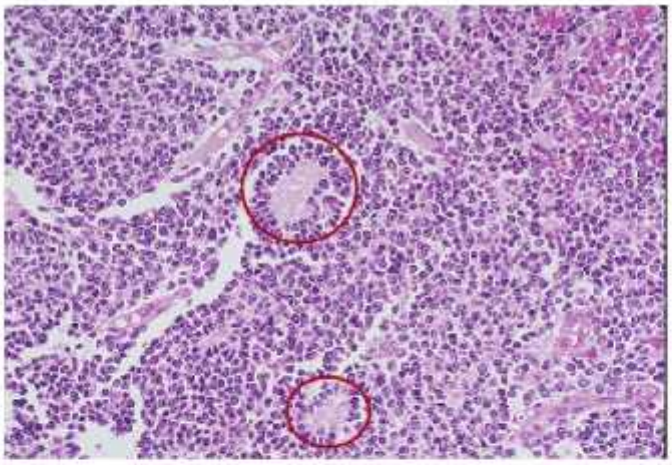
Genetic translocation:

The Ewing's sarcoma gene located on chromosome 22, is translocated with one of two genes:

1)FLY-1: chromosome 11 (11q24)

2)ERG: Chromosome 21 (21q22)

The fusion of these genes leads to the formation of a new protein and the activation of transcription factors. The new proteins are called chimeric genes(fusion proteins).



The most common site for Ewing's sarcoma is the femur.

It is a highly invasive, destructive tumor. This tumor creates flower-like patterns of cells called **rosettes**.

Characteristic to Ewing's sarcoma is periosteum activation, which leads to new bone synthesis and an "onion skin" appearance.

Metastasis

Bone is a site for low perfusion. This means that the bones have relatively low blood delivery. Bone marrow perfusion is slightly increased in bone metastases. The most common site for metastasis is the axial skeleton, followed by the femur.

Cancers, themselves, do not cause physical damage to bones, as they are very solid structures. However, they synthesize hormones which cause bone erosion, such as parathyroid-related peptides(PTH-RP), which resemble the parathyroid hormone.

Some cancers activate osteoblasts and form new bone. We refer to the masses formed as osteoblastic lesions. The most common ones are those that occur in prostate cancer. Prostate cancer metastasizes through the bone, and aid in the formation of these lesions. Cancers can also synthesize sclerotic, or osteoclastic lesions. Most cancers are out of control and synthesize both, so we see mixture of both lesions.

We've discussed all the cancers, except for giant cell tumors, which is not important.

A special thank you to Mohamad Al-Hindi for thoroughly editing this sheet.