MSS

PATHOLOGY

Sheet #5

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BONE-FORMING TUMORS

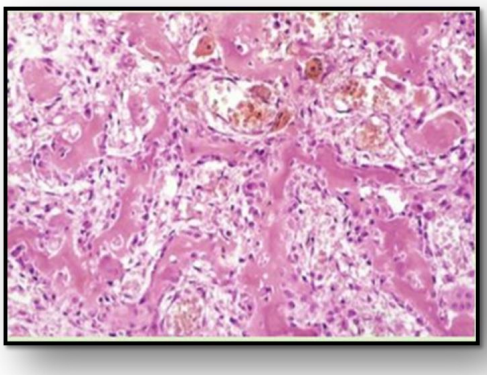
❖ In our level, we need to know the *General Features* of Osteoid osteoma & Osteoblastoma.

Osteoid osteoma (more common than osteoblastoma)

- Osteoid osteoma is, by definition, Benign osteoma or benign lesion less than 2 cm in diameter , and is most common in young men.
- About 50% of cases involve the femur and tibia (the most common locations) , it starts with a nidus that is surrounded by a bone reaction.
  (Nidus : a center where the bone starts building around)
- It presents with Severe nocturnal (at night) pain (The pain is probably caused by prostaglandin E2 (PGE2)) and relieved by aspirin & Non-steroidal anti-inflammatory drugs (NSAIDS)
- Treated by: radiofrequency ablation (Removal of tumor by using strong radiation) or surgery

Osteoblastoma

- Osteoblastoma is, by definition, Benign osteoma or benign lesion more than 2 cm in diameter and involves the posterior components of the vertebrae more frequently . Histologically if they tumor is removed , you don't see a rim of bone reaction like the ones which you see in osteoid osteoma.
- Pain unresponsive to aspirin and Non-steroidal anti-inflammatory drugs (NSAIDS) - (one of the differentiating features on clinical basis)
- Treated by curetting (surgical scraping or cleaning) .
  - Osteoid osteoma and osteoblastoma are benign bone producing tumors that have similar histologic features so It's difficult to differentiate between them under microscope , but differ clinically and radiographically.
  - both look like rim of reactive bone with some hemorrhage and reactive giant cells, you don't see atypia.



OSTEOSARCOMA

- Osteosarcoma (osteogenicsarcoma) is a malignant osteogenic tumor (forming abnormal bone- woven bone).
- Excluding hematopoietic tumors (myeloma and lymphoma), osteosarcoma is the most common primary malignant tumor of bone.
- Osteosarcoma has a bimodal age distribution; 75% of osteosarcomas occur in adolescents (between 10-15).
- The smaller second peak occurs in older adults (between 55-65) who frequently suffer from conditions known to predispose to osteosarcoma, such as Paget disease, TB of bone and previous radiation. These are referred to as secondary osteosarcomas.

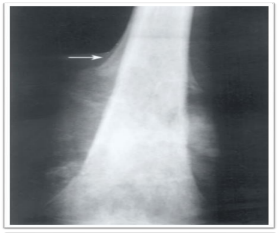
- Overall, men are more commonly affected than women (1.6:1).
- The most common sites are the metaphyseal regions of long bone (distal femur and proximal tibia) around the knee, but it can happen in another location.
- Patients present with Progressive pain or pathologic fracture.
- Imaging: large destructive and infiltrative lesions with Codman triangle
- The tumor frequently starts in the bone, and they go deep into the medulla and outside into the periosteum followed by infiltration of the periosteum and the surrounding soft tissue, they elevate the periosteum, and they start producing abnormal woven bone leading to the appearance of an angle, known radiographically as Codman triangle .

  Side Note : Codman triangle is not specific for osteosarcomas; It can be seen in any infiltrative bone lesions whether infectious or other tumors.

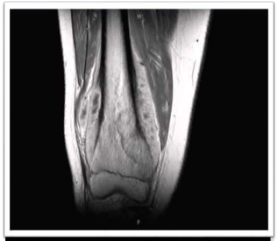
- Approximately 70% of osteosarcomas have acquired genetic abnormalities: mutations in RB (retinoblastoma) gene, TP53 gene (tumor suppressor 53 gene which is the most common tumor suppressor gene involved in human malignancies), CDKN2A (p16 & p14), MDM2 & CDK2.
- the molecular genetic changes of osteosarcoma are actually complex and we don't use them routinely for diagnosis or for prognosis, the histology imaging is more than enough and it is not really a difficult diagnosis.

OSTEOSARCOMA FEATURES

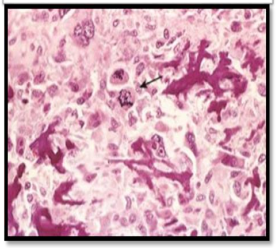
- simple x-ray morphology, distal femur showing a process which started in medulla of the bone and infiltrates the surrounding tissue elevating the periosteum and this angle between actual bone and the periosteum is called Codman's triangle.



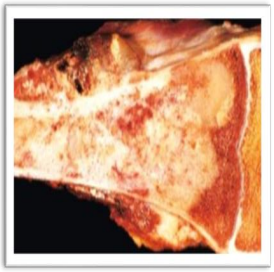
- MRI morphology shows the processes, tumor arises at the metaphysis and extends to the soft tissue, the skeletal muscle infiltrated by this tumor, and this is the periosteal elevation causing Codman triangle.



- In this picture , which is histological section, contains malignant osteoid by malignant osteoblast with haphazard patterns of frequent abnormal mitosis , it's all woven bone.



- In a gross examination of the specimen, if we cut the distal head of femur longitudinally, we see an excess articular cartilage arises from it .



OSTEOSARCOMA TREATMENT:

- Osteosarcoma is treated with a multimodality approach (MDTeam) that consists of (1) neoadjuvant chemotherapy ((using chemotherapy before the main treatment which is surgery)), (2) surgery (3) chemotherapy and radiation.

- ✓ *Chemotherapy → to prevent or to kill any metastatic possibility .*
- ✓ *Radiation → to control the local diseases .*
- ✓ *Surgery → to remove the tumor.*

- Most of the time, There is a new adjuvant chemotherapy before Surgery followed by Local radiation to have a good local control.
- These aggressive neoplasms spread hematogenously to the lungs. There are some exceptions, they don't usually go to the lymph nodes.
- Although the prognosis has improved substantially since the advent of chemotherapy, with 5-year survival rates reaching 60% to 70% probably, it's improving now 75-80% in patients without detectible metastases at initial diagnosis.
- the outcome for patients with metastases, recurrent disease, or secondary osteosarcoma is still poor.
- presence of mets (metastases) at diagnosis is a bad prognostic factor.

CARTILAGE-FORMING TUMORS

- These tumors are characterized by the formation of hyaline cartilage.
- Benign cartilaginous tumors are much more common than malignant ones.
- Osteochondroma, known clinically as benign exostosis, is a benign cartilage capped tumor that is attached to the underlying skeleton by a bony stalk (composed of benign bone covered by benign cartilage)
- Osteochondromas develop in bones of endochondral origin and arise from the metaphysis near the growth plate of long tubular bones

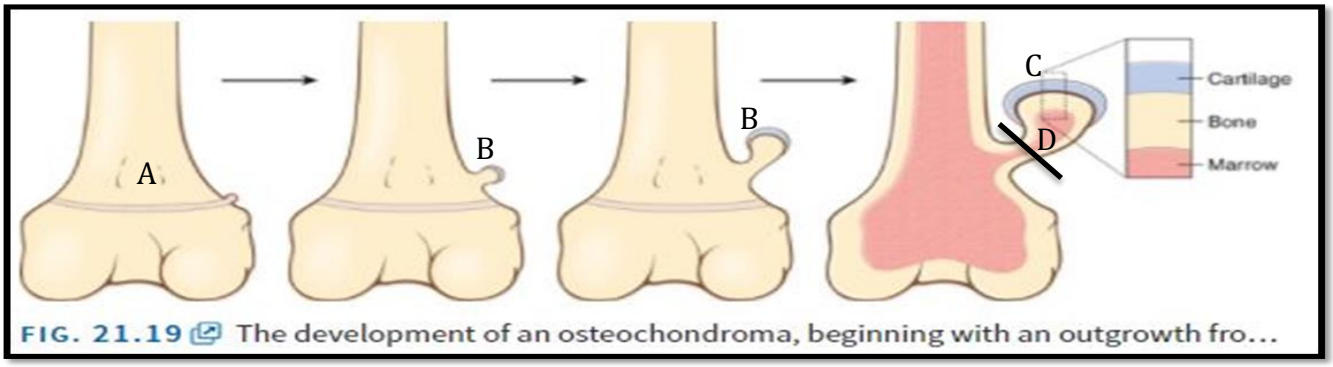


FIG. 21.19 The development of an osteochondroma, beginning with an outgrowth fro...

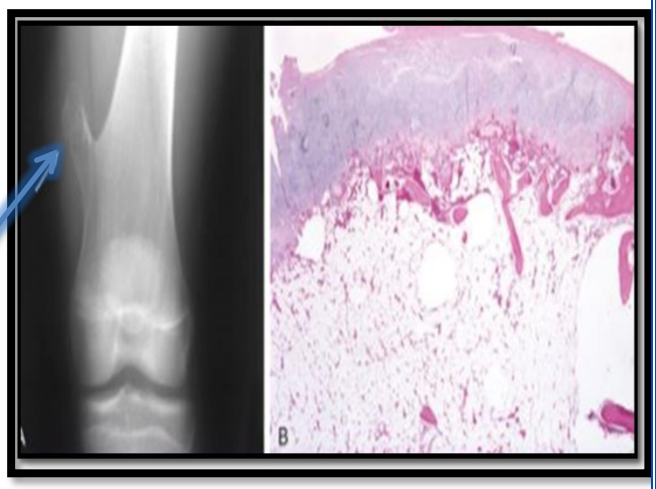
- *A → It can occur in any bone BUT the most common location is around the cartilaginous growth plate of the long bones.*
- *B → Extension of this bone and bone marrow goes out.*
- *C → then, it will be covered by benign cartilage.*
- *D → if you cut there, you will see normal cartilage, normal periosteum, and normal bone marrow.*

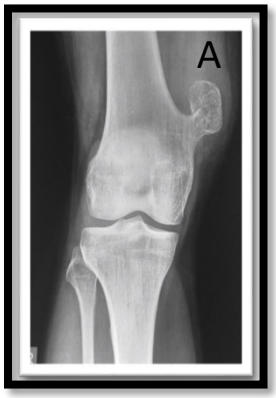
- About 85% are solitary (in a specific area) . The remainder are seen as part of the multiple hereditary exostoses (MHE) syndrome .
- Hereditary exostoses are associated with germline loss of function mutations in either the EXT1 or the EXT2 gene.
- It is rarely transformed to chondrosarcoma (<3-5%), if they do, usually they do in cases when they are MHE (More Common in MHE).

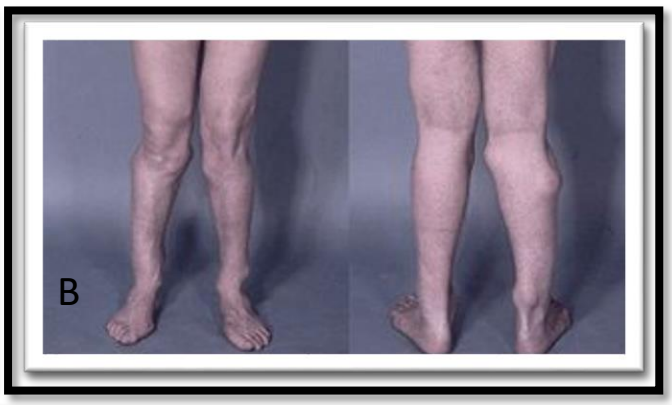
If you diagnose a patient with MHE ,you have to follow up closely to watch those osteochondromas to avoid transforming to malignant chondrosarcoma.

OSTEOCHONDROMA

- X-Ray of the distal femur: osteochondroma, notice the tumor with normal bone and cartilage. very classic appearing of a mass with normal cartilaginous cap, you don't see destruction of the tissue around it ((no infiltration or Codman triangle))
- Microscopic histology: if you cut this tumor and you look at it, you will see normal cartilage, normal subchondral bone and bone marrow .



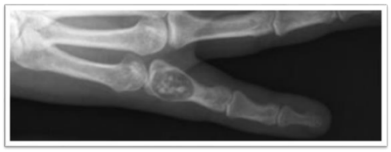


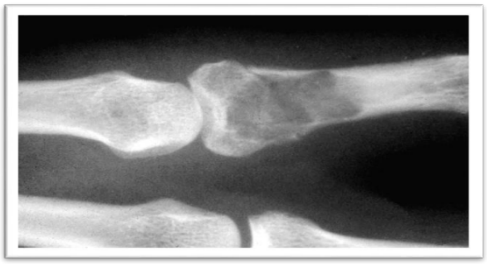


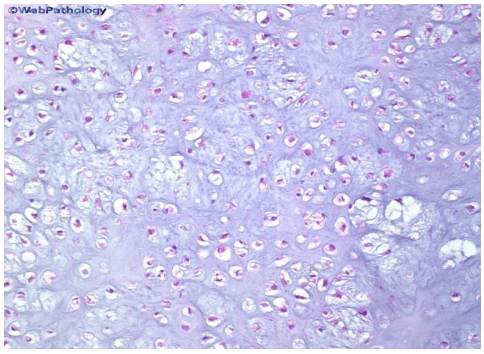
- *A* → They cause pain and pathological fractures.
- *B* → This is a case of MHE

CHONDROMA (ENCHONDROMA)

- Chondroma are benign tumors of hyaline cartilage that usually occur in bones of endochondral origin.
- They arise within the medullary cavity (medullary enchondroma) or on the cortical surface (cortical chondroma).
- Enchondromas are usually diagnosed in individuals 20 to 50 years of age.
- Typically, they appear as solitary metaphyseal lesions of the tubular bones of the hands and feet.
- Ollier disease and Maffucci syndrome are disorders characterized by multiple enchondromas (enchondromatosis)
- Maffucci syndrome also is associated with skin hemangiomatosis.
- Chondrocytes of enchondromas have been identified to have genetic mutations in IDH1 & IDH2 genes .



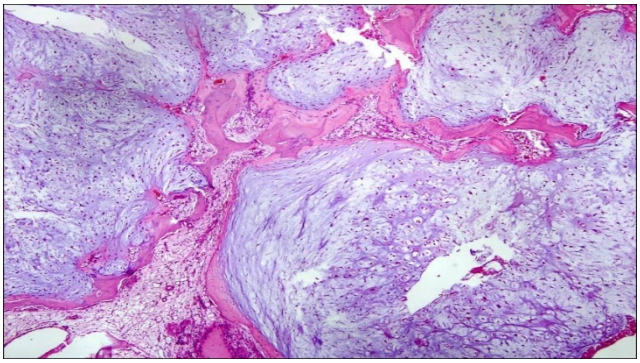




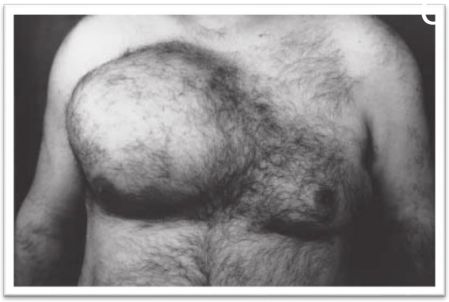
- Microscopic histology: normal benign cartilage & No atypia
- X-ray Radiology: Cartilaginous appearance on x-ray, no destruction or infiltration, no elevation in the periosteum (no Codman's triangle)

Chondrosarcoma

- Chondrosarcomas are malignant tumors that produce cartilage.
- Chondrosarcoma is about half as common as osteosarcoma (50% incidence of osteosarcoma)
- chondrosarcoma is less common, if you treat 20 cases of osteosarcoma, you will maybe treat 10 in chondrosarcoma.
- Individuals with conventional chondrosarcoma are usually in their 40-50 years of age .
- These tumors affect men twice as frequently as women (M:F 2:1).
- Chondrosarcomas commonly arise in the axial skeleton, especially in the pelvis, shoulder and the ribs. Usually present as painful, progressively enlarging masses ((large tumors)) .
- Chondrosarcoma does not have a signature genetic mutation.
- Multiple genes can be involved including EXT, IDH1, IDH2, COL2A1 and CDKN2A.
- Prognosis of chondrosarcoma depends on the grade (Grade 1: excellent prognosis / Grade 3: bad prognosis)
- Tumor stage measures the extent of tumor spread in the body
- Grading is determined by cytologic and histologic appearance of the tumor
- Treatment: surgical treatment +/- chemotherapy & radiotherapy (to prevent metastasis).

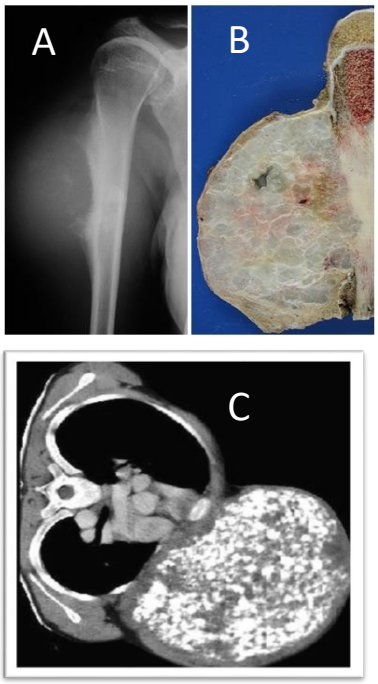


Histologically: abnormal malignant cartilage (it may be grade 1 or 2 but not grade 3 yet because you can still see the cartilaginous differentiation is obvious → low grade tumor).



chondrosarcoma of the ribs.

- *A → Huge chondrosarcoma in the diaphysis of the humerus, there's Codman triangle, the tumor is infiltrating into the bone marrow and outside of the soft tissue elevating the periosteum.*
- *B → the gross specimen which when it was removed, characteristic cut surface of cartilaginous, it's large and infiltrating the soft tissue and the medulla bone.*
- *C → Probably CT scan, where huge mass with a cartilaginous morphology on imaging, this is called bubble soap appearance*

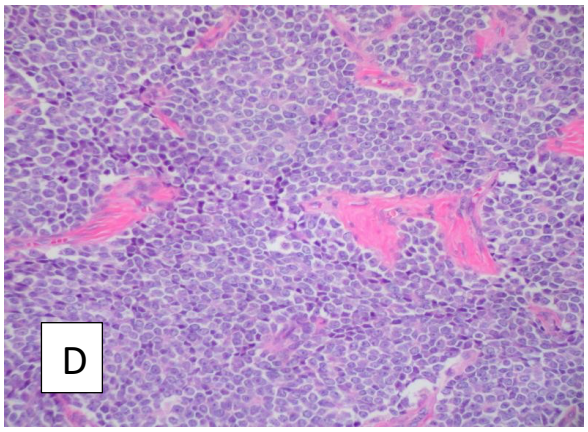


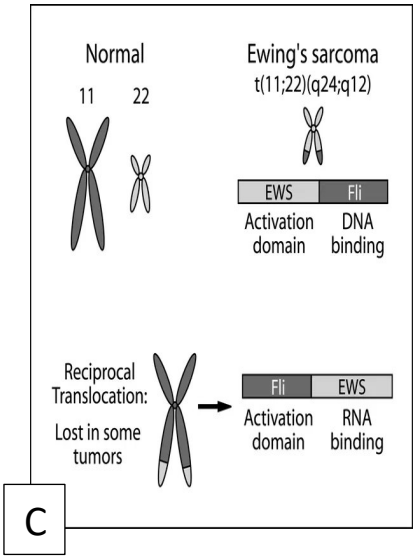
Tumors of Unknown Origin

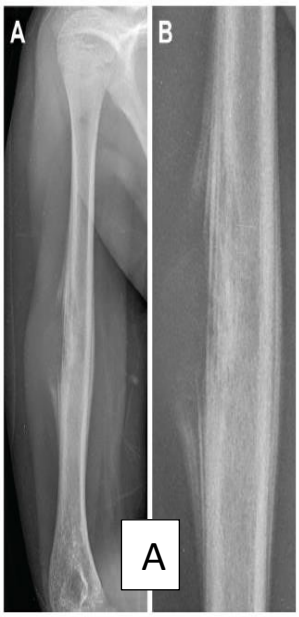
Ewing Sarcoma

- Dr. James Ewing (1866-1943) described this tumor in 1920.
- Ewing sarcoma is a malignant tumor composed of primitive round cells.
- Entities previously classified as Primitive neuroectodermal tumor (PNET). Also called Small blue cell tumor. (Note that small blue cell tumor isn't a specific diagnosis for Ewing Sarcoma, it is also present in lymphoma, neuroblastoma, rhabdomyosarcoma and others).
- 2nd most common sarcoma of bone after osteosarcoma.
- Of all bone sarcomas, Ewing sarcomas have the youngest average age at presentation (80% are younger than 20 years).
- The tumors usually arise in the diaphysis of long bones.
- Has a specific signature genetic translocation.
- The most common translocation, which is present in about 90% of Ewing sarcoma cases, is t(11;22) (q24;q12). This mutation generates an aberrant transcription factor through fusion of the EWSR1 gene with the FLI1 gene.
- FLI1 gene is translated to a FLI1 protein that can be targeted by a specific antibody.
- Ewing sarcomas are treated with neoadjuvant chemotherapy followed by surgical excision with or without radiation.
- long-term survival now reaches 75% of patients.
- Ewing sarcoma Histologically: round cells with small amounts of clear cytoplasm (large nucleus, small cytoplasm)

Ewing Sarcoma FEATURES





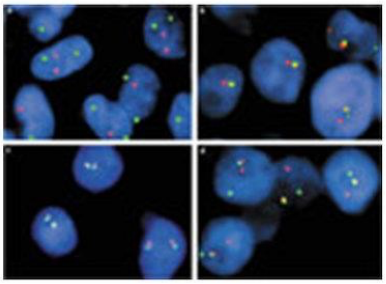


Positive translocation of EWS gene:

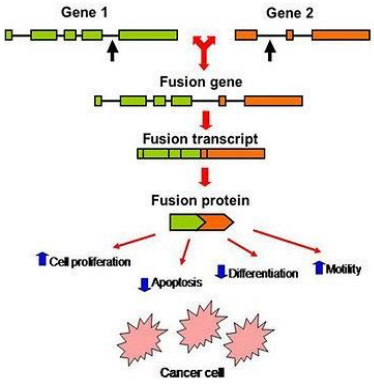
EWS FLI1 t(11;22)(q24;q12)

EWS FLI2 t(21;22)(q22;q12)

B



Pozit. EWS/FLI1 - FISH



A -(radiologic) this is an example of Ewing sarcoma in the diaphysis of the humerus , note that this tumor has infiltrated the soft tissue and elevated the periosteum causing Codman triangle , which helps you to understand that Codman triangle is not specific characteristic for osteosarcoma only.

B -this is a translocation t (11,22), there are 2 of them actually (EWS FLI1), (EWS FLI2). this is a picture of fish analysis, so this is probably the most sensitive test for Ewing sarcoma using florescent in situ hybridization (FISH).

C - this is the old method by classic cytogenetic analysis, where the translocation occurs between the chromosome 11 which is a bigger chromosome than chromosome 22. and this method shows the fusion protein that is produced from this translocation.

D -(histologic) : when patients comes with a pain or pathologic fractures , biopsy is taken, and under the microscope , you will see a lot of small blue tumor cells destroying the bone .

GOOD LUCK