8

MSS

Musculoskeletal System

Pathology

Doctor 2018 | Medicine | JU

Done by

Rama Abbady

Contributed In The Scientific Correction

Abdulrhman Al-Jashaam

Contributed In The Grammatical Correction

Shaimaa Abu saileek

Doctor

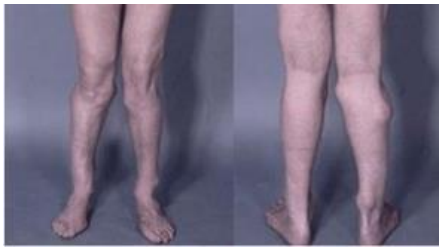
Mousa Al-Abbadi

➢ Cartilage-Forming Tumors

- These tumors are characterized by the formation of hyaline cartilage. Benign cartilaginous tumors are much more common than malignant ones.

❖ Osteochondroma: (contains both bone and cartilage)

- Osteochondroma is known clinically as exostosis. It is a benign cartilage tumor that is attached to the underlying skeleton by a bony stalk.
- Under the microscope, it looks like normal bone and normal cartilage and sometimes normal bone marrow.
- About 85% are solitary. The remainder are seen as part of the multiple hereditary exostoses syndrome (MHE).
- Hereditary exostoses are associated with germline mutations in either the EXT1 or the EXT2 gene.
- Osteochondroma is presented as slow-growing masses, which can be painful if they impinge on a nerve or if the bony stalk is fractured.



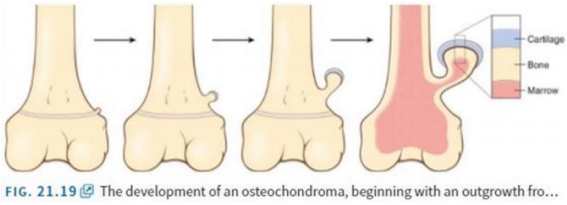
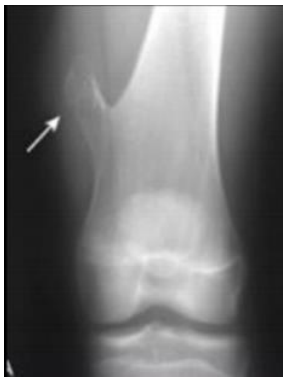
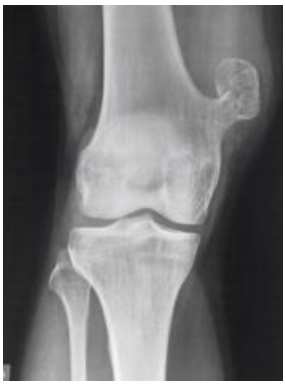
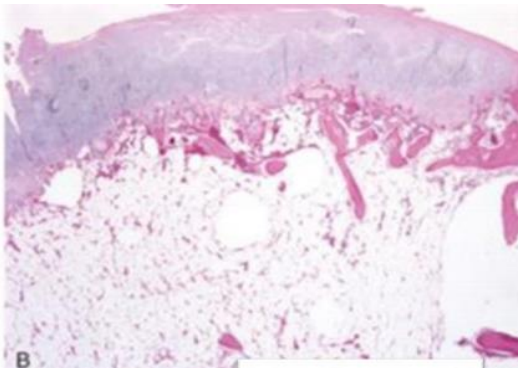


FIG. 21.19 The development of an osteochondroma, beginning with an outgrowth fro…





Radiographs of an osteochondroma arising from the distal femur

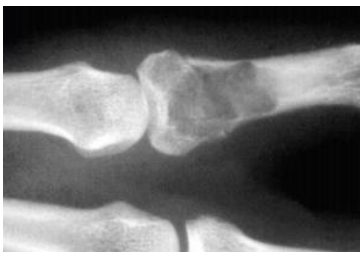


The cartilage has the histologic appearance of disorganized growth-plate like cartilage

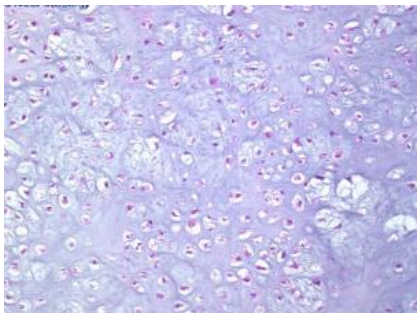
- It is rarely transformed to chondrosarcoma (3-5%), more common in MHE.

❖ Chondroma (Enchodroma):

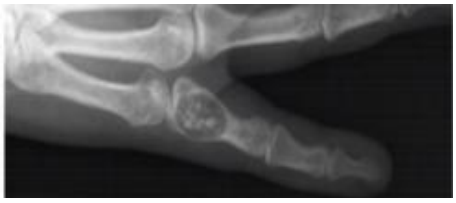
- Chondroma are benign tumors of hyaline cartilage that usually occur in bones with endochondral origin.
- They arise within the medullary cavity (medullary enchondroma) or on the cortical surface (cortical chondroma).



- 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 hand and feet.
- Histologically, it appears as normal cartilage.
- Ollier disease and Maffuci syndrome are disorder characterized by multiple enchondromas.
- Maffuci syndrome is also associated with other rare tumors (multiple enchondromas + skin hemangiomatosis).

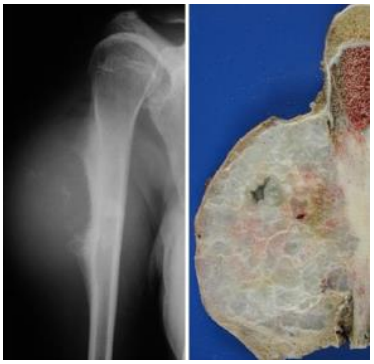


- Chondrocytes of enchondromas have been identified to have genetic mutations in IDH1 & IDH2 genes, coding for the enzyme isocitrate dehydrogenase.

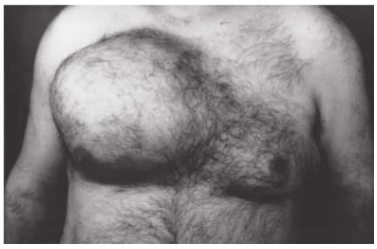


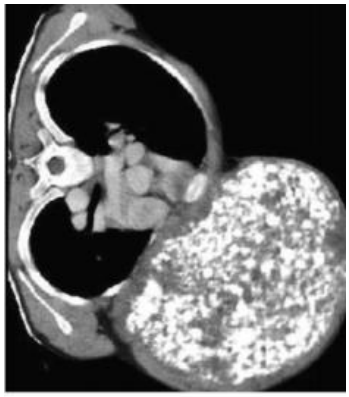
❖ Chondrosarcoma:

- Chondrosarcomas are malignant tumors that produce cartilage.
- Chondrosarcoma is about half as common as osteosarcoma. It is the third most common bone tumor.
- Individuals with chondrosarcoma are usually in their 40s or older (40-50 years). The tumors affect men twice as frequently as women (2:1).
- Chondrosarcomas commonly arise in the axial skeleton, especially in the pelvis, shoulder and the ribs. Usually present as painful, progressively enlarging masses.

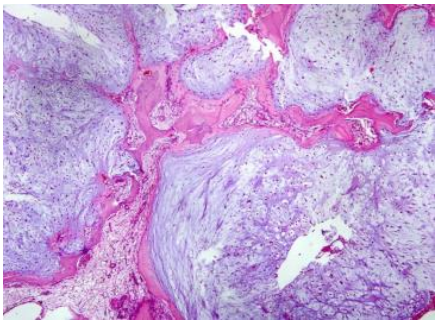


- Under X-ray it appears as Codman triangle as in osteosarcoma (so it isn't pathgnomic)
- Chondrosarcoma does not have a signature genetic mutation. Multiple genes can be involved including EXT, IDH1, IDH2, COL2A1 and CDKN2A.
- Prognosis of chondrosarcoma depends on the grade:
  - ∝ Grade 1: excellent prognosis, Grade 3: bad prognosis (Grade 1 chondrosarcomas rarely metastasize whereas 70% of grade 3 tumors spread especially to the lungs).
  - ∝ Grade 3's appearance is the worst histologically.
- Treatment: surgical treatment +/- chemotherapy & radiotherapy (to prevent metastasis).
- Chondrosarcomas features: radiography: soap bubble appearance.



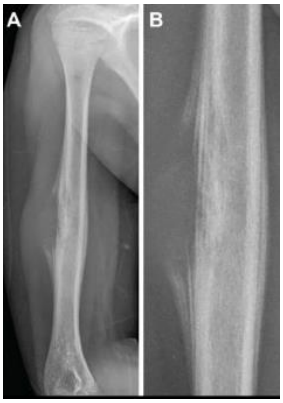


- Histologically: abnormal malignant cartilage (it may be grade 1 or 2 but not grade 3 yet).

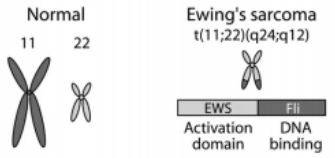


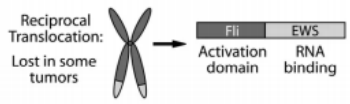
➢ Tumors of Unknown Origin

❖ Ewing Sarcoma

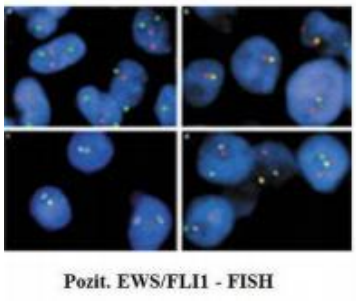


- Dr. James Ewing (1866-1943) described this tumor in 1920.
- Ewing sarcoma is a malignant tumor composed of primitive round cells. Primitive neuroectodermal tumor (PNET).
- Also called Small blue cell tumor. (Note that small blue cell tumor isn't a specific diagnosis for Ewing Sarcoma, it is also present 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.

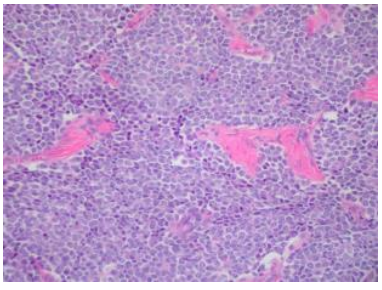




- Has a specific signature genetic translocation.
- The most common translocation, which is present in about 90% of Ewing sarcoma cases, is t(11;22)(q24;q12). This mutation generates an aberrant transcription factor through fusion of the EWSR1 gene with the FLI1 gene.


Pozit. EWS/FLI1 - FISH

- Ewing sarcomas are treated with neoadjuvant chemotherapy followed by surgical excision with or without radiation. With chemotherapy, 5-year survival of 75% and long-term cure in 50% of patients is possible (now reaches 75%).



- Ewing sarcoma Histologically: round cells with small amounts of clear cytoplasm (large nucleus, small cytoplasm).

❖ Giant Cell Tumor

- Giant cell tumor is so named because of the presence of multinucleated osteoclast-type giant cells histologically.
- It is a locally aggressive neoplasm that affects adults.
- Giant cell tumors arise in the epiphyses of long bones, most commonly the distal femur and proximal tibia.
- The neoplastic cells express high levels of RANKL (which promotes the proliferation and differentiation of normal osteoclast precursors into osteoclasts).
- Rare malignant behavior (mostly benign, 90% don't metastasize but 5-10% can metastasize to the lung).
- Characteristic of the tumor: osteoclast-like giant cells.
- Treatment: curetting.
- NOTE: the presence of giant cells can be present in any tumor of bone as a reaction, but once the whole tumor is composed of giant cells and small cells with similar nuclei inside it is a characteristic of giant cell tumor of bone.

Giant cell tumors often destroy the overlying cortex, producing a bulging soft tissue mass delineated by a thin shell of reactive bone (Fig. 21.25). Grossly, they are red-brown masses that frequently undergo cystic degeneration. Microscopically, the tumor conspicuously lacks bone or cartilage, consisting of numerous osteoclast-type giant cells with 100 or more nuclei with uniform, oval mononuclear tumor cells in between (Fig. 21.26).

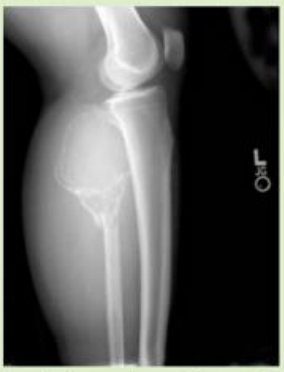


FIG. 21.25 Radiographically, giant cell tumor of the proximal fibula is predomi...

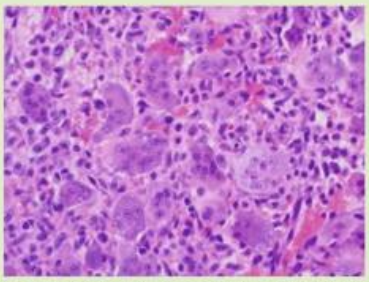
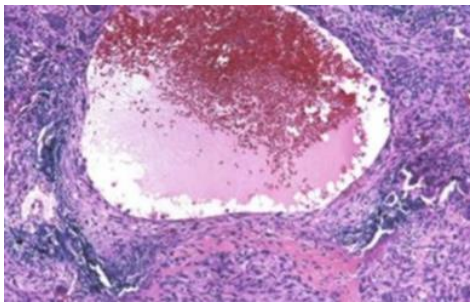
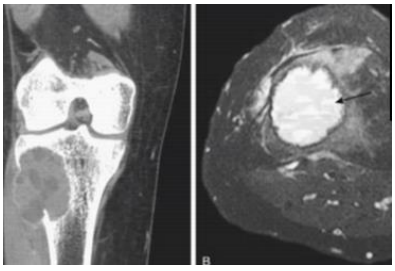


FIG. 21.26 Giant cell tumor illustrating an abundance of multinucleated giant c...

❖ Aneurysmal Bone Cyst

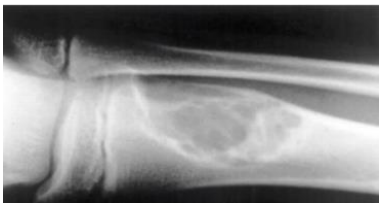


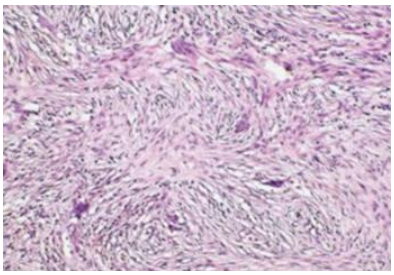
- Aneurysmal bone cyst (ABC) is a benign tumor characterized by blood-filled cystic spaces.
- Some argue that ABC is not a true neoplasm (probably caused by a hidden trauma).
- It most frequently develops in the metaphysis of long bones.
- Affects adults.
- Pain and swelling are common.
- *Aneurysm: Abnormal blood vessel dilation



➢ Lesions Simulating Primary Neoplasms

❖ Nonossifying Fibroma





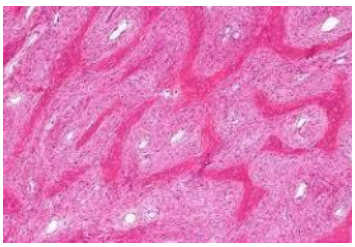
- Benign lesion, likely reactive.
- Not a true neoplasm.
- Other names: fibrous cortical defect (FCD) & metaphyseal fibrous defect (MFD).
- The vast majority arises in the metaphysis of the distal femur and proximal tibia (long bones).
- Histologically: bland fibroblastic proliferation.
- May resolve spontaneously.

❖ Fibrous Dysplasia (FD)

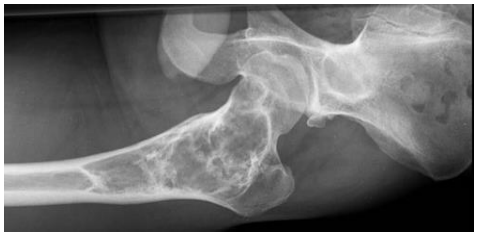
- Fibrous dysplasia is not a real tumor; it is a developmental abnormality of bone genesis due to mutations in GNAS1 gene; a specific signature genetic mutation.
- This mutation promotes cellular proliferation by increasing cellular levels of cAMP (cAMP mediated osteoblast differentiation).
- Note that dysplasia in this context is not “premalignant”.
- The lesions arise during skeletal development and appear in several distinctive but sometimes overlapping clinical patterns (different forms):

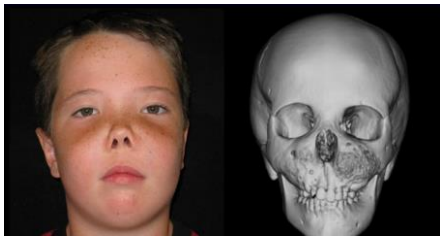
a. Monostotic: involvement of a single bone
b. Polyostotic: involvement of multiple bones
c. Mazabraud syndrome: fibrous dysplasia and soft tissue myxoma
d. McCune-Albright syndrome: polyostotic fibrous dysplasia, café-au-lait skin pigmentations (brownish pigmentation), and endocrine abnormalities, especially precocious puberty (early).

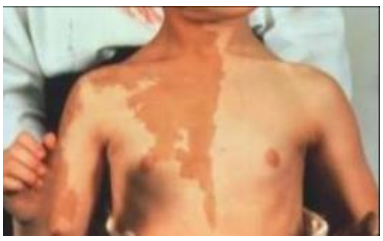
- McCune-Albright syndrome:



✓ Abnormal bone that’s somehow similar to Paget disease.
✓ We can differentiate between McCune-Albright syndrome and Paget histologically. McCune-Albright syndrome has a Chinese letters appearance while in Paget disease the bone appears in a mosaic pattern (pathgnomic).
✓ The following pictures represents features of McCune-Albright syndrome:

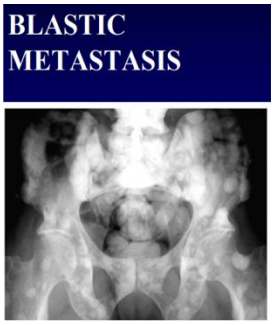


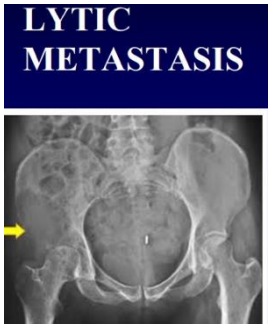




➢ Metastatic Tumors

- Metastatic tumors greatly outnumber primary bone cancers (much more common).
- Any cancer can spread to bone, but in adults more than 75% of skeletal metastases originate from cancers of the prostate, breast, kidney, lung ,thyroid and liver (bonophilic carcinomas).
- In children, metastasis to bone originate from neuroblastoma, Wilms tumor, and rhabdomyosarcoma.
- Skeletal metastasis typically involves the axial skeleton, especially the vertebral column due to hematogenous spread.
- The radiographic appearance of metastasis may be purely lytic (bone destroying), purely blastic (bone forming), or mixed. These lesions appear as a result of secretion of certain mediators.
- Lytic metastasis is the most common.





Summary

Bone Tumors and Tumorlike Lesions

Primary bone tumors are classified according to the cell of origin or the matrix that they produce. The remainder is grouped according to clinicopathologic features. Most primary bone tumors are benign. Metastases, especially from lung, prostate, kidneys, and breast, are far more common than primary bone neoplasms.

Major categories of primary bone tumors include

- **Bone forming:** Osteoblastoma and osteoid osteoma consist of benign osteoblasts that synthesize osteoid. Osteosarcoma is an aggressive tumor of malignant osteoblasts, predominantly occurring in adolescents.
- **Cartilage forming:** Osteochondroma is an exostosis with a cartilage cap. Sporadic and syndromic forms arise from mutations in the *EXT* genes. Chondromas are benign tumors producing hyaline cartilage, usually arising in the digits. Chondrosarcomas are malignant tumors of chondroid cells that involve the axial skeleton in adults.
- **Ewing sarcomas** are aggressive, malignant, small round cell tumors most often associated with t(11;22).
- **Fibrous dysplasia** is an example of a disorder caused by gain-of-function mutations that occur during development.

➢ Arthritis

❖ Basic Knowledge About Joints

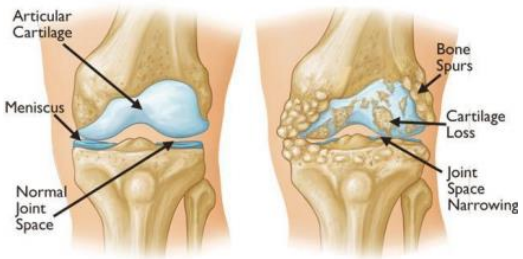
- Joints provide motion & stability to our skeleton.
- They are classified as solid (non-synovial) and cavitated (synovial).
- The solid joints, also known as synarthroses, provide structural integrity and allow only minimal movement (mostly immobile).
- Synovial joints, in contrast, have a joint space that allows for a wide range of motion. Synovial membranes enclose these joints.
- The membranes are lined by type A synoviocytes that are specialized macrophages with phagocytic activity and type B synoviocytes that are similar to fibroblasts.
- The synovial lining lacks a basement membrane (Laminin + Collagen type 4), which allows efficient exchange.
- Synovial joints are covered by hyaline cartilage.
- Hyaline cartilage is a unique connective tissue ideally suited to serve as an elastic shock absorber and wear-resistant surface. It lacks a blood supply, lymphatic drainage, and innervation (that's why joint tumors are rare).
- Hyaline cartilage is composed of water (70%), type II collagen (10%), proteoglycans (8%), and chondrocytes.

❖ Osteoarthritis

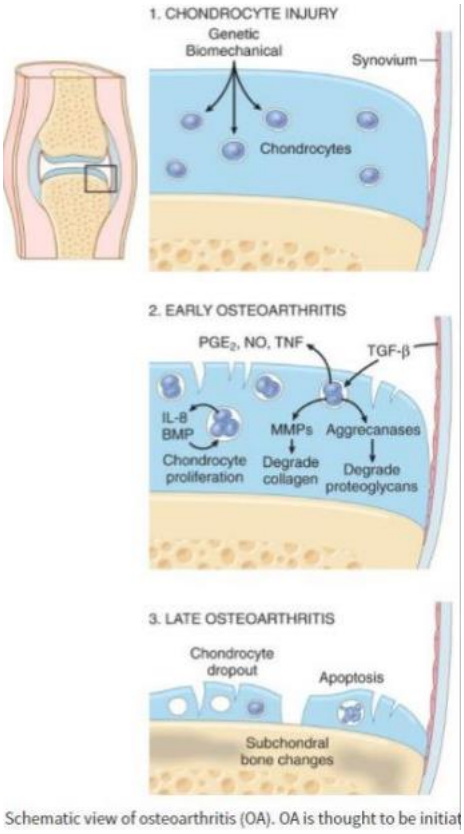
- Osteoarthritis (OA), also called degenerative joint disease (DJD), is characterized by degeneration of articular cartilage that results in structural and functional failure of synovial joints.
- Although the term osteoarthritis implies an inflammatory disease, it is not a true inflammation (not true -ITIS).
- Osteoarthritis can be classified into:

a. Idiopathic or primary osteoarthritis: without apparent initiating cause, as a result of aging. In these cases, the disease is usually oligoarticular (affects few joints).
b. Secondary osteoarthritis: due to pre-existing diseases.

- It is an insidious disease; the prevalence of OA increases exponentially beyond the age of 50, and about 40% of people older than 70 are affected.
- The lesions of OA arise from degeneration of the articular cartilage and its disordered repair (continuous degeneration & disordered repair).



- Osteoarthritis begins with chondrocyte injury; degradation of articular cartilage exceeds synthesis. This injury could progress to early osteoarthritis by the secretion of repair mediators and certain cytokines.
- Early osteoarthritis is mediated by certain mediators (for repair) secreted by chondrocytes and synovial cells. These mediators include TNF, NO, PGE2 and TGF-β which induce the secretion of MMPS by chondrocytes. MMPs secreted by chondrocytes degrade the type II collagen network. These mediators also induce Aggrecanases which degrade proteoglycans.
- Continuous (injury → mediators→ repair) leads to chondrocytes' death → chondrocyte dropout (Apoptosis). Ultimately, chondrocyte loss and a severely degraded matrix mark the late stage of the disease.

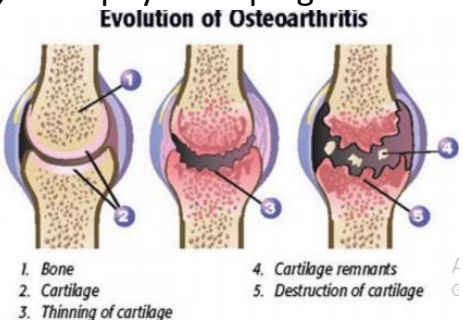


Schematic view of osteoarthritis (OA). OA is thought to be initiat

- Eburnation of the articular cartilage exposes the underlying bone. The exposed subchondral bone plate becomes the new articular surface so it is stimulated to form osteophytes and loose bodies following the eburnation.

- Osteoarthritis clinically:

✓ Characteristic symptoms include joint pain that worsens with use (unlike rheumatoid arthritis), morning stiffness, crepitus, and limitation of range of movement, radicular pain (due to pressure on nerves) , osteophytes impingement on vertebrae, muscle spasm & atrophy.



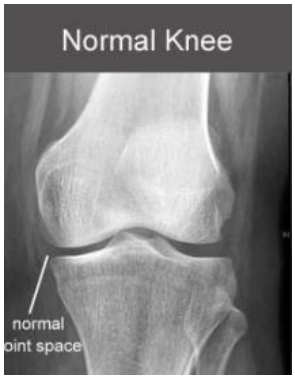
✓ There are no magic preventive strategies of OA; no satisfactory means of preventing primary OA, and no effective methods of halting its progression. Best strategy is to lose weight.

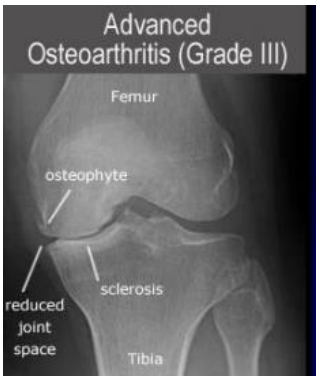
✓ Therapy includes management of pain (paracetamol first then if pain persists give steroids), NSAIDs to reduce inflammation, intra-articular corticosteroids, activity modification, and, for severe cases (Grade 5), arthroplasty (joint replacement).

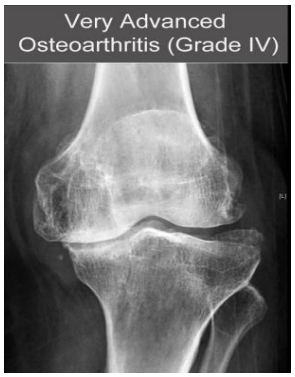
✓ Osteoarthritis has large health cost on countries.

✓ Some people are more likely to develop OA than others (genetic predisposition).

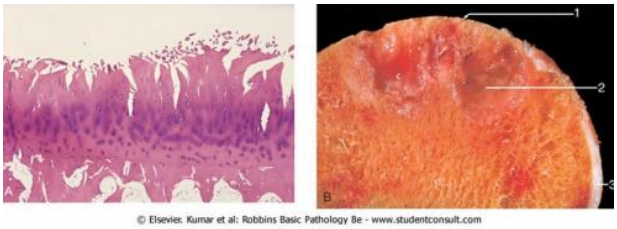
- Grading of osteoarthritis: the level of disease severity is detected radiographically.
  - ✓ Mild forms of OA: small narrowing of the articular cartilage.
  - ✓ Severe forms of OA: severe narrowing of the articular cartilage → eburnation which leads to the formation of osteophytes by the subchondral bone and some of them separate forming loose bodies in the joint.







- Histologic appearance of osteoarthritis:
  - ✓ Notice the eburnated surface exposing the subchondral bone and the subchondral cyst formation.



- Osteoarthritis. **A,** Histologic demonstration of the characteristic fibrillation of the articular cartilage. **B,** Severe osteoarthritis with 1, Eburnated articular surface exposing subchondral bone. 2, Subchondral cyst. 3, Residual articular cartilage

❖ Rheumatoid Arthritis

- Rheumatoid arthritis (RA) is a **chronic** inflammatory disorder of **autoimmune** origin that principally attacks the joints, producing a non-suppurative proliferative (no pus) and inflammatory **synovitis**.
- Main target of rheumatoid arthritis is the synovium (primary); involvement of the articular cartilage is secondary (unlike OA).
- RA often leads to the destruction of the articular cartilage and, in some cases ankylosis (adhesion) of the joints.
- Rheumatoid arthritis is a systemic disease; extra-articular lesions may occur in the skin, heart, blood vessels, and lungs (any organ can be involved). Death caused by RA is due to organ failure.
- The prevalence in the United States is approximately 1%, and it is three times more common in women than in men. The peak incidence is in the 4th through 5th decades of life.
- Genetic predisposition & environmental factors play a role in the development, progression and chronocity of the disease.