MSS Pathology 2021
Lecture 1

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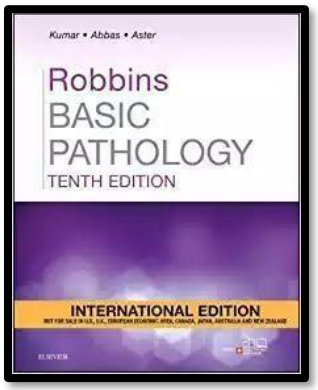
MY DUTIES

- **10 recorded lectures (1st 5 for midterm)**
- **2 meetings (Microsoft teams) for inquiries (1 before midterm and 1 before final)…u must attend**
- **Simplify**



YOUR DUTIES

- **Understand the concepts**
- **Help U all Understand…understand… understand X 10…only then memorize**
- **Answer questions (exception) & inquiries**
- **Respect the whole process…I paid my dues…it is your future**
- **No inquiries about the nature of the exam…I don't answer questions of the exam…don't even try**

PLEASE DON'T ASK THESE QUESTIONS AT ALL

- **How many questions on my material?**
- **What should we concentrate on?**
- **Are the slides enough?**
- **Should we memorize this or that?**
- **Is this or that required?**

[YOU SHOULD NOT ONLY STUDY FOR THE EXAM]

[YOU ARE NOT STUDYING FOR ME EITHER]

[YOU ARE LEARNING SO THAT YOU WILL BE A GOOD CARING & THOROUGH PHYSICIAN WHO WILL APPLY THE STNADRAD OF CARE]

OUTLINE & OBJECTIVES

- **Remember the basic structure & function of bone**
- **Congenital diseases of bone and cartilage**
- **Metabolic disorders of bone**
- **Paget disease of bone**
- **Fractures**
- **Osteonecrosis**
- **Osteomyelitis**

CONTINUE…OUTLINE AND OBJECTIVES

- **Arthritis:**
  - **Osteoarthritis; RA; Juvenile Idiop A**
  - **Seronegative Spondyloarthropathies**
  - **Infectious arthritis; Lyme arthritis**
  - **Crystal-induced arthritis**
- **Joint tumors & tumorlike conditions**
- **Soft tissue tumors:**
  - **Adipose tissue; fibrous tissue; skeletal muscle**
  - **Smooth muscle; tumors**

E learning (will be sent to you too)

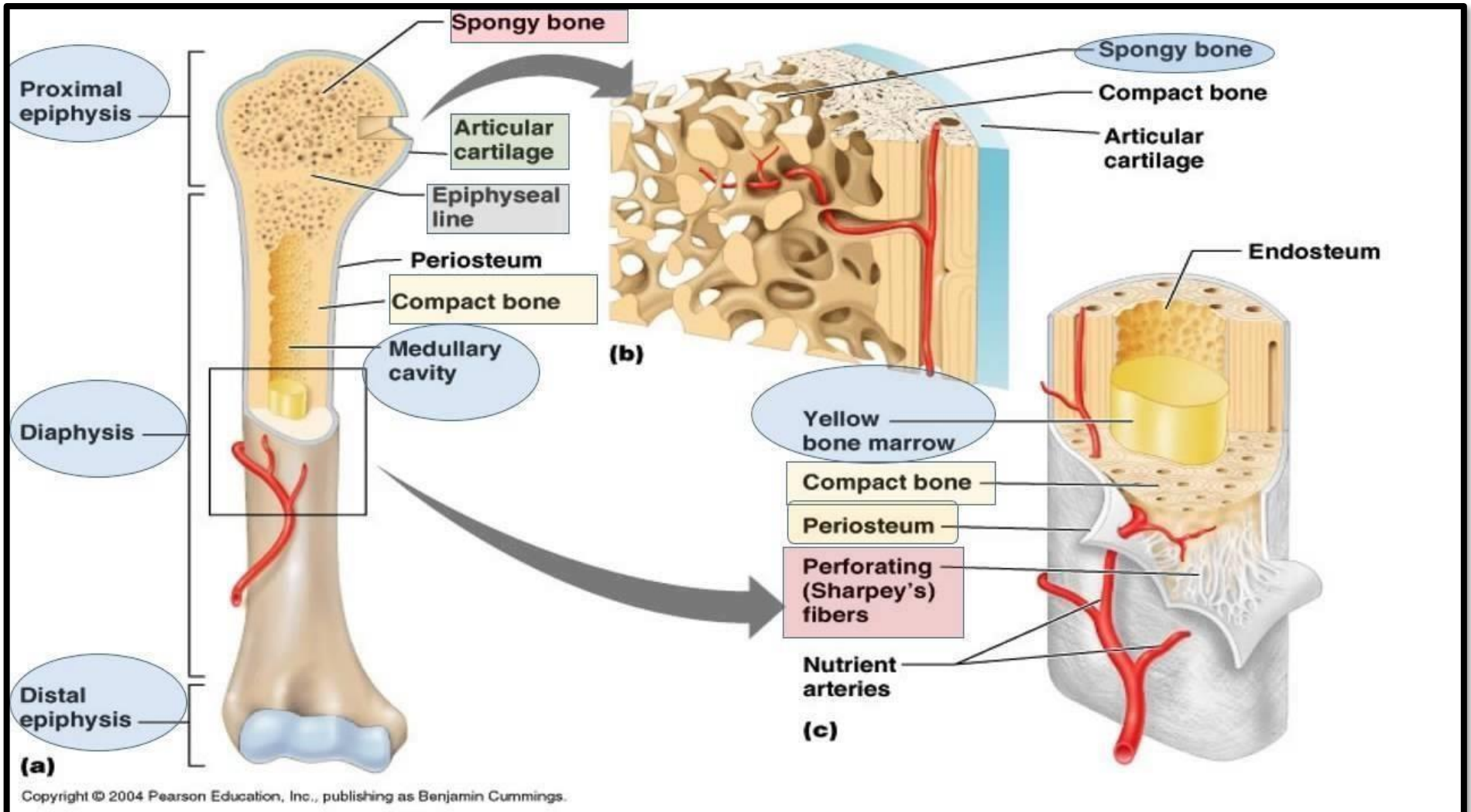
Bone development	**https://www.youtube.com/watch?v=xXgZap0AvL0&ab_channel=INTELECOM**
Osteoporosis	https://youtu.be/eT_G9NHIyV0 https://youtu.be/VwCkyf0lQwo
Osteoarthritis	https://youtu.be/BBqjltHNOrc https://youtu.be/pnKaBMvVUs0
Rheumatoid arthristis	https://youtu.be/Yc-9dfem3lM https://youtu.be/ld8PhyAHov8
Osteoarthristis vs rheumatoid arthritis	https://youtu.be/6lx_774GuTw
Osteomyelitis	https://youtu.be/mpUq6Ui6yew
Gout	https://youtu.be/bznoU5bke4U
Bone tumors	https://youtu.be/wezFzUX-UWY
Bone and soft tissue tumors	https://youtu.be/gPCzAdD6mIw
Soft tissue tumors	https://youtu.be/qpkPKk3HxUQ
Ossifications	https://youtu.be/Vwethc4jt7U https://youtu.be/vOKLFdP4pjE

BONE FUNCTIONS

- **Mechanical support**
- **Forces transmission**
- **Protection**
- **Mineral homeostasis**
- **Hematopoiesis**

BONE STRUCTURE

- **Matrix (osteoid 35% and minerals 65%):**
  - **Osteoid: organic type I collagen and glycosaminoglycans & other proteins**
  - **Inorganic hydroxyapetite [$Ca_{10}(PO_4)_6(OH)_2$]**
  - **Woven vs lamellar bone**
- **Cells:**
  - **Osteoblasts: forms bone**
  - **Osteoclasts: resorbs bone**
  - **Osteocytes: mature bone cells**



Structure of a Typical Long Bone

WOVEN VS LAMELLAR BONE

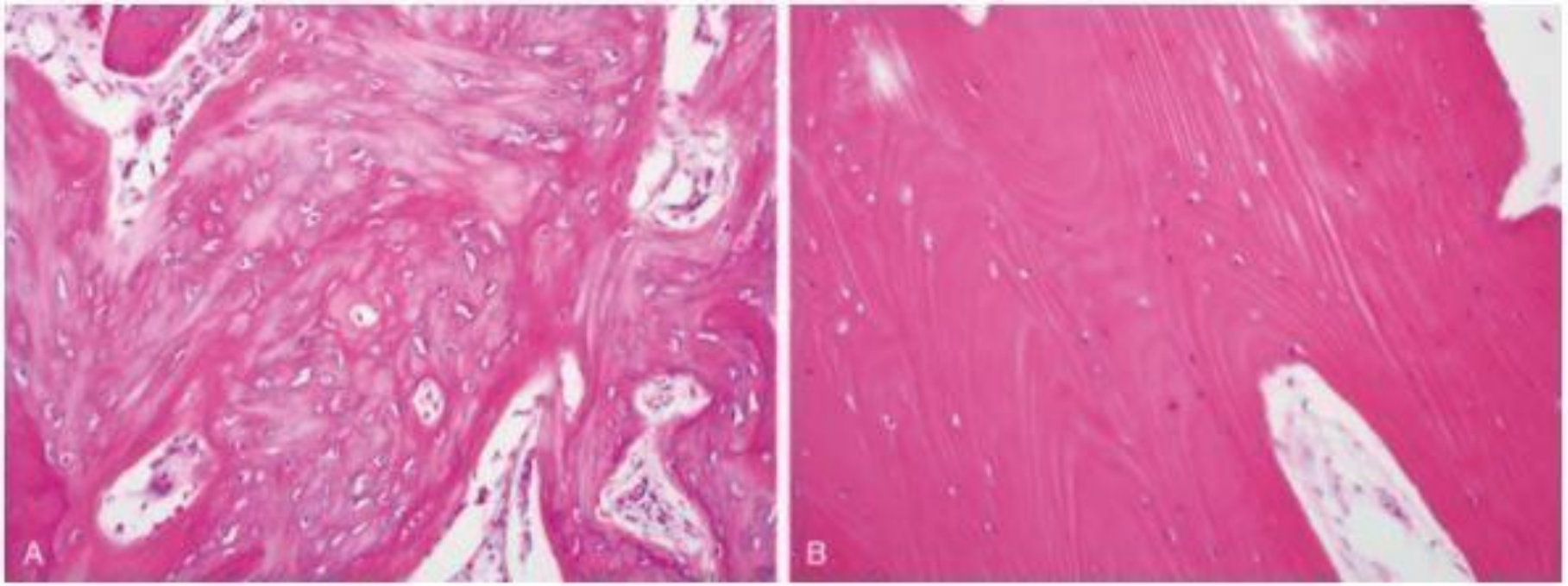


FIG. 21.1 Woven bone (A) is more cellular and disorganized than lamellar bone (B).

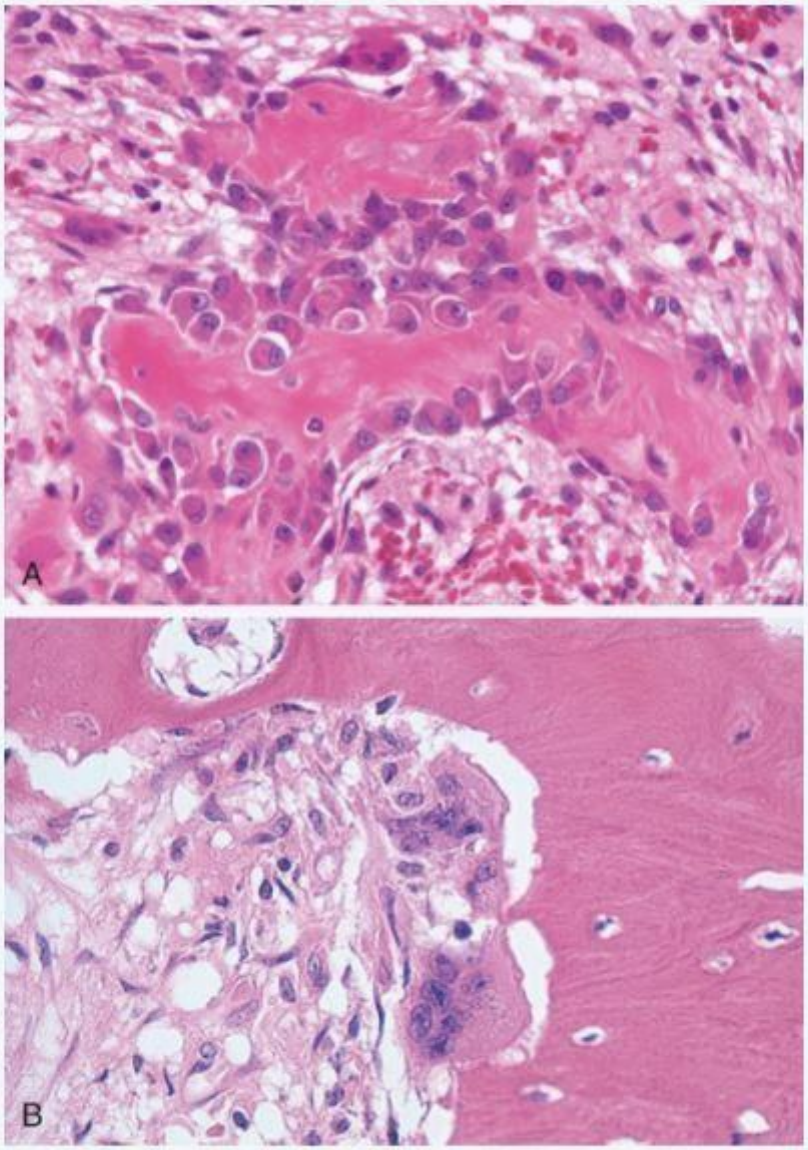
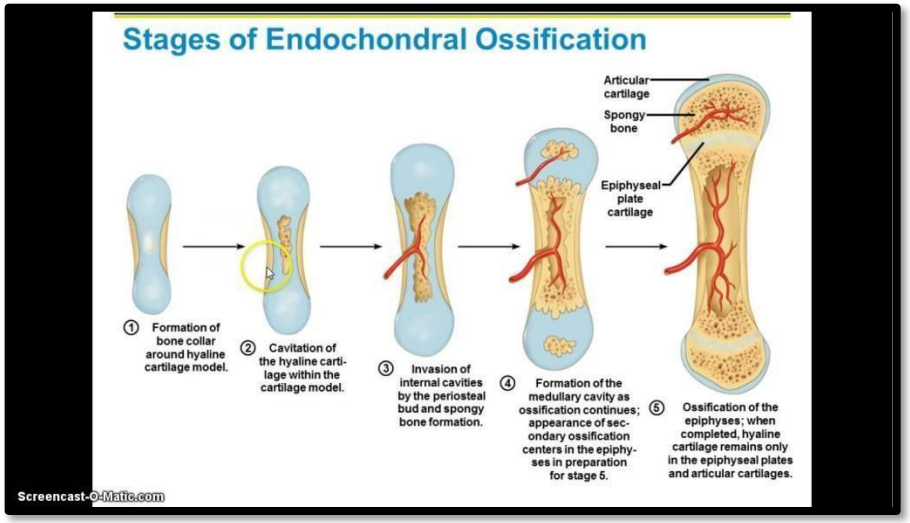


FIG. 21.2 (A) Active osteoblasts synthesizing bone matrix. The surrounding spindle c…

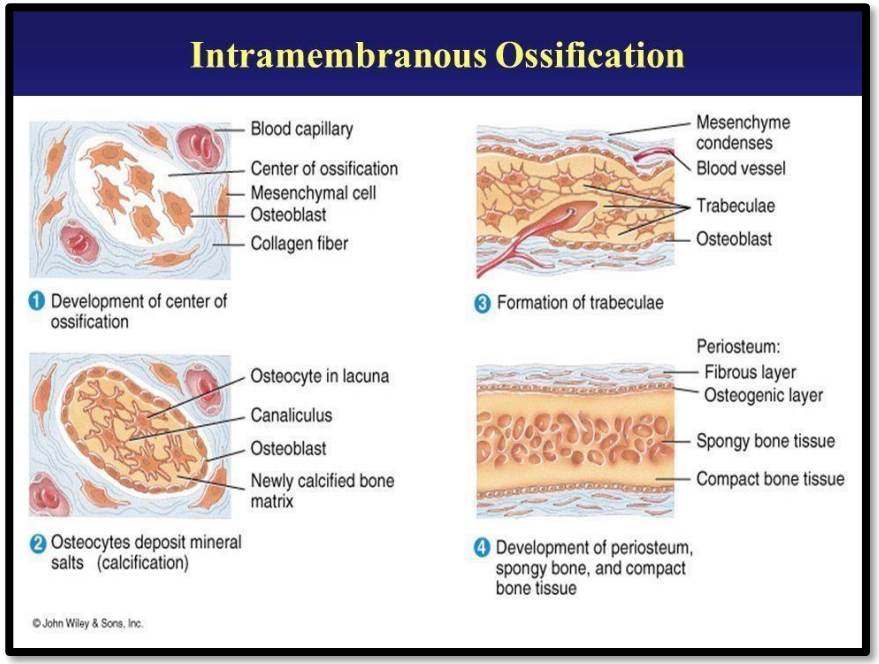
OSTEOBLASTS

DEVELOPMENT

LONG BONES



FLAT BONES



HOMEOSTASIS & REMODELING

- **Continuous and dynamic complex process even in adult mature skeleton (microscopic level)**
- **Peak bone mass is reached in early adulthood after completion of skeletal growth**
- **Resorption > bone formation on 4th decade**

+ Osteoclast differentiation	- Osteoclast differentiation
PTH **IL-1** **Steroids**	**BMPs (bone morphogenic proteins)** **Sex hormones (estrogen & test.)**

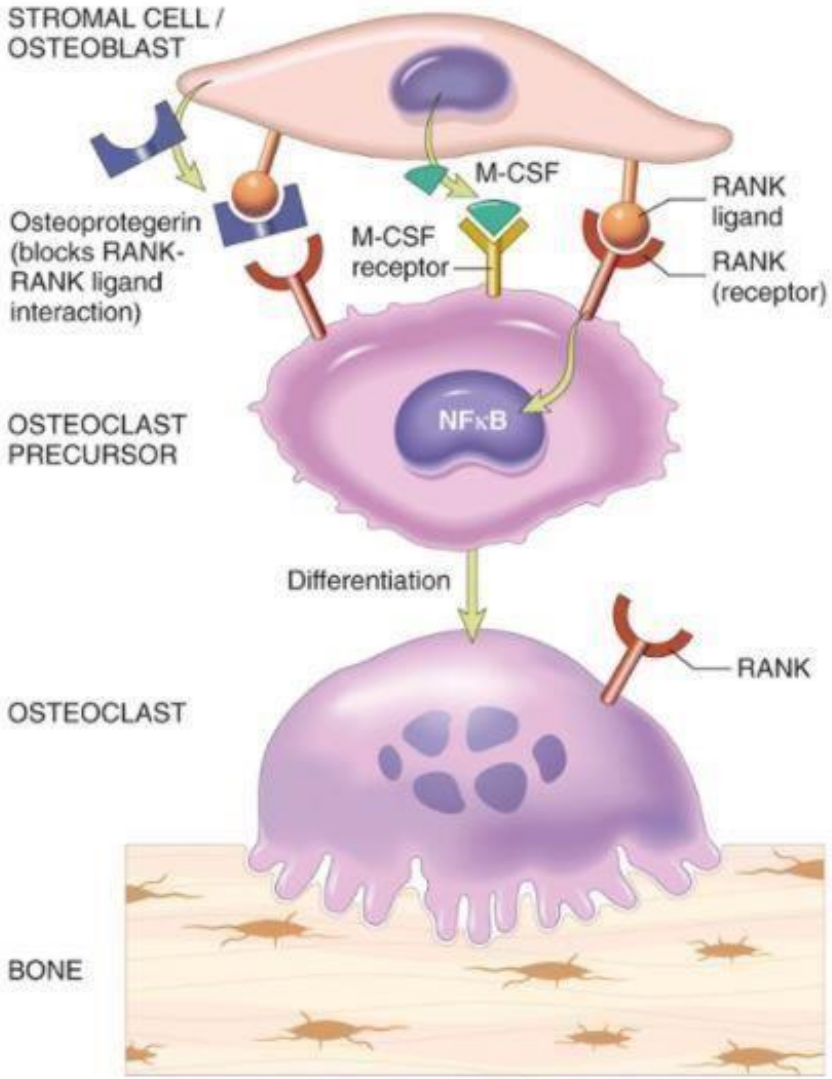


FIG. 21.4 Paracrine molecular mechanisms that regulate osteoclast formation and fun...

Lecture 2

CONGENITAL DISORDERS

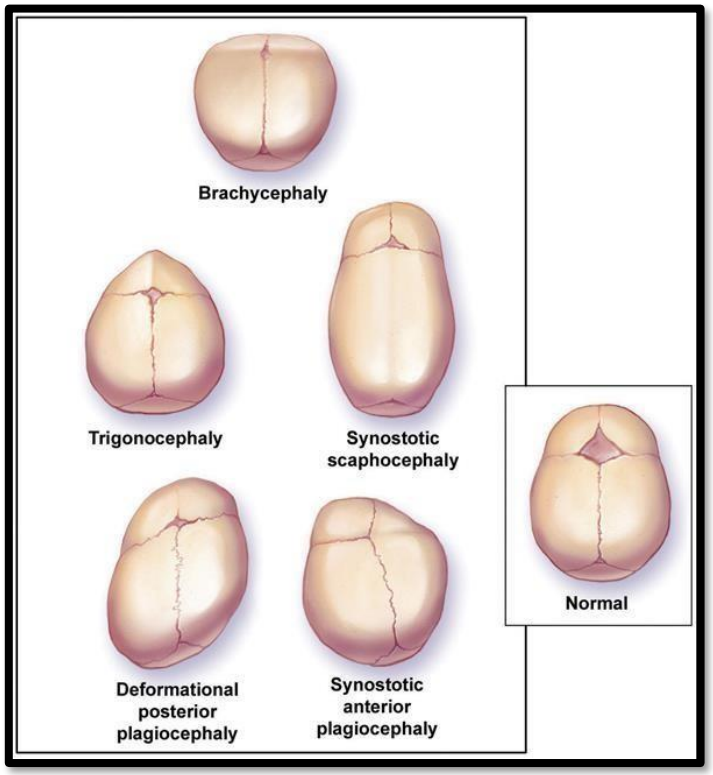
DYSOSTOSIS

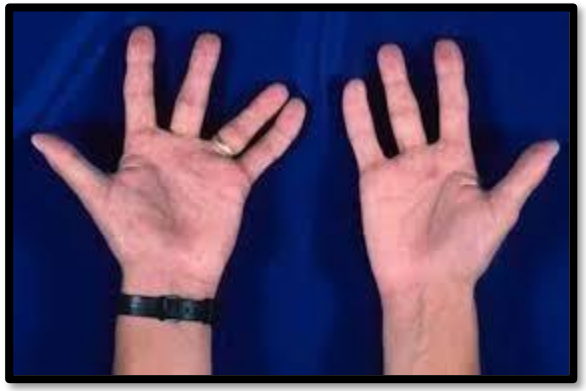
- **Abnormal condensation & migration of mesenchyme**
- **Genetic abnormalities of homeobox genes, cytokines and its receptors**
  - **Aplasia**
  - **Supernumerary digit**
  - **Syndactyly & craniosynostosis**

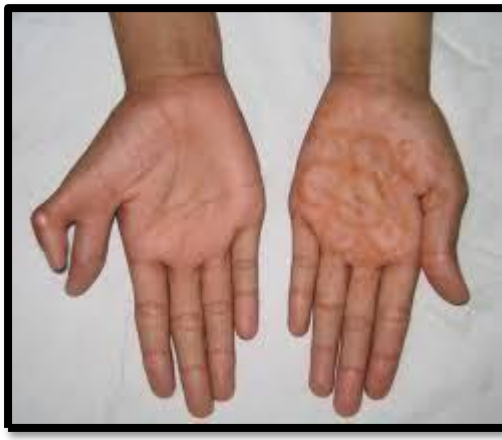
DYSPLASIA

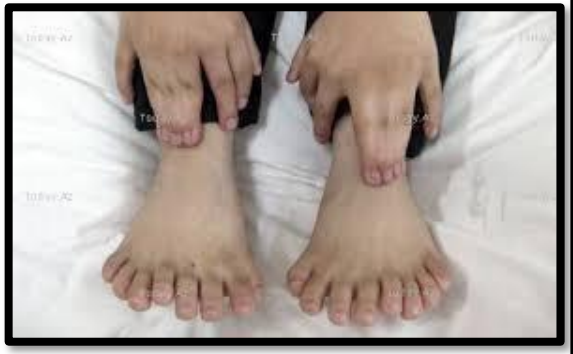
- **Disorganized bone & cartilage**
- **Gene mutations that control development and remodeling**
- **Dysplasia here: not premalignant**

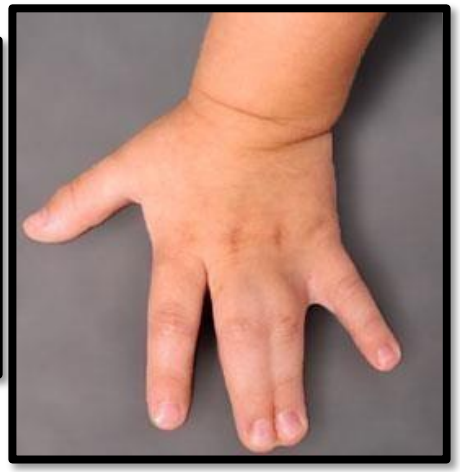
DYSOSTOSIS


Brachycephaly
Trigonocephaly
Synostotic scaphocephaly
Normal
Deformational posterior plagiocephaly
Synostotic anterior plagiocephaly



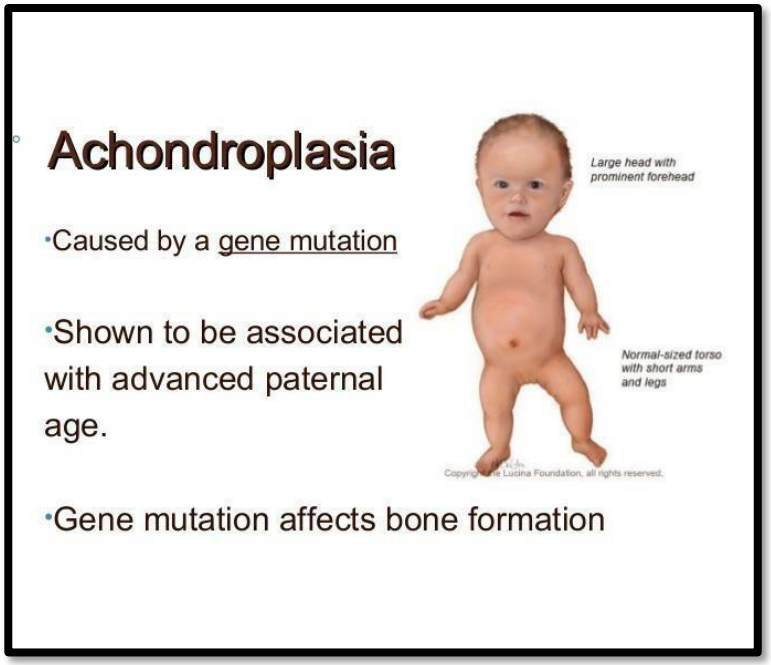






DYSPLASIAS

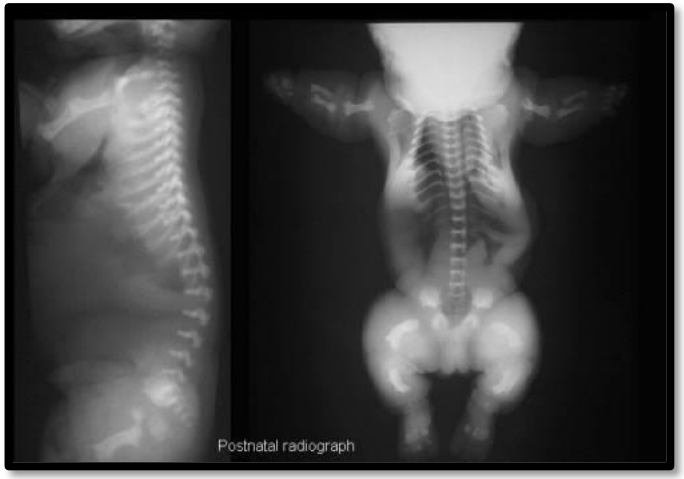
- **Achondroplasia (dwarfism): most common**
- **Mutations in FGFR3**
- **No impact on longevity, intelligence or reproductive status**

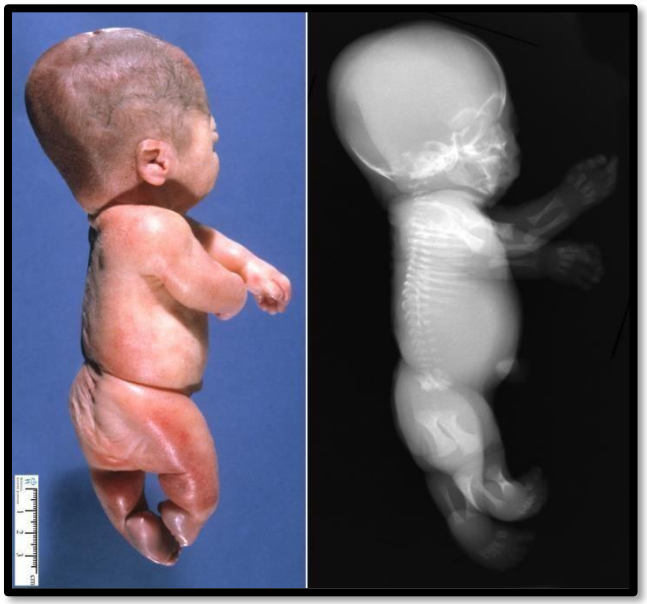


Peter Dinklage: 48-years-old, married with 2 children from USA, New Jersey
“Game of thrones”

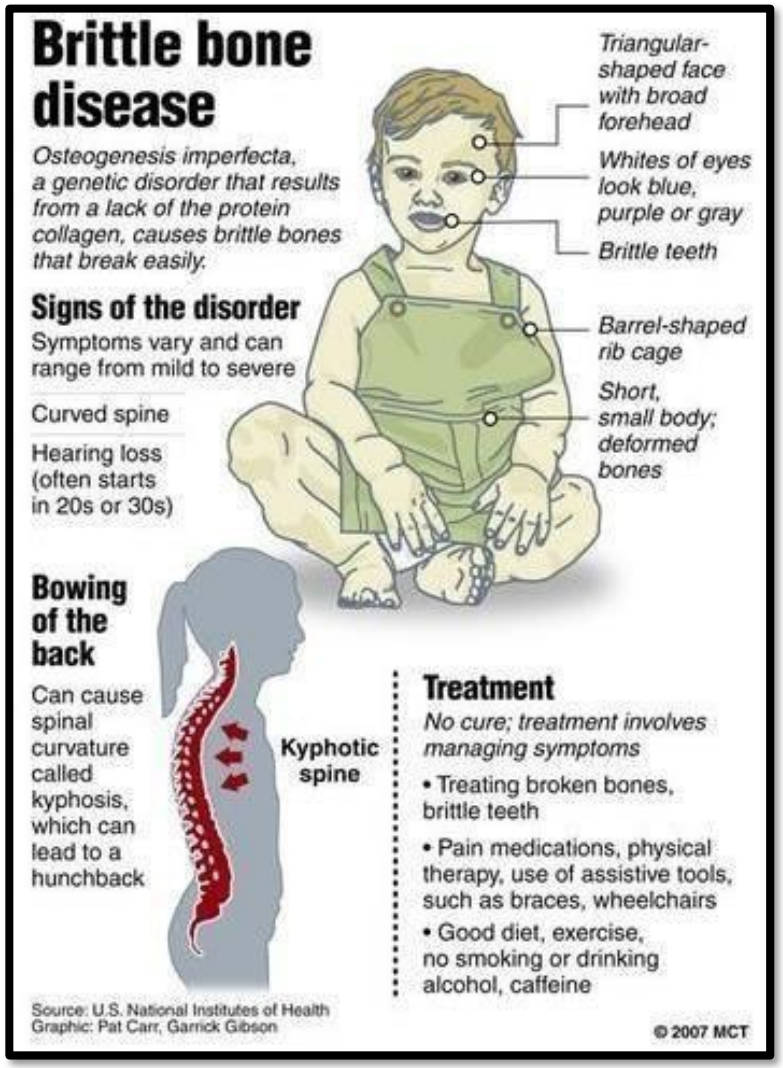
THANATOPHORIC DYSPLASIA

- **Most common lethal form of dwarfism**
- **FGFR3 mutations (different from Achondroplasia)**
- **Die at birth or shortly after (small chest leading to resp. insufficiency)**





OSTEOGENESIS IMPERFECTA

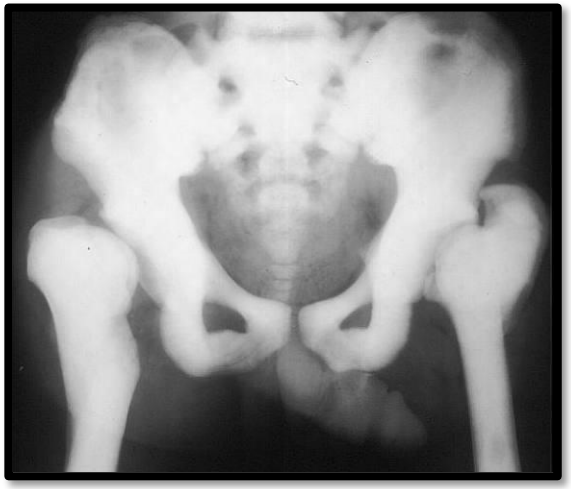


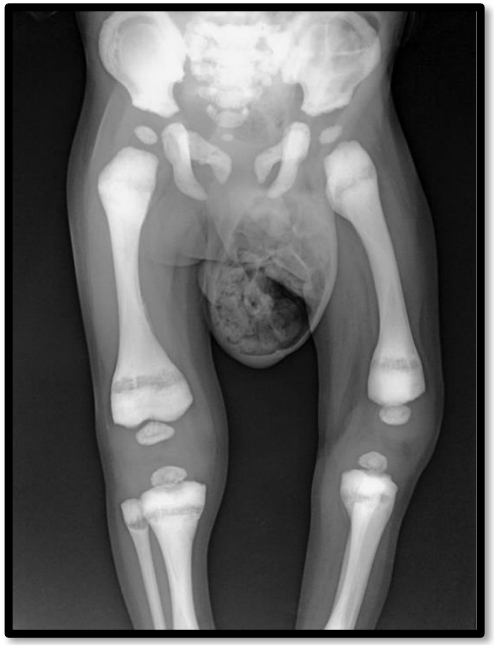
disorders of connective tissue

- **Group of disorders; AD; deficiency of type I collagen synthesis**
- **Too little bone; fragility**
- **Blue sclera; hearing loss; teeth abnormalities**
- **Type 2 (lethal) and type I (relatively normal life)**

OSTEOPETROSIS

- **Marble bone disease "stone bone" (group of disorders); rare**
- **Impaired osteoclast function: reduced bone resorption leading to diffuse sclerosis**
- **Dx: X-ray**
- **Fractures and leukopenia in severe forms**





Summary

Congenital Disorders of Bone and Cartilage

Abnormalities in a single bone or a localized group of bones are called **dysostoses** and arise from defects in the migration and condensation of mesenchyme. They manifest as absent, supernumerary, or abnormally fused bones. Global disorganizations of bone and/or cartilage are called **dysplasias.** Developmental abnormalities can be categorized by the associated genetic defect.

- FGFR3 mutations are responsible for achondroplasia and thanatophoric dysplasia, both of which manifest as dwarfism.
- Mutations in the genes for type I collagen underlie most types of osteogenesis imperfecta (brittle bone disease), characterized by defective bone formation and skeletal fragility.
- Mutations in *CA2* and *TCIRG1* result in osteopetrosis (in which bones are hard but brittle) and renal tubular acidosis.

METABOLIC DISORDERS

- **Osteopenia: decreased bone mass (1-2.5 SD below the mean).**
- **Osteoporosis: severe osteopenia; > than 2.5 SD below the mean with increase risk for fractures**
- **Generalized (much more common) or localized**

PRIMARY OSTEOPOROSIS	SECONDARY OSTEOPOROSIS
Much more common Senile (aging) & postmenopausal	Much less common Hyperthyroidism, malnutrition, steroids

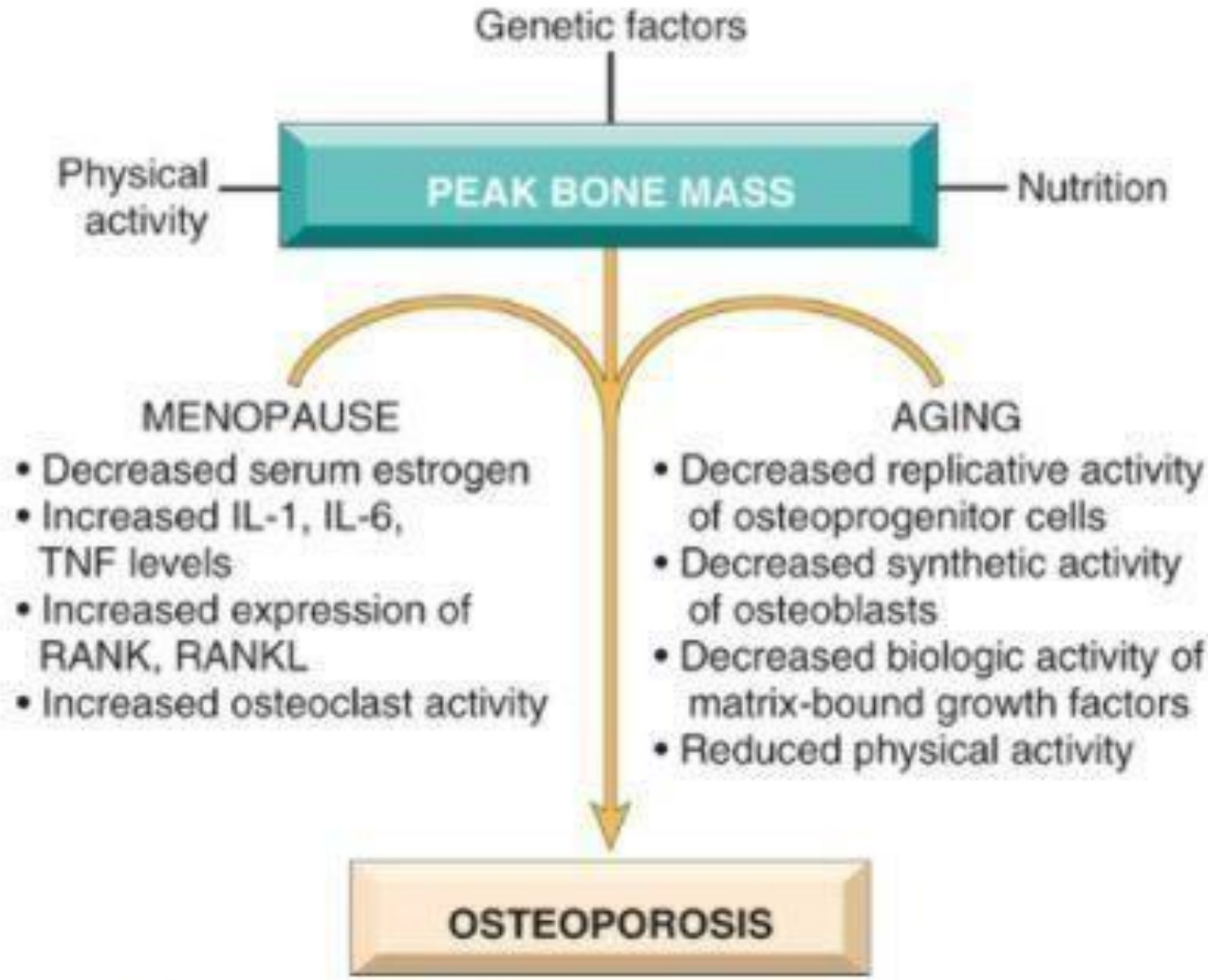


FIG. 21.5 Pathophysiology of postmenopausal and senile osteoporosis (see text).

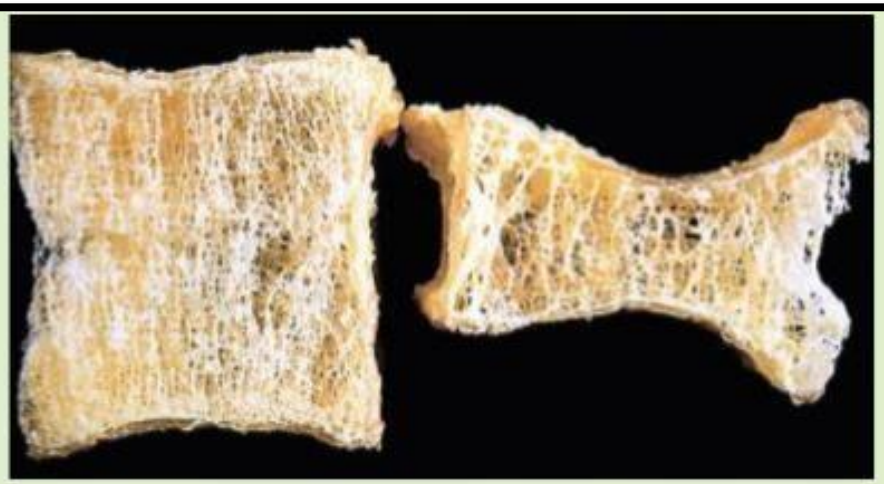


FIG. 21.6 Osteoporotic vertebral body *(right)* shortened by compression fractur..

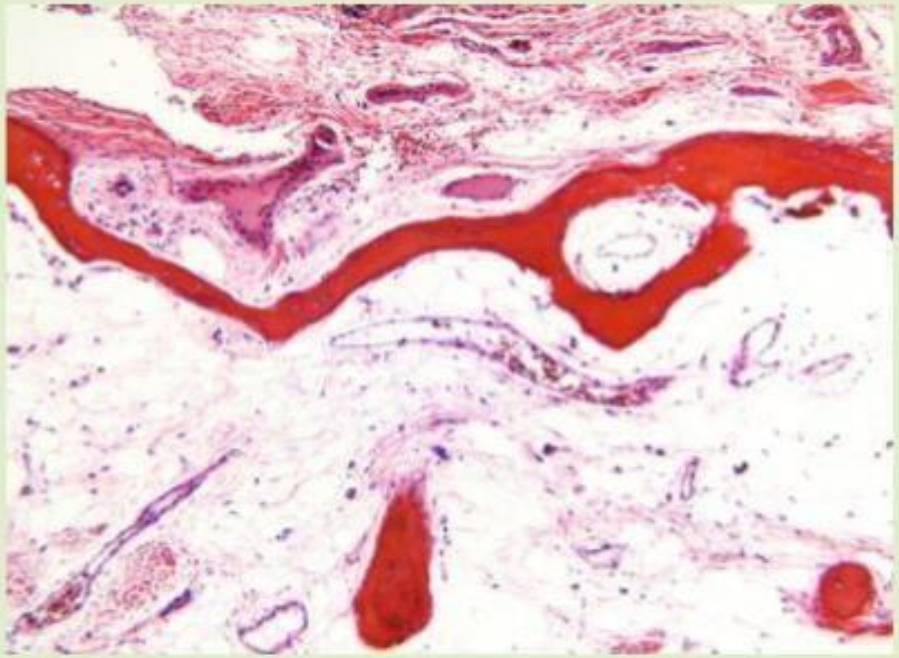
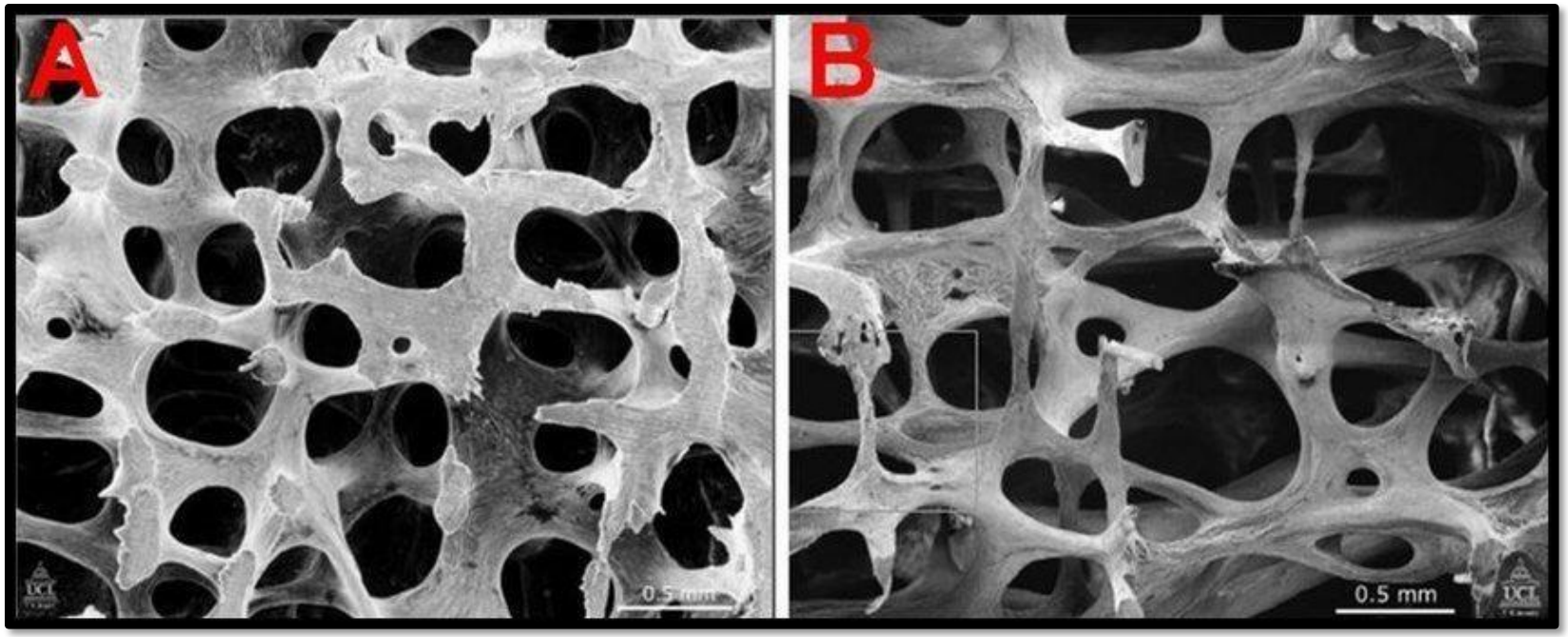
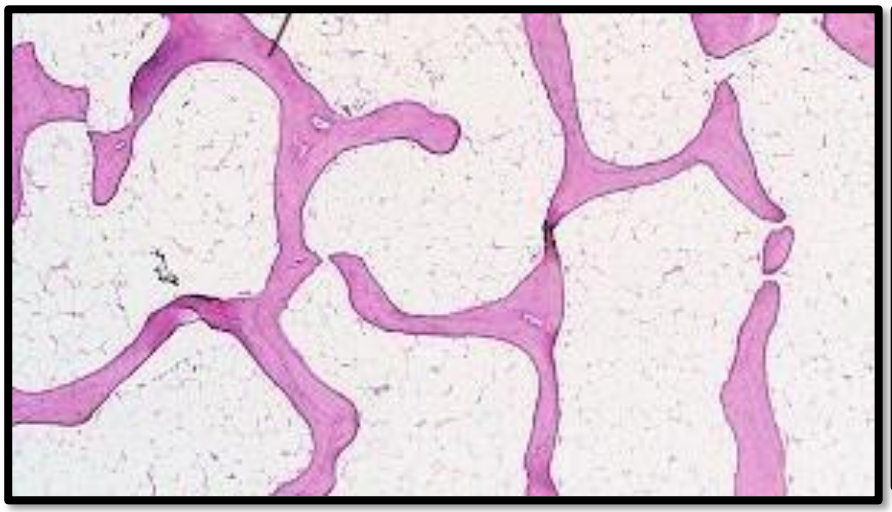


FIG. 21.7 In advanced osteoporosis, both the trabecular bone of the medulla *(b..*

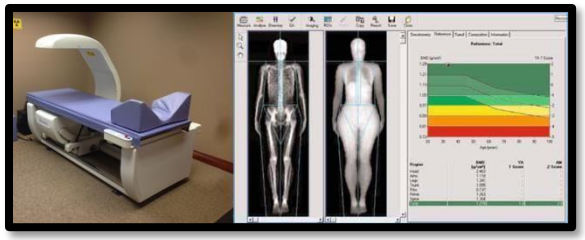
Normal bone : Osteoporosis





OSTEOPOROSIS CLINICALLY

- **Vertebral fractures**
- **Femur and pelvic fractures: immobility, PEs, pneumonia (40-50K death/yr in USA)**
- **Diagnosis: special imaging technique, bone mineral density (BMD scan): dual-energy X-ray absorptiometry (DXA or DEXA scan) or bone densitometry**

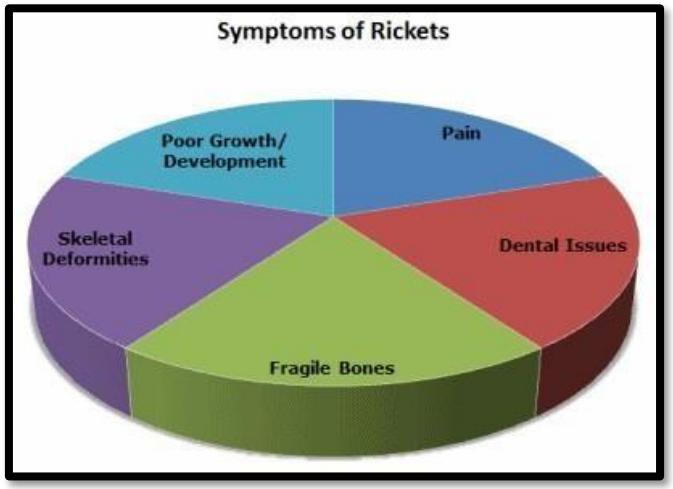


PREVENTION AND TREATMENT

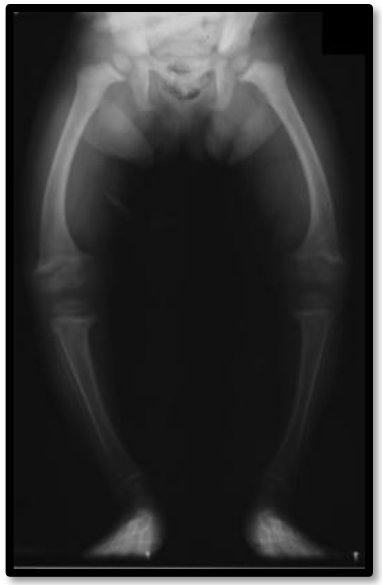
- **Exercise**
- **Calcium & vitamin D**
- **Bisphosphonates: reduce osteoclast activity and induce its apoptosis**
- **Denosumab: anti-RANKL; blocking osteoclast activation**
- **Hormones (estrogen): risking DVT and stroke**

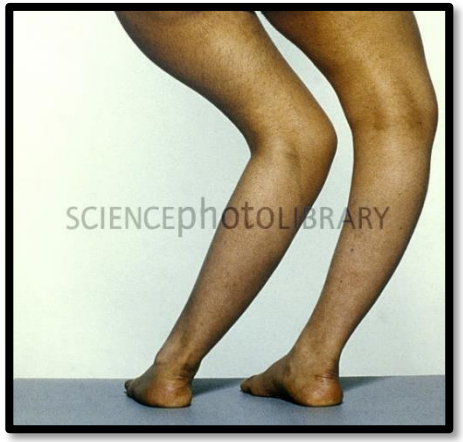
Lecture 3

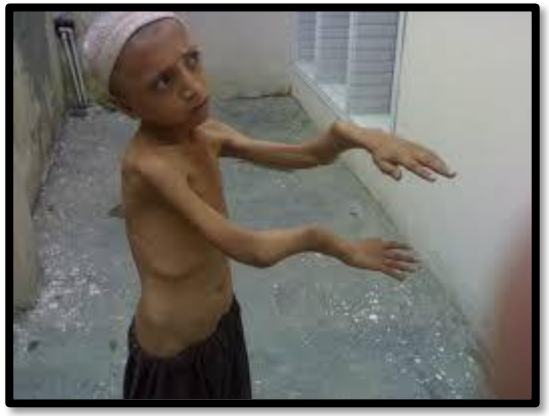
RICKETS & OSTEOMALACIA



- **Vitamin D deficiency or abnormal metabolism of vitamin D.**
- **Children: Rickets**
- **Adults: osteomalacia**
- **Decreased mineralization of bone, unmineralized matrix**
- **Increase risk of fractures**







HYPERPARATHYROIDISM (HPT)

Hyperparathyroidism classification

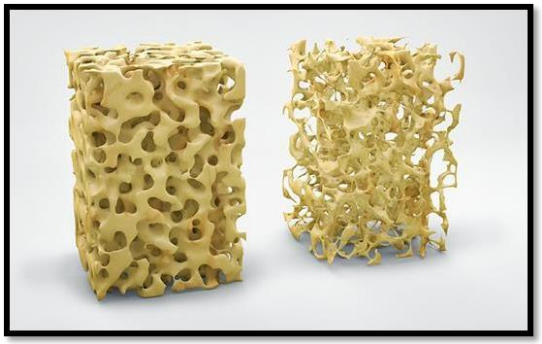
Different causes and features of hyperparathyroidism - raised parathormone (PTH).

	primary	secondary	tertiary
pathology	Hyperfunction of parathyroid cells due to hyperplasia, adenoma or carcinoma.	Physiological stimulation of parathyroid in response to hypocalcaemia.	Following long term physiological stimulation leading to hyperplasia.
associations	May be associated with multiple endocrine neoplasia.	Usually due to chronic renal failure or other causes of Vitamin D deficiency.	Seen in chronic renal failure.
serum calcium	high	low / normal	high
serum phosphate	low / normal	high	high
management	Usually surgery if symptomatic. Cincacalcet can be considered in those not fit for surgery.	Treatment of underlying cause.	Usually cinacalcet or surgery in those that don't respond.

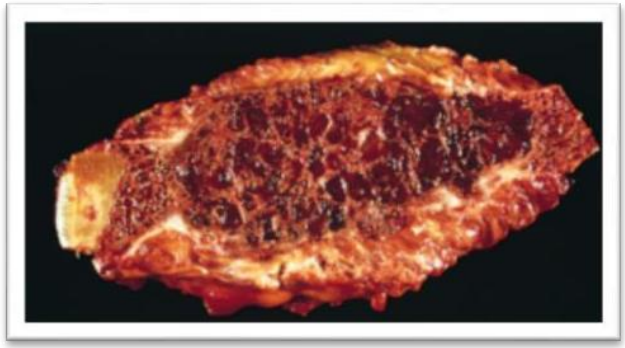
NICE have issued guidance for the use of cinacalcet in what they call refractory secondary hyperparathyroidism which is classified as tertiary hyperparathyroidism in this tblable. http://www.nice.org.uk/TA117

HPT CLINICALLY

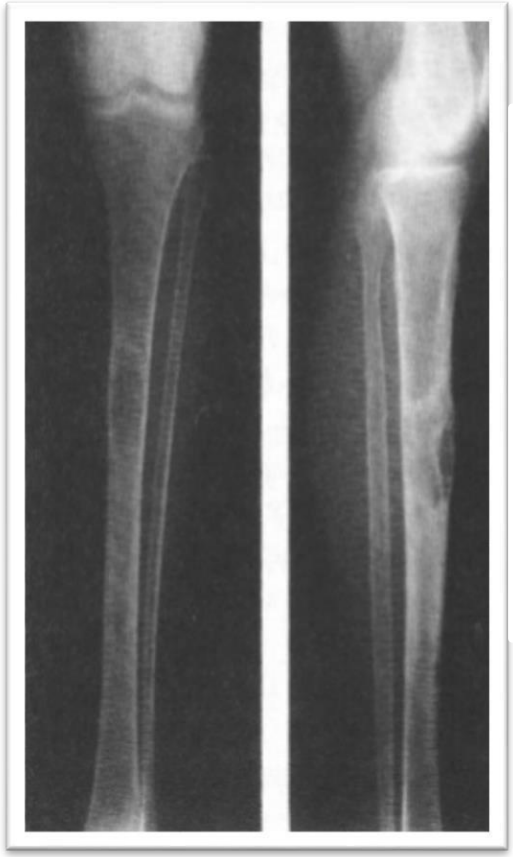
osteoporosis



Brown tumor



OSTEITIS FIBROSA CYSTICA



Abbreviated OFC, also known as osteitis fibrosa, osteodystrophia fibrosa, and von Recklinghausen's disease of bone (not to be confused with von Recklinghausen's disease, neurofibromatosis type I)

Summary

Metabolic Disorders of Bone

- **Osteopenia** and **osteoporosis** represent histologically normal bone that is decreased in quantity. In osteoporosis the bone loss is sufficiently severe to significantly increase the risk of fracture. The disease is very common, with marked morbidity and mortality from fractures. Multiple factors including peak bone mass, age, activity, genetics, nutrition, and hormonal influences contribute to its pathogenesis.
- **Osteomalacia** is characterized by bone that is insufficiently mineralized. In the developing skeleton, the manifestations are characterized by a condition known as **rickets.**
- **Hyperparathyroidism** arises from either autonomous or compensatory hypersecretion of PTH and can lead to **osteoporosis**, **brown tumors,** and **osteitis fibrosa cystica**. However, in developed countries, where early diagnosis is the norm, these manifestations are rarely seen.

PAGET DISEASE OF BONE (OSTEITIS DEFORMANS)

- **Increased badly formed bone structure.**
- **3 phases (lytic, mixed, sclerotic)**
- **1% in USA; geographic variation**
- **Genetic and environmental factors**
- **50% of familial Paget and 10% of sporadic have SQSTM1 gene mutations (+RANK & -OPG)**
- **Viruses (measles and RNA viruses)??**

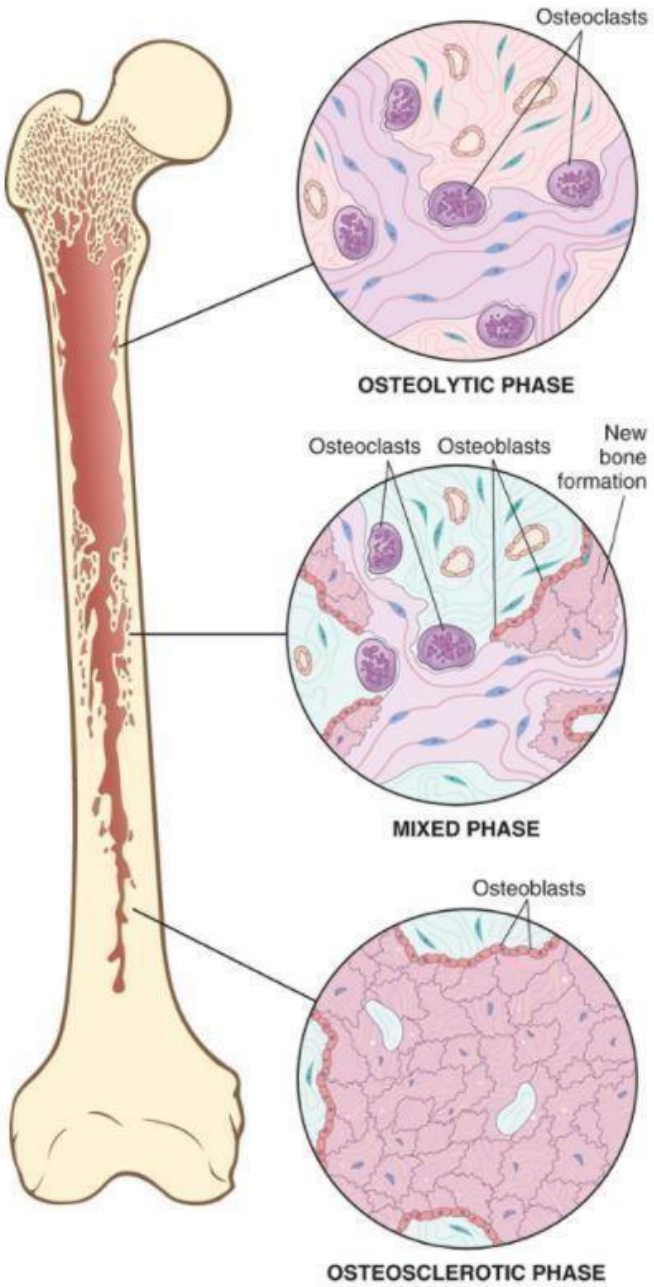
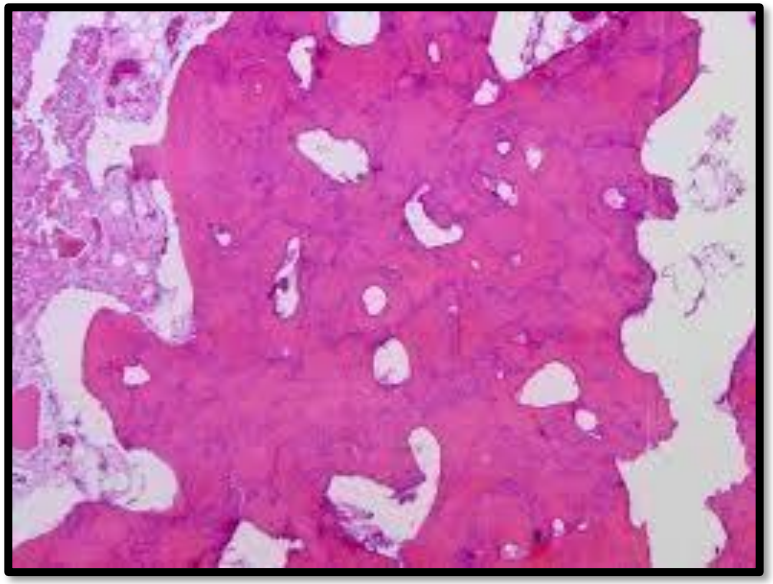
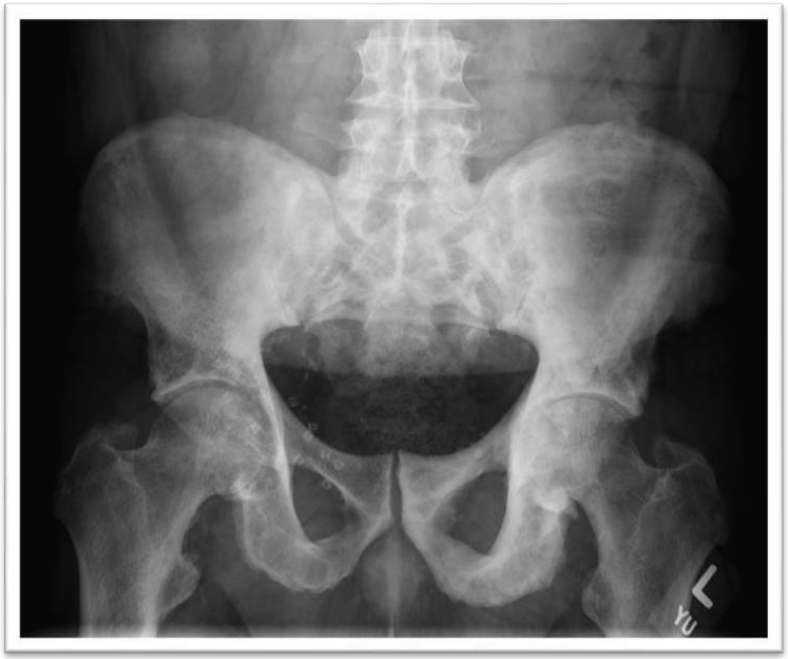
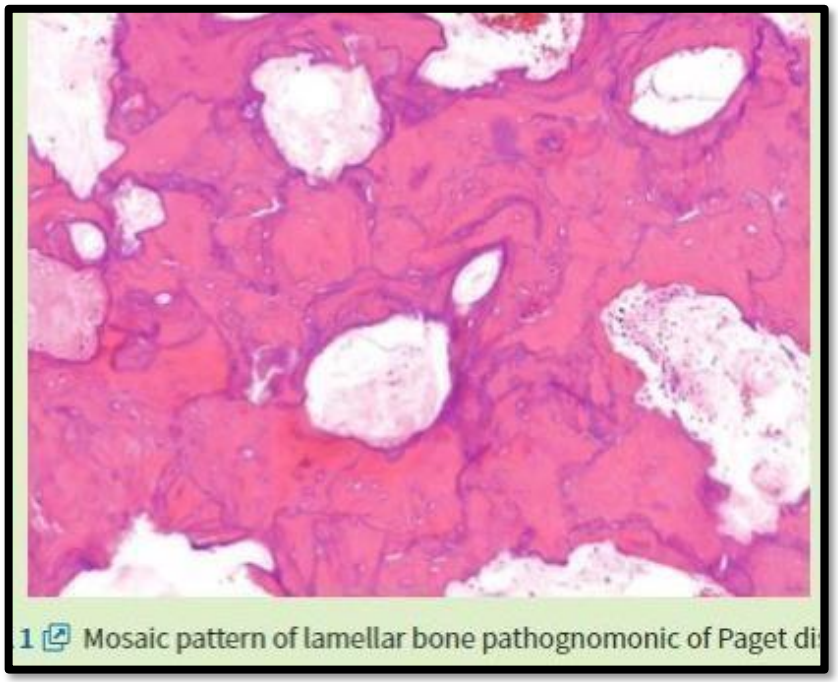


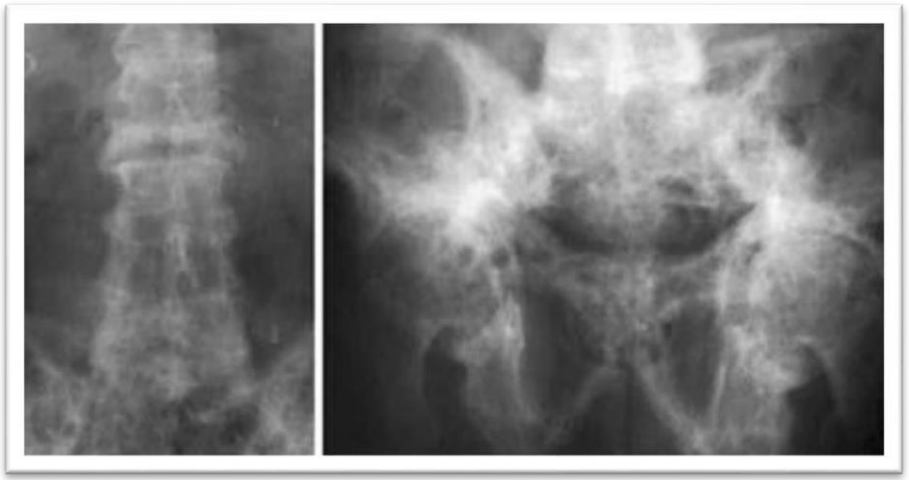
FIG. 21.10 Diagrammatic representation of Paget disease of bone demonstrating the t...







1 Mosaic pattern of lamellar bone pathognomonic of Paget di



PAGET CLINICALLY:

- **85% polystotic; 15% monostotic**
- **Axial skeleton more affected (prox. Femur)**
- **Most are mild and asymptomatic (pain)**
- **Pain: microfractures or nerve compression**
- ***Leontiasis ossea* (lion face); *platybasia* (invagination of skull base); secondary osteoarthritis; fractures; osteosarcoma (1%)**
- **DX: x-ray; ↑ serum Alk P, Normal Ca and PO4**

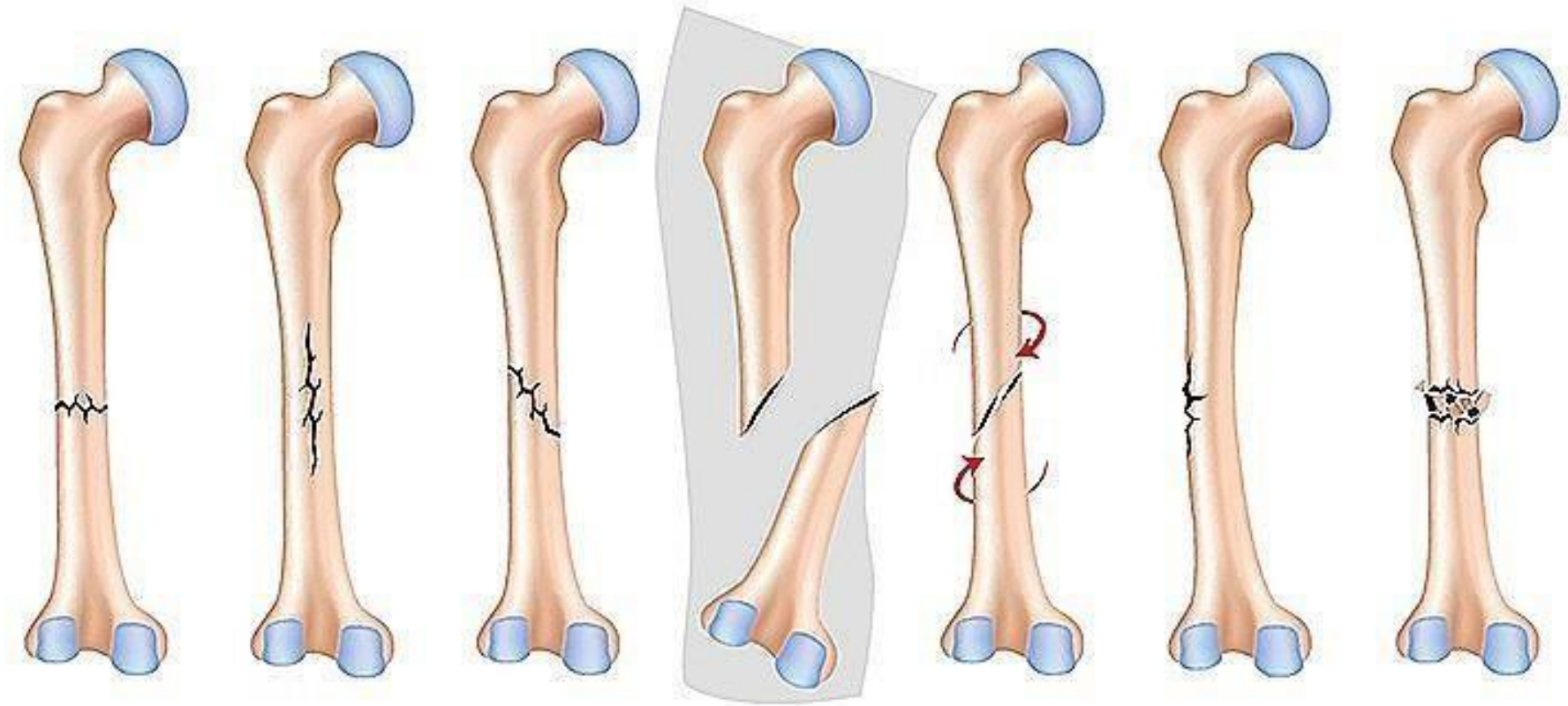
Leontiasis ossea (lion face); platybasia

Lecture 4

FRACTURES #:

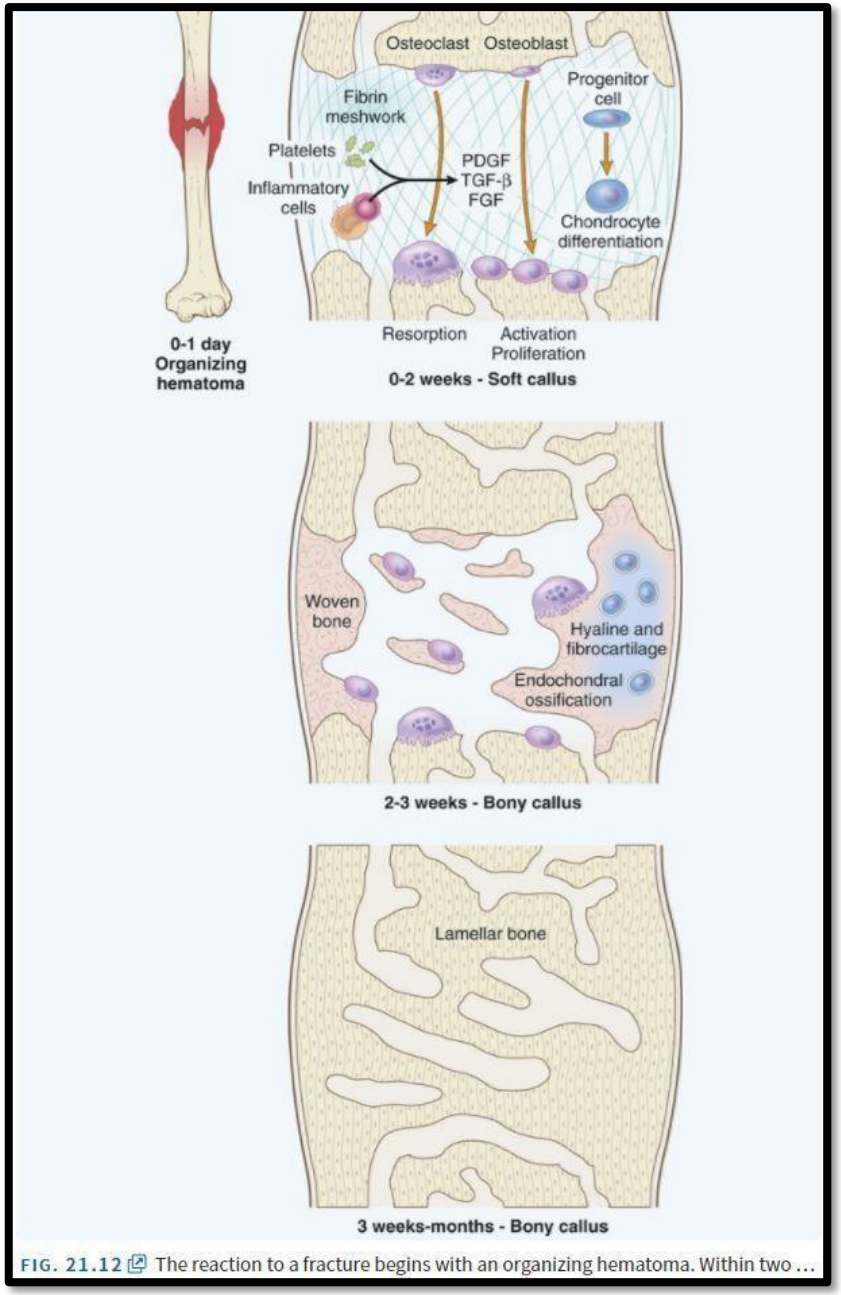
- **Loss of bone integrity from mechanical injury &/or diminished bone strength**
- **Most common pathology of bone:**
  - **Simple #: skin is intact**
  - **Compound #: communicates with overlying skin**
  - **Displaced #: ends are not aligned**
  - **Stress #: repetitive slowly progressive**
  - **Greenstick #: soft bone fracture**
  - **Pathologic #: bone abnormal (tumor)**

Types of Bone Fractures



FACTORS IMPACTING PROPER HEALING:

- Displaced and comminuted #s
- Inadequate immobilization (delayed union or nonunion)
- Pseudoarthrosis
- Infection (open #s)
- Malnutrition
- Steroids/AIDrugs



OSTEONECROSIS (AVASCULAR NECROSIS)

Infarction (ischemic necrosis) of bone and marrow

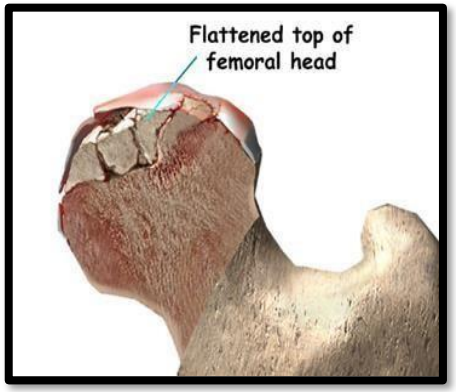
ASSOCIATED CONDITIONS:

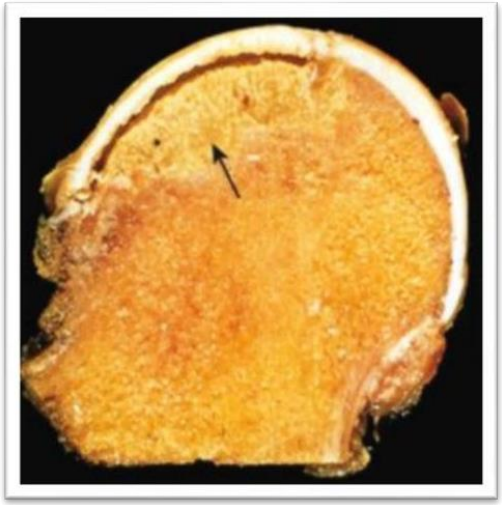
- **Vascular injury: trauma, vasculitis**
- **Drugs: steroids**
- **Systemic disease: Sickle**

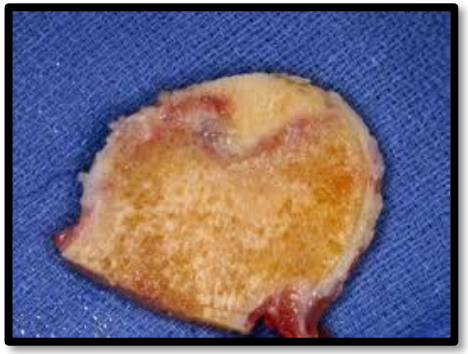
-Radiation

MECHANISM:

- **Mechanical disruption**
- **Thrombotic occlusion**
- **Extravascular**







OSTEOMYELITIS:

- **Inflammation of bone/marrow due to infection**
- **Part of systemic infection or primary solitary focus (much more common)**
- **Any organism can cause osteomyelitis**
- **Pyogenic osteomyelitis: bacteria; *staph. aureus* (80-90%). *E. Coli, Pseudomonas & Klebsiella* are more common when UTI or IV drug abuse are present**

PYOGENIC OSTEOMYELITIS:

- **Mechanism: 1. Hematogenous spread (children). 2. Extension from contiguous site (adults, diabetic foot). 3. Direct implantation after compound # or orthopedic procedure**
- **Neonates: *Haemophilus influenzae & Group B strept***
- **Sicklers: *Salmonella***
- **50% of cases: no organisms isolated**
- **Long bones: metaphysis & epiphysis in adults; in children: epiphysis or metaphysis (not both)**

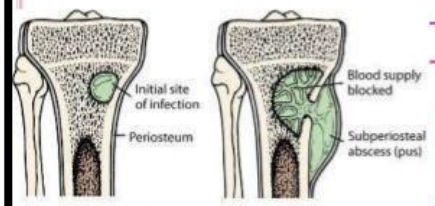
PATHOLOGY

These are end-artery branches of the nutrient artery

↓

acute inflammatory response due to infection

↓



tissue necrosis, breakdown of bone

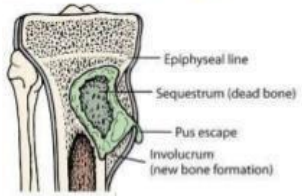
↓

Obstruction

↓

Avascular necrosis of bone

↓

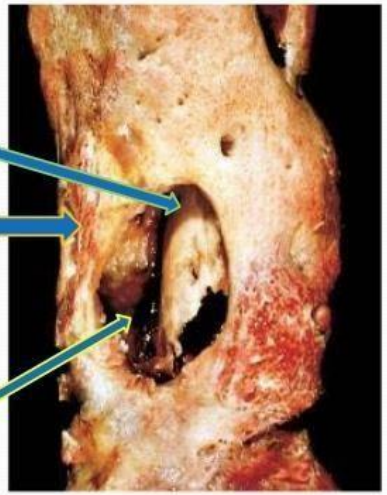


Squestra formation

↓

Chronic osteomyelitis

- **Sequestrum** is the necrotic bone that is embedded in the pus/infected granulation tissue.
- **Involucrum** is the new bone laid down by the periosteum that surrounds the sequestra.
- **Cloaca** is the opening in the involucrum through which pus & sequestra make their way out.



Acute inflammation of marrow tissues → Spread of exudate along the marrow spaces → Thrombosis of vessels due to compression → Necrosis of bone → Liquefaction of necrotic tissues → Lifting of periosteum causing further necrosis

Finally ,Osteoclastic activity >>> SEQUESTRUM

ACUTE	PUS & NEUTROPHILS
CHRONIC	LYMPHOCYTES AND PLASMA CELLS

OSTEOMYELITIS CLINICALLY:

- **Hematogenous OM: fever, malaise, chills, leukocytosis, throbbing pain locally**
- **Infants: subtle. Adults: local pain**
- **DX: high index of suspicion; X-ray maybe normal in early phases (should not wait till we see x ray lytic changes)**
- **Tx: admission, IV antibiotics and sometimes surgical drainage of pus**

CHRONIC OSTEOMYELITIS:

- 5-25% of Acute OM persists as chronic OM
- Very bad debilitating disease

Causes:

- **Delay in diagnosis**
- **Extensive necrosis**
- **Inadequate therapy (A. biotics or surgery)**
- **Weakened host immunity**

COMPLICATIONS OF CH. OM:

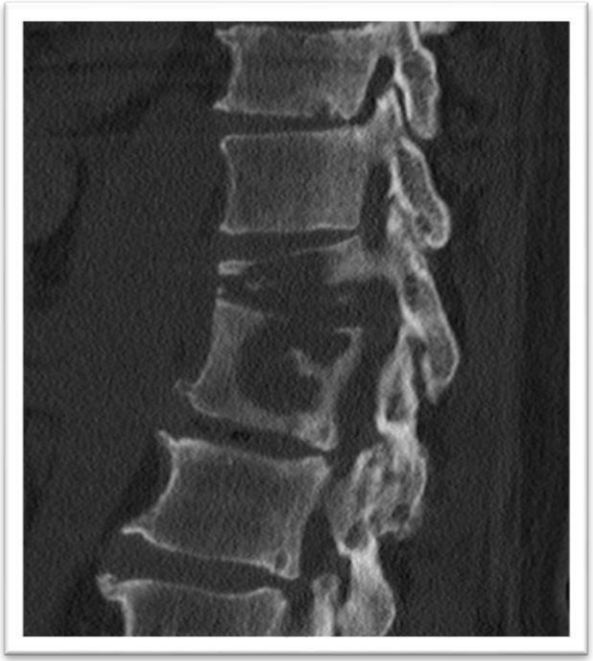
- **Pathologic #s**
- **Secondary amyloidosis**
- **Endocarditis**
- **Sepsis**
- **SQ. cell Ca of draining sinus**
- **Sarcoma of bone**

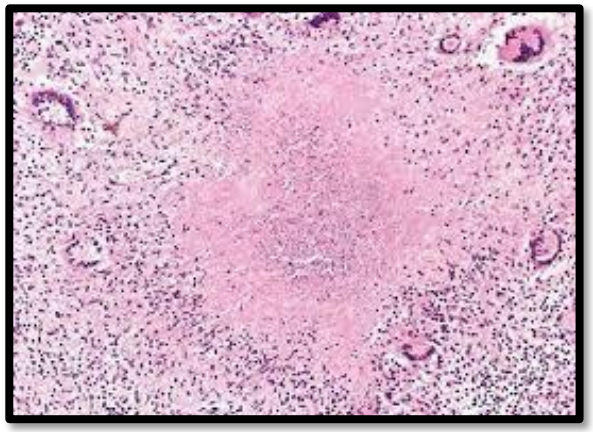
MYCOBACTERIAL OSTEOMYELITIS:

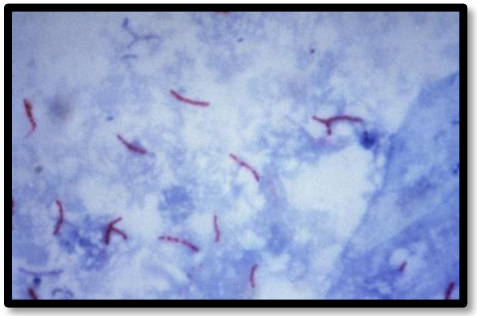
- **Used to be a disease of developing countries**
- **Now: more cases in developed countries: immigration and immunocompromised pts**
- **1-3% of pts with pulmonary or extrapulm TB: can have bone involvement**
- **Hematogenous or direct spread**
- **Clinically: maybe subtle and chronic course**
- **Pathology: necrotizing (caseating) granulomas**

TB SPNDYLITIS (POTT DISEASE):

- **Destructive spine TB**
- **Difficult to treat**
- **May lead to #s, neurologic deficit, scoliosis, kyphosis**







Lecture 5

BONE TUMORS AND TUMORLIKE CONDITIONS:

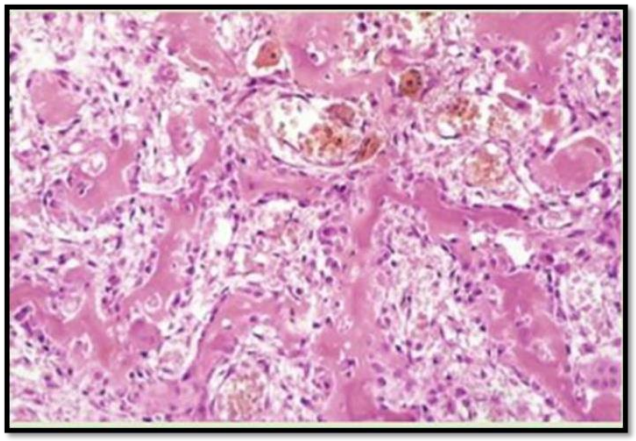
- **Primary bone tumors are rare**
- **Benign >>>> malignant tumors**
- **First 3 decades (benign); adults more to be malignant**
- **Trx: aims to optimize survival while maintaining function**
- **Age & location help narrow ddx**
- **S&S: asymptomatic, pain, path #**

Category	Behavior	Tumor Type	Common Locations	Age (yr)	Morphology
Cartilage forming	Benign	Osteochondroma	Metaphysis of long bones	10–30	Bony excrescence with cartilage cap
—	—	Chondroma	Small bones of hands and feet	30–50	Circumscribed hyaline cartilage nodule in medulla
—	Malignant	Chondrosarcoma (conventional)	Pelvis, shoulder	40–60	Extends from medulla through cortex into soft tissue, chondrocytes with increased cellularity and atypia
Bone forming	Benign	Osteoid osteoma	Metaphysis of long bones	10–20	Cortical, interlacing microtrabeculae of woven bone
—	—	Osteoblastoma	Vertebral column	10–20	Posterior elements of vertebra, histology similar to osteoid osteoma
—	Malignant	Osteosarcoma	Metaphysis of distal femur, proximal tibia	10–20	Extends from medulla to lift periosteum, malignant cells producing woven bone
Unknown origin	Benign	Giant cell tumor	Epiphysis of long bones	20–40	Destroys medulla and cortex, sheets of osteoclasts
—	—	Aneurysmal bone cyst	Proximal tibia, distal femur, vertebra	10–20	Vertebral body, hemorrhagic spaces separated by cellular, fibrous septae
—	Malignant	Ewing sarcoma	Diaphysis of long bones	10–20	Sheets of primitive small round cells

BONE-FORMING TUMORS

- **< 2 cm**
- **Young men**
- **Femur & tibia; nidus with surrounding bone reaction**
- **Severe nocturnal pain (PGE2) relieved by aspirin & NSAIDS**
- **Treated by: radiofrequency ablation or surgery**

- **> 2 cm**
- **Posterior vertebrae; no rim of bone reaction**
- **Pain unresponsive to aspirin**
- **Treated by curetting**



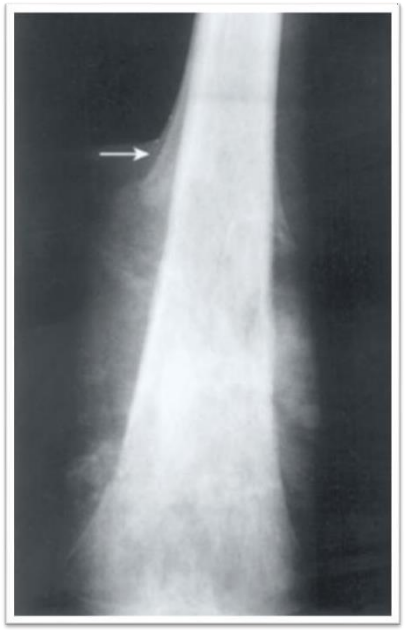
OSTEOSARCOMA:

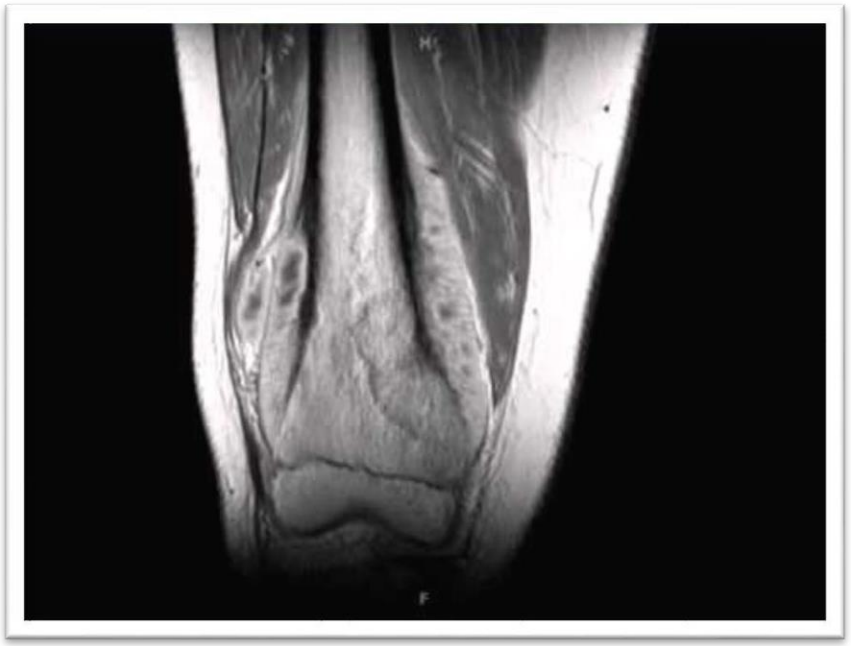
- **Malignant osteogenic tumor**
- **Excluding hematopoietic malignancies; it is the most common primary malignant tumor of bone**
- **75% adolescents; another peak in older (secondary osteosarcoma)**
- **Males > females (1.6:1.0)**
- **Metaphysis of long bones (distal femur & proximal tibia)**

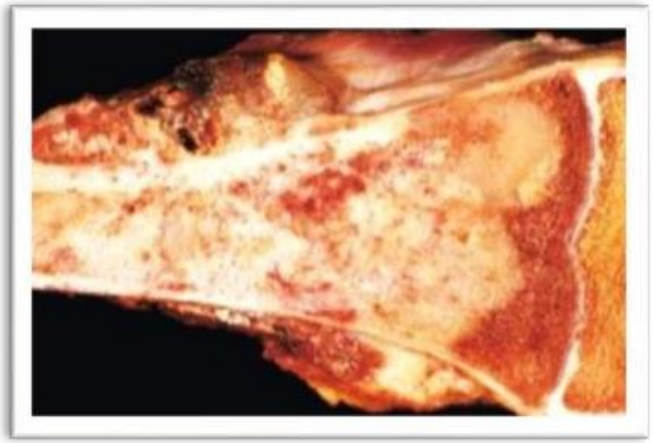
OSTEOSARCOMA:

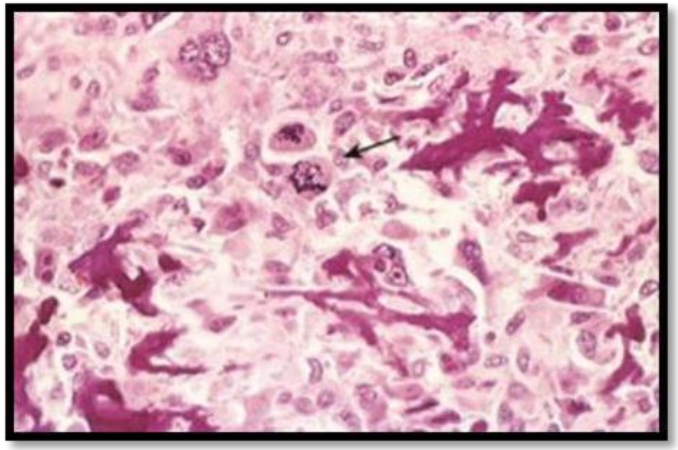
- **Progressive pain or #**
- **Imaging: large destructive and infiltrative lesions with Codman triangle**
- **Genetic abnormalities: mutations in RB gene, TP53 gene, CDKN2A (p16 & p14), MDM2 & CDK2**

OSTEOSARCOMA FEATURES:









OSTEOSARCOMA TREATMENT:

- **Multimodality approach (MDTeam)**
- **1. Neoadjuvant chemotherapy 2. Surgery 3. Chemotherapy**
- **Hematogenous spread to lungs**
- **5 year survival reaches 60-70%**
- **Presence of mets at diagnosis is a bad prognostic factor**

CARTILAGE-FORMING TUMORS:

- **Osteochondroma (benign exostoses): solitary (85%); part of multiple hereditary exostoses (MHE): EXT1, EXT2 gene mutations**
- **Rare (<3-5%) transformation to chondrosarcoma (more common in MHE)**

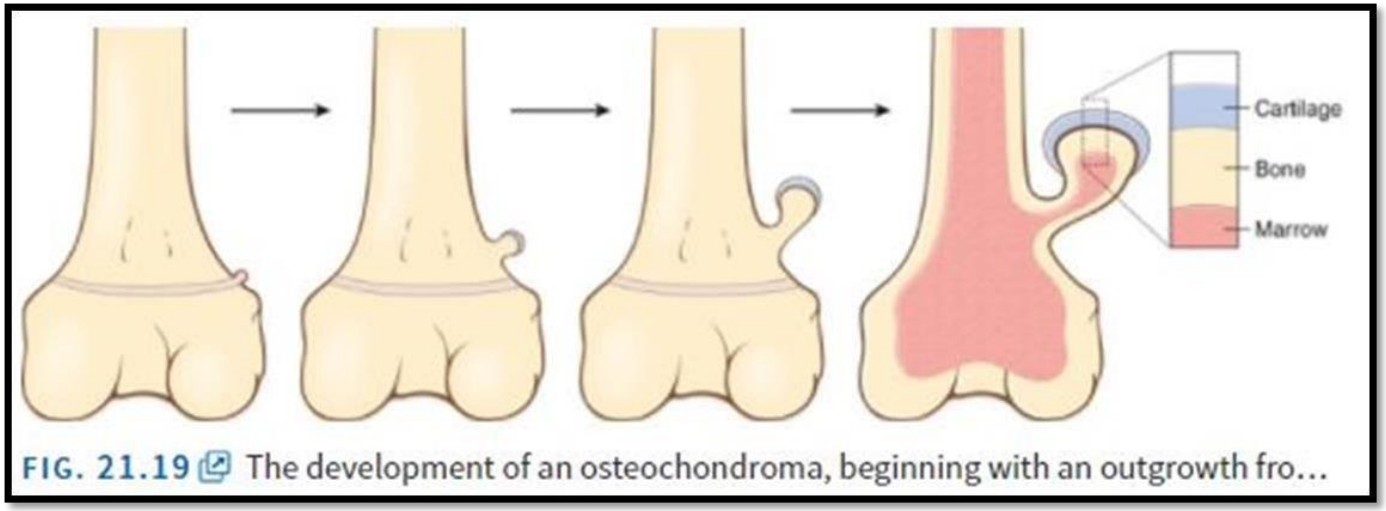
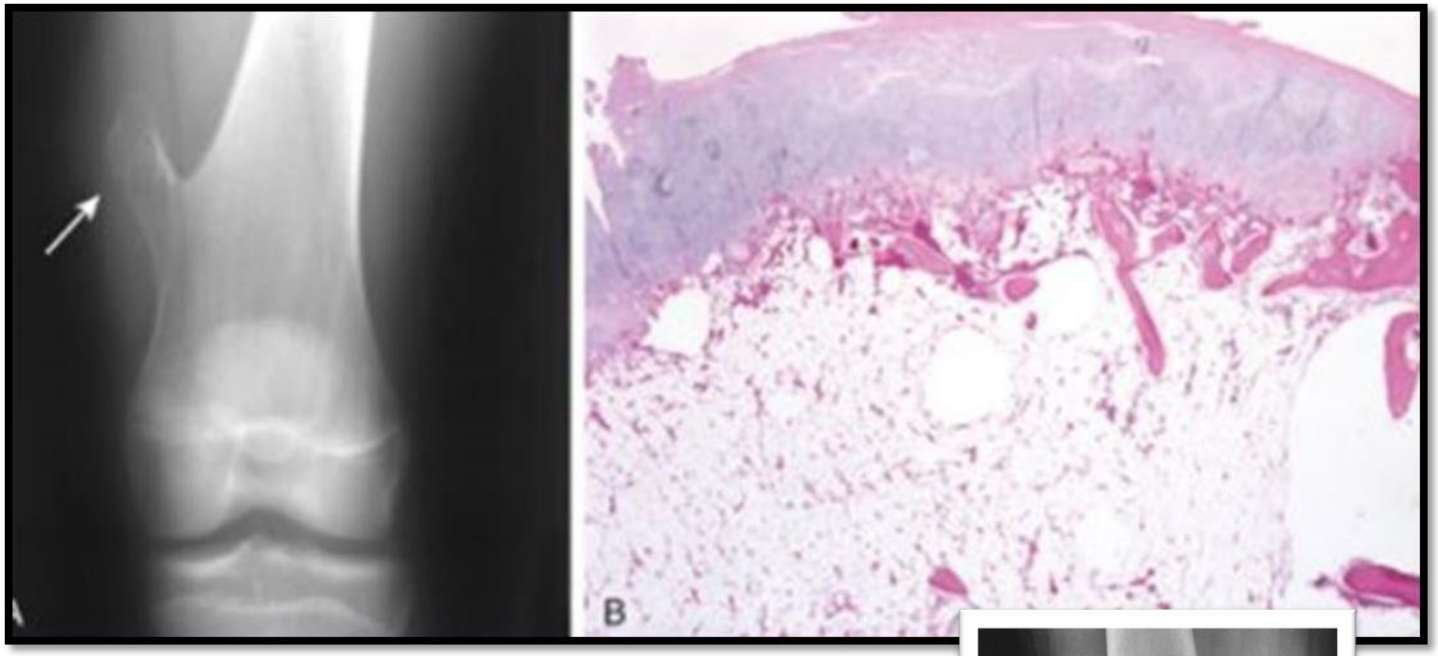
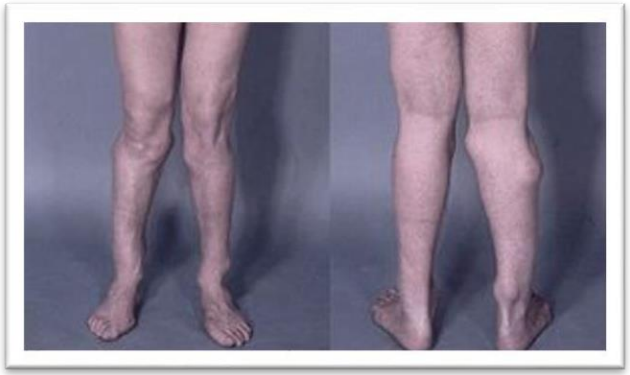
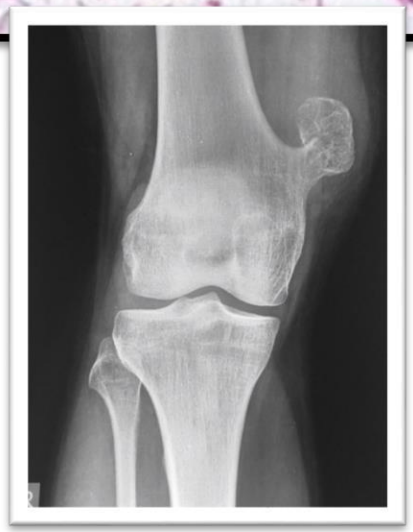


FIG. 21.19 The development of an osteochondroma, beginning with an outgrowth fro…

OSTEOCHONDROMA:

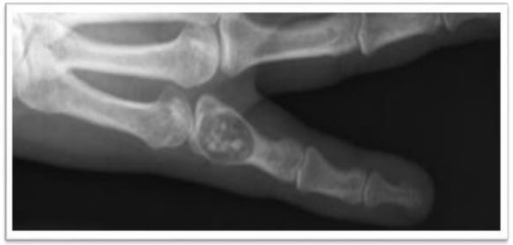


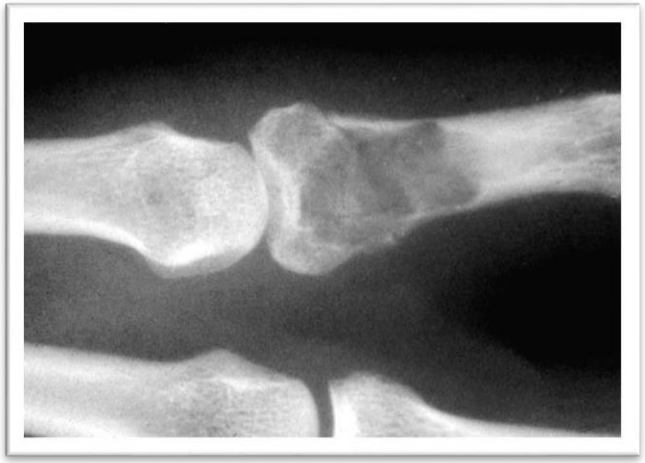


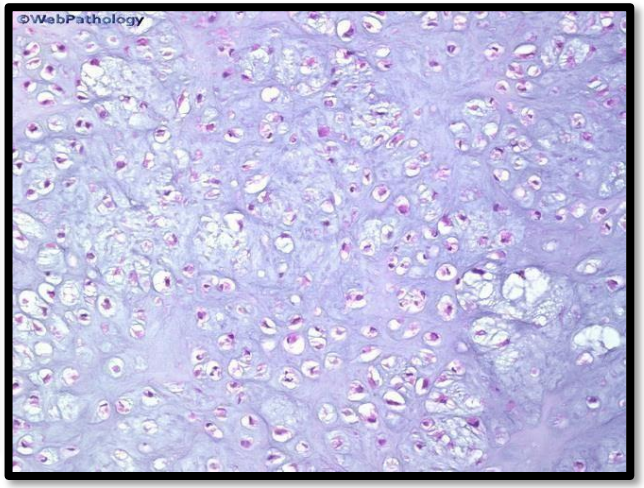


CHONDROMA (ENCHONDROMA):

- **Benign hyaline cartilage tumors in bones with endochondral origin; medullary enchondroma or cortical chondroma**
- **Solitary metaphyseal lesions; 20-50 years**
- **Multiple enchondromas: Ollier disease**
- **Maffucci syndrome: multiple enchondromas + skin hemangiomatosis**
- **IDH1 & IDH2 gene mutations**



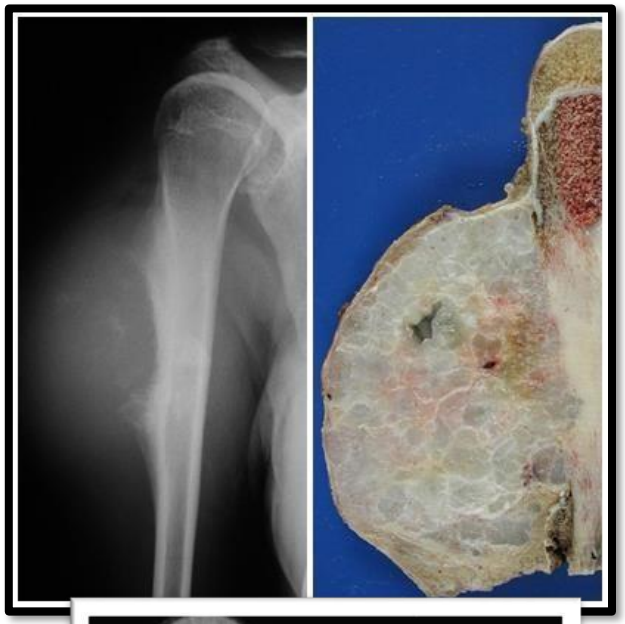


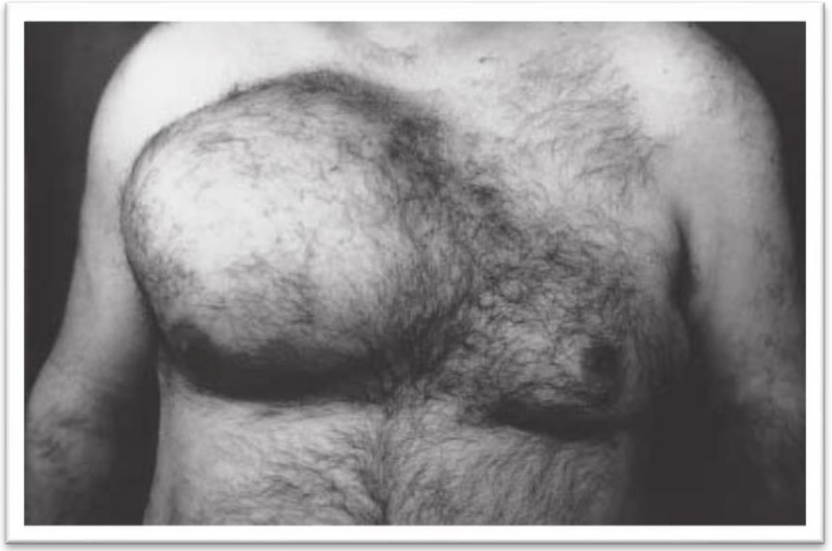


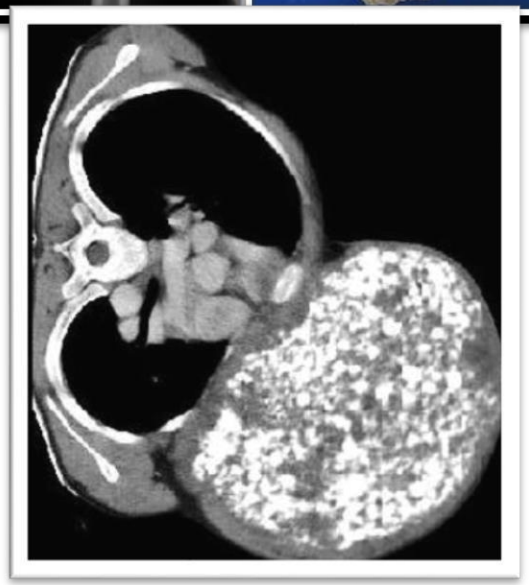
CHONDROSARCOMA:

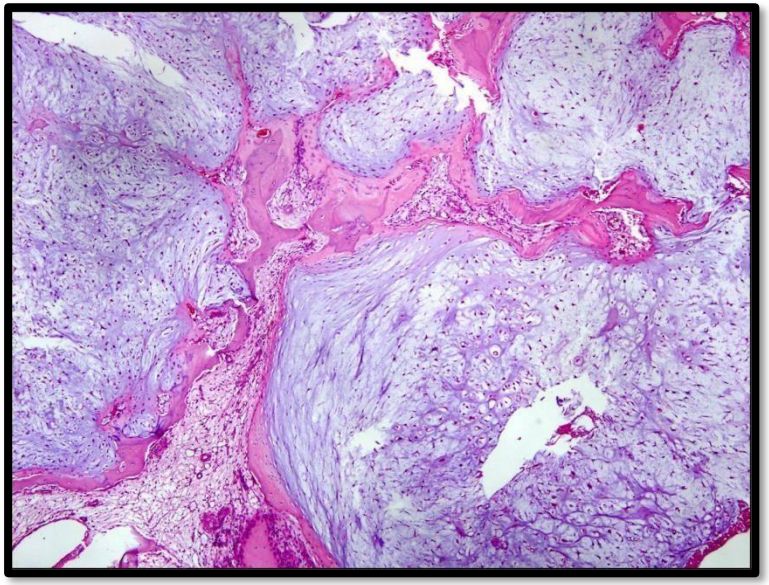
- **Malignant tumors producing cartilage**
- **50% incidence of osteosarcoma**
- **40-50 years of age; M:F (2:1)**
- **Large masses; shoulder, pelvis, ribs**
- **Genes: *EXT, IDH1, IDH2, COL2A1, CDKN2A***
- **Px: depends on grade (grade 1 excellent px)**
- **Trx: surgical +/- chemotherapy**

CHONDROSARCOMA FEATURES:





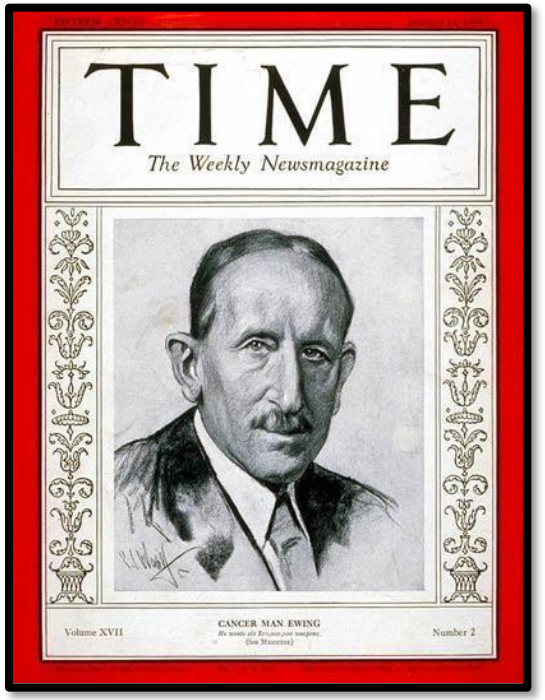




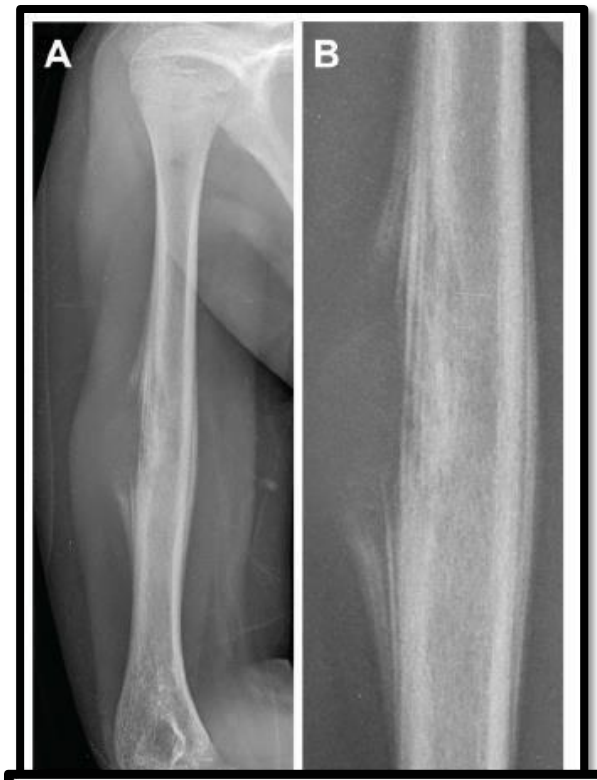
Lecture 6

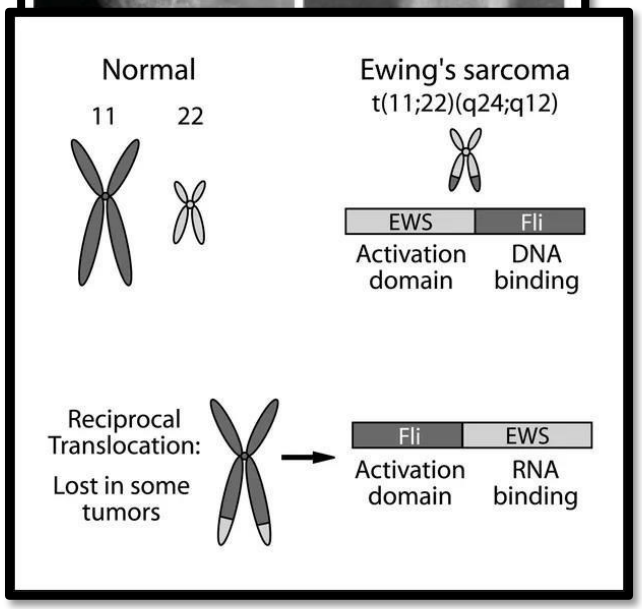
EWING SARCOMA:

- **Dr. James Ewing (1866-1943). Described this tumor 1920**
- **Small blue cell tumor (PNET)**
- **2nd most common sarcoma of bone after osteosarcoma**
- **< 20 years, diaphysis**
- **The most common translocation, present in about 90% of Ewing sarcoma cases, is t(11;22)(q24;q12),which generates an aberrant transcription factor through fusion of the EWSR1 gene with the FLI1 gene.**
- **Trx: neoadjuvant CT followed by surgery; long term survival now reaches 75%**



ES FEATURES:

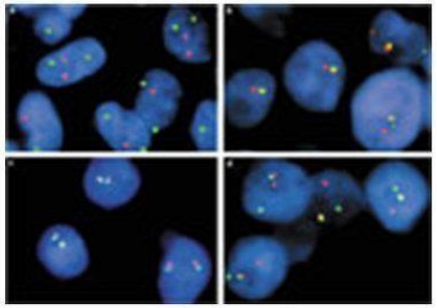




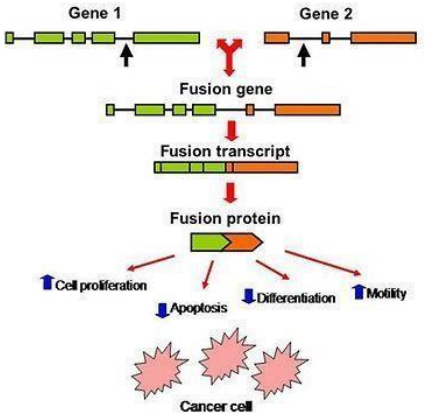
Positive translocation of EWS gene:

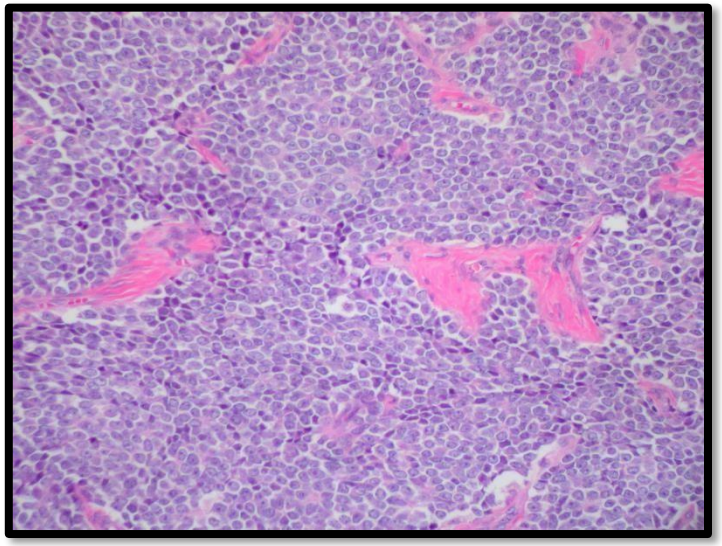
EWS FLI1 t(11;22)(q24;q12)

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



Pozit. EWS/FLI1 - FISH





GIANT CELL TUMOR OF BONE:

- Locally aggressive neoplasm of adults.
- Epiphyses of long bones
- Osteoclast-like giant cells
- Rare malignant behavior
- Cells contain high levels of RANKL
- Trx: curetting

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).

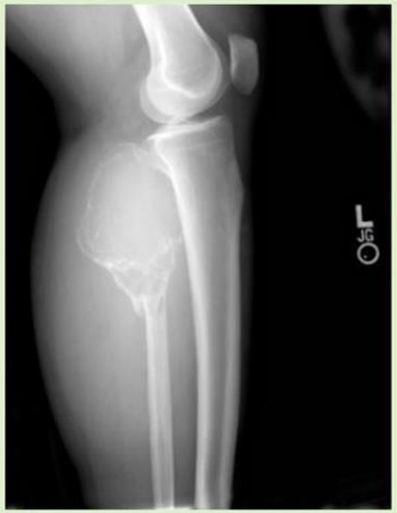


FIG. 21.25 Radiographically, giant cell tumor of the proximal fibula is predomi…

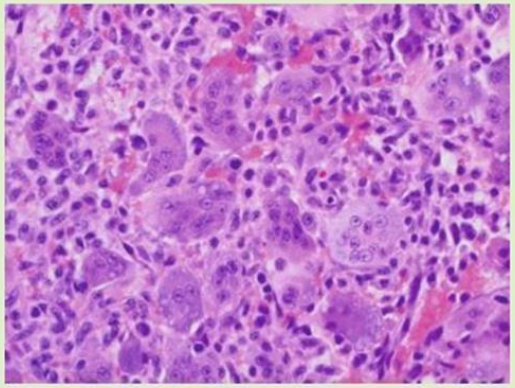
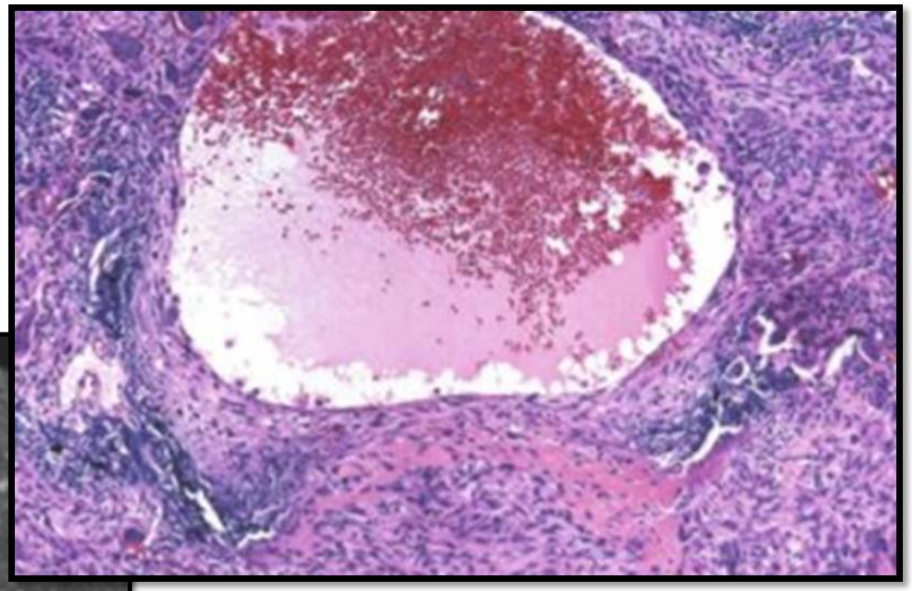
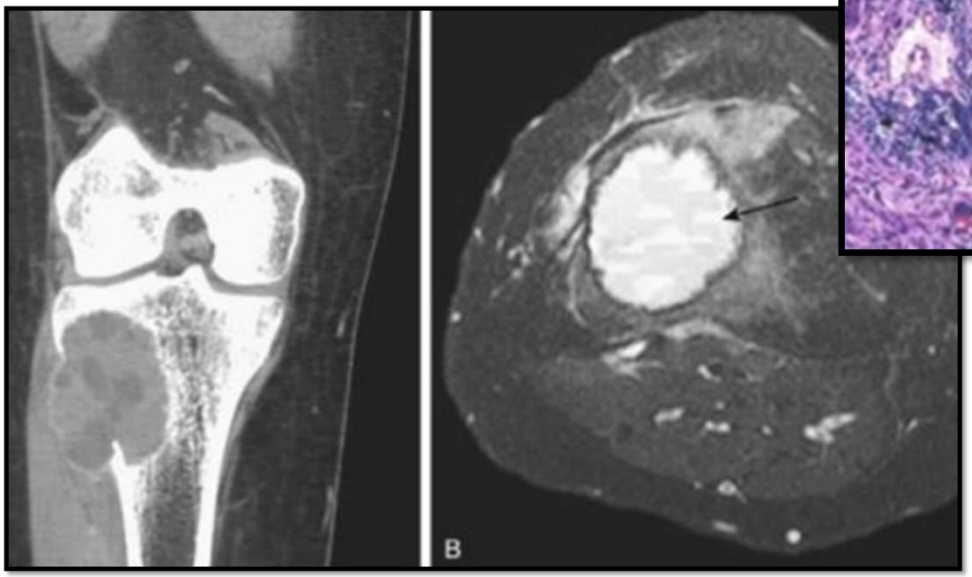


FIG. 21.26 Giant cell tumor illustrating an abundance of multinucleated giant c…

ANEURYSMAL BONE CYST:

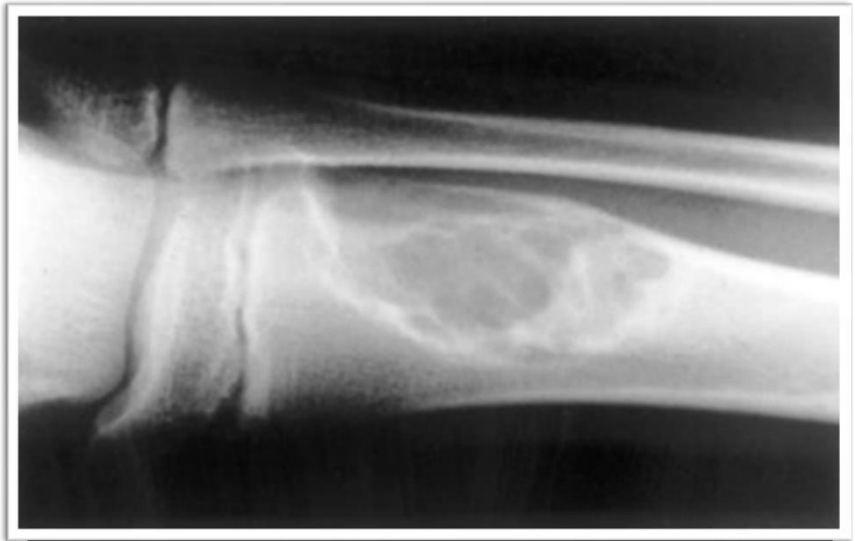
- **Blood filled cyst**
- **Metaphysis of long bones; adults**

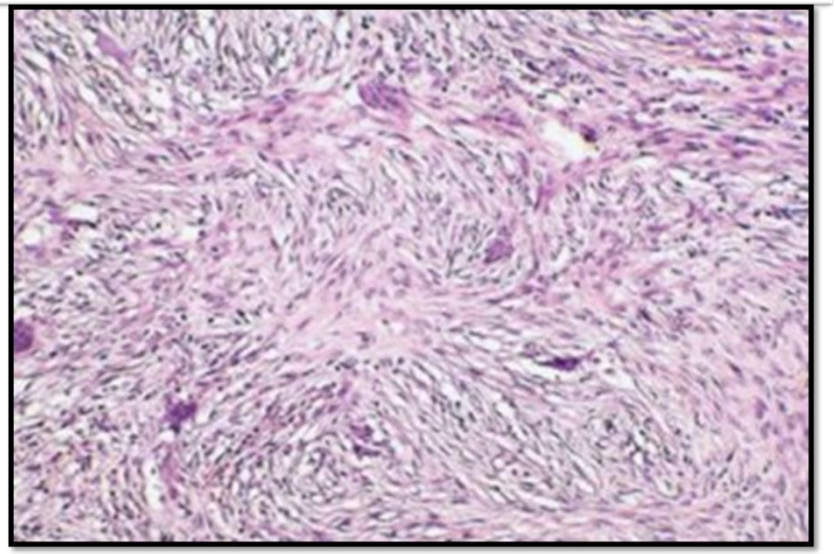




NONOSSIFYING FIBROMA:

- **Benign lesion, maybe reactive not a true neoplasm (other names: FCD, MFD**
- **Metaphysis**
- **Histology: bland fibroblastic proliferation**
- **May resolve spontaneously**

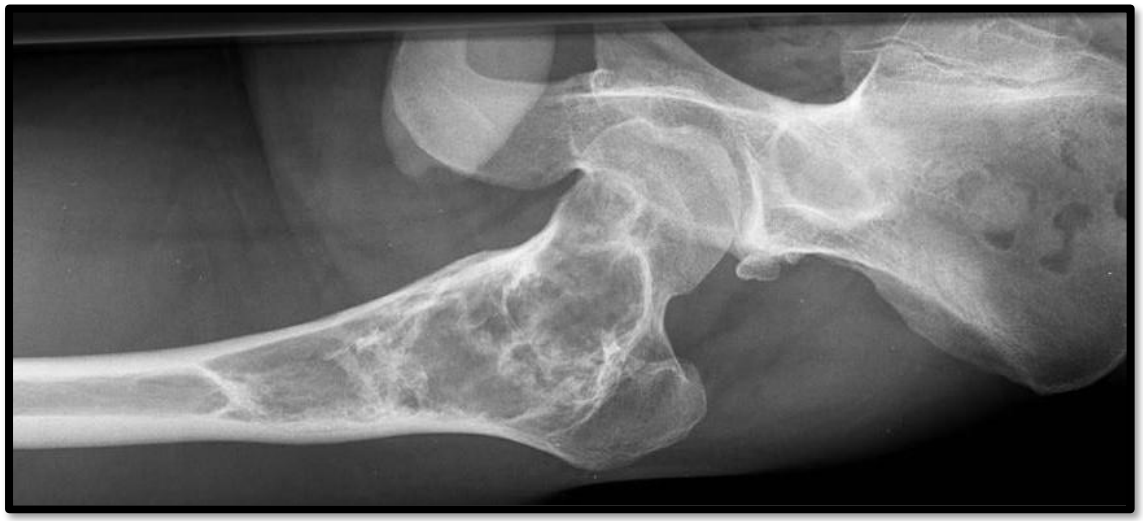


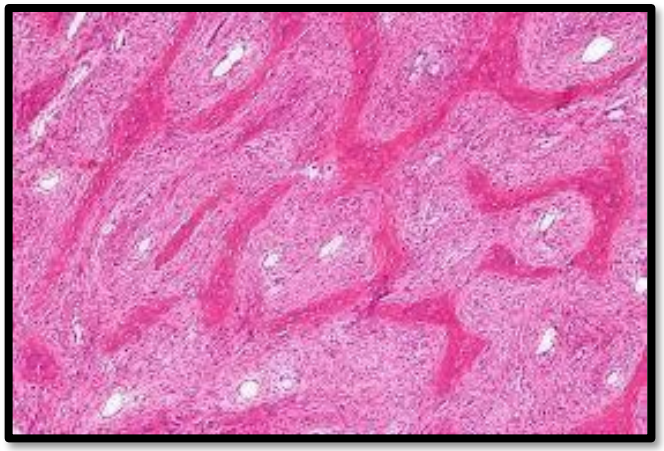


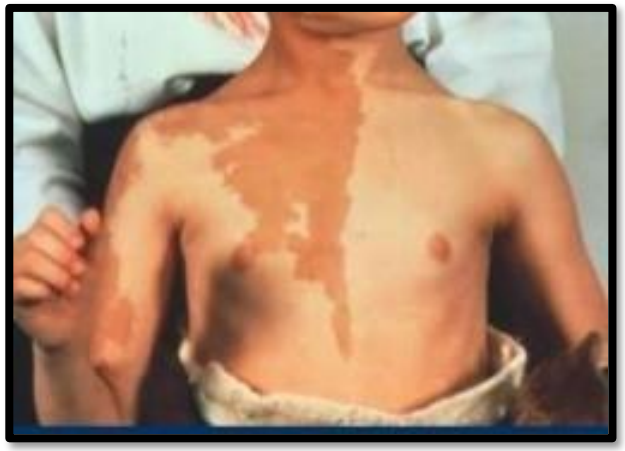
FIBROUS DYSPLASIA (FD):

- **Not a real tumor; rather a developmental abnormality of bone genesis due to mutations in GNAS1 gene (cAMP mediated osteoblast differentiation).**
- **Forms of FD:**
  - **Monostotic: affecting one bone**
  - **Polystotic: multiple bones**
  - **Mazabraud syndrome: FD + soft tissue myxoma**
  - **McCune-Albright syndrome: polystotic FD + café-au-lait skin pigmentation + endocrine abnormalities**

McCUNE-ALBRIGHT SYNDROME:



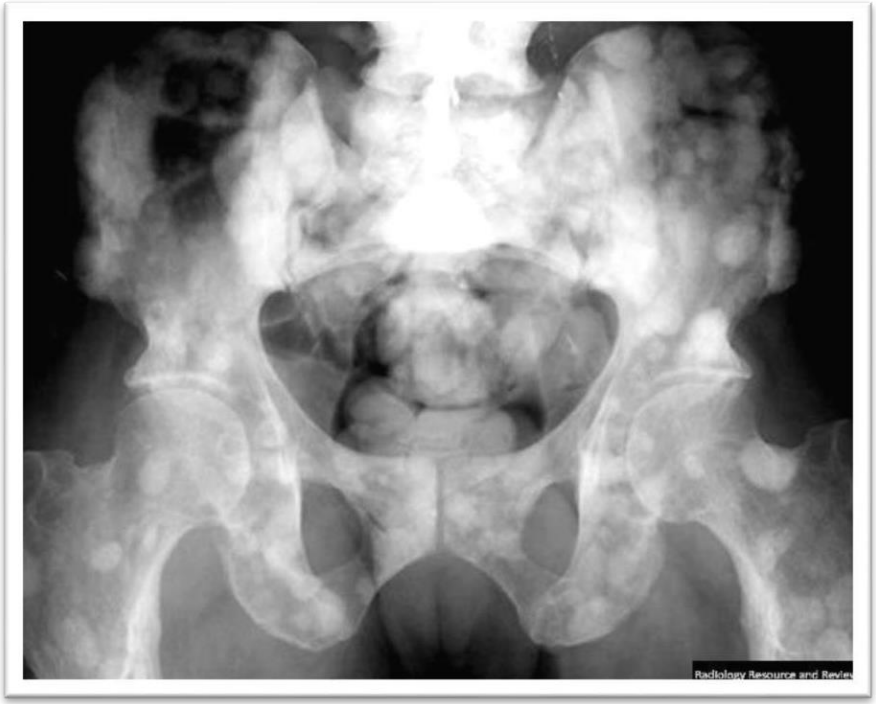




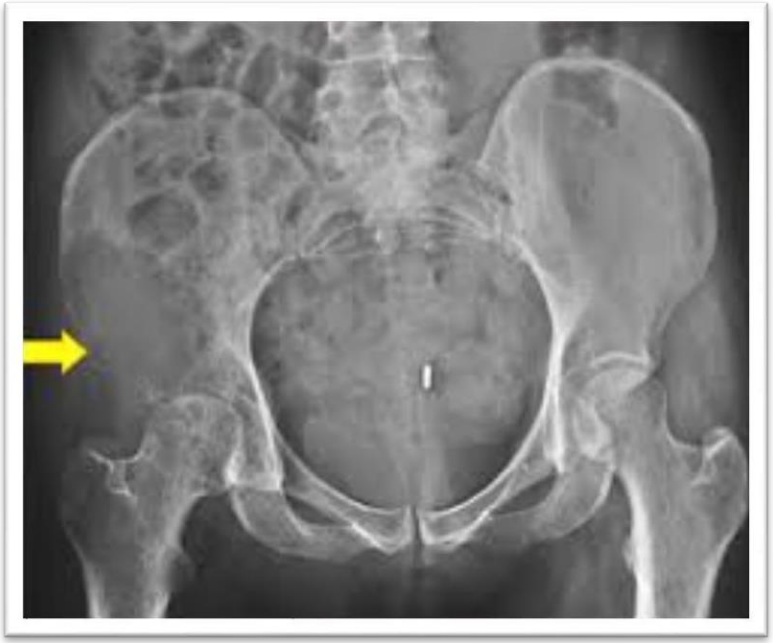
METASTATIC TUMORS TO BONE:

- **Much more common than primary bone tumors**
- **In adults: most are carcinomas; lung, prostate, breast, kidney, thyroid & liver**
- **In children: Neuroblastoma, Wilms tumor and rhabdomyosarcoma**
- **Usually multiple and axial; mostly hematogenous spread.**
- **Lytic, blastic or mixed (via mediators**

BLASTIC METASTASIS



LYTIC METASTASIS



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.

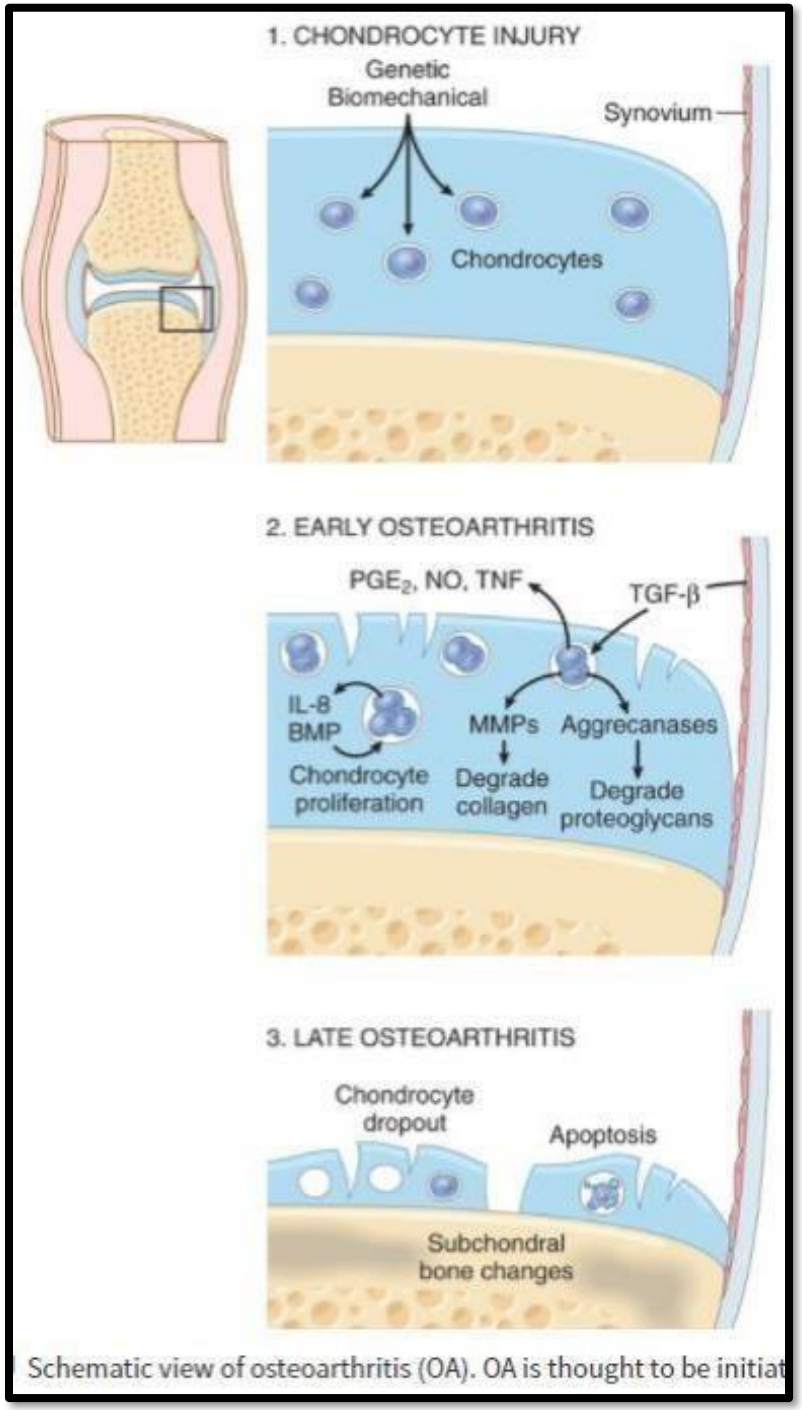
Lecture 7

JOINTS (BASIC KNOWLEDGE):

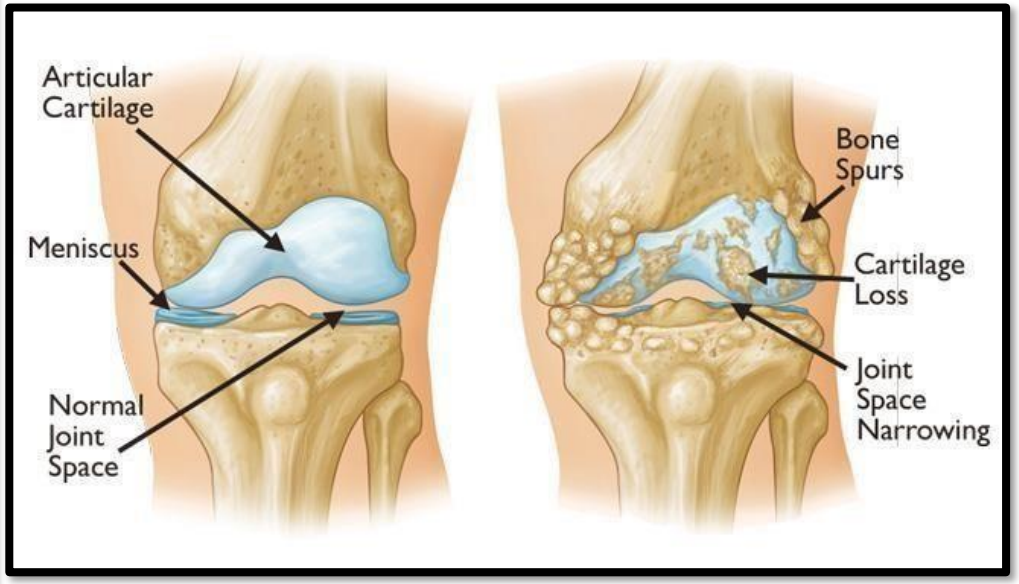
- **Provide motion & stability to our skeleton**
- **Synovial (cavitated): synovial joints, wide motion (knee, elbow…)**
- **Non synovial (solid): synarthrosis, minimal movement (skull, sternum…)**
- **Synovial joints covered by hyaline cartilage (70% water, 10% type II collagen, 8% proteoglycans + chondrocytes**
- **Synovial membrane contains: A synoviocytes (diff. macrophages), and B synoviocytes fibroblast-like**
- **Synov membrane lacks basement membrane**
- **Hyaline cartilage: no blood supply, no nerves, no lymphatics**

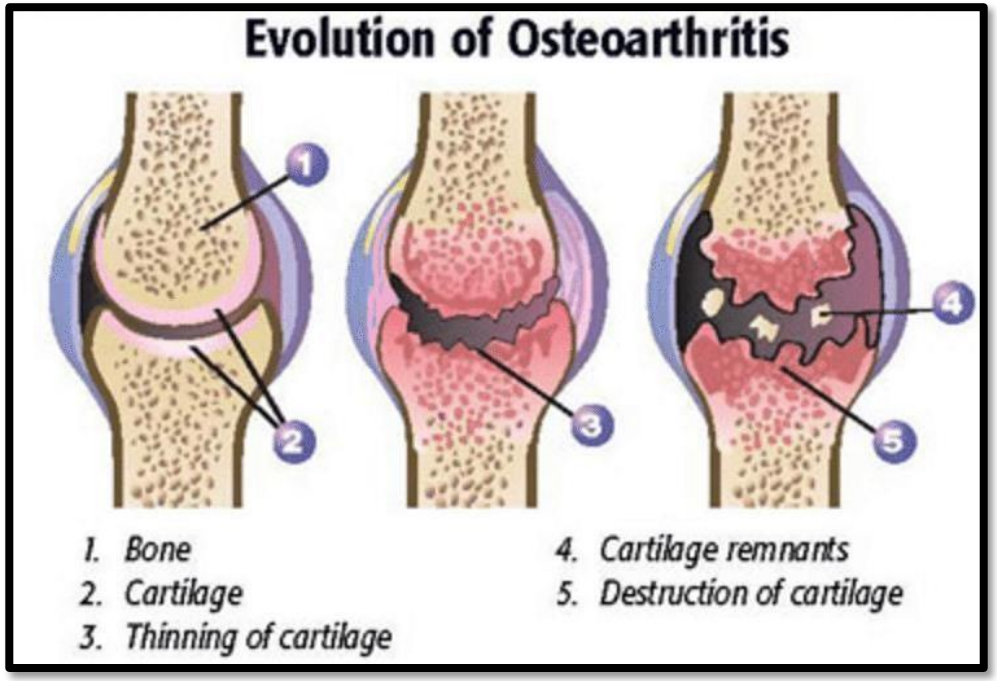
OSTEOARTHRITIS (DJD):

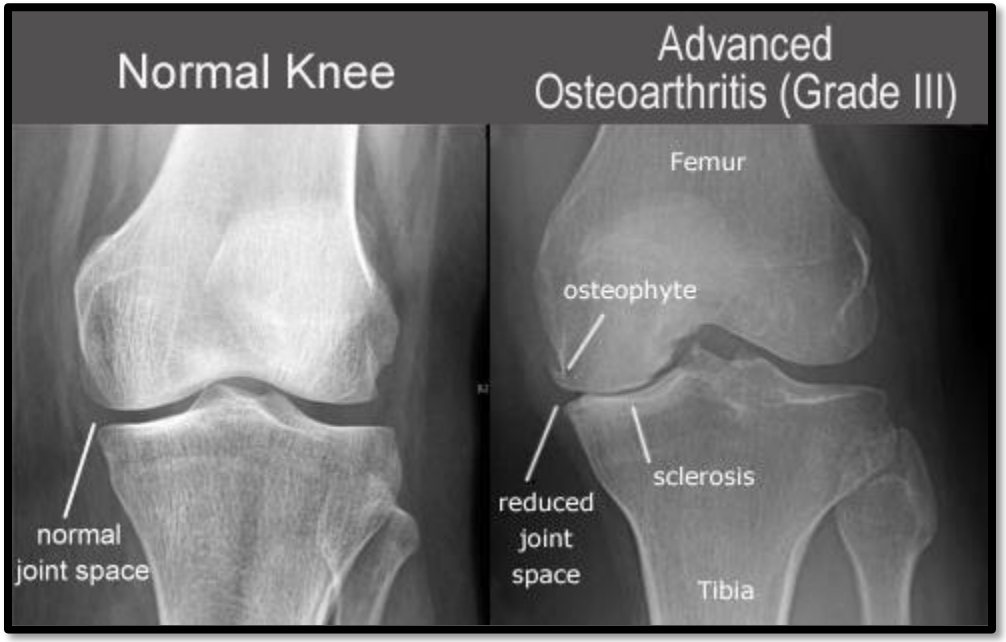
- **Degeneration of cartilage, not true – *ITIS***
- **Primary or idiopathic: aging process; few joints**
- **Secondary: due to pre existing diseases**
- **Insidious; increase with age (>50 yr); 40% of people > 70 years are affected**
- **Degeneration of cartilage >> repair and proliferation**

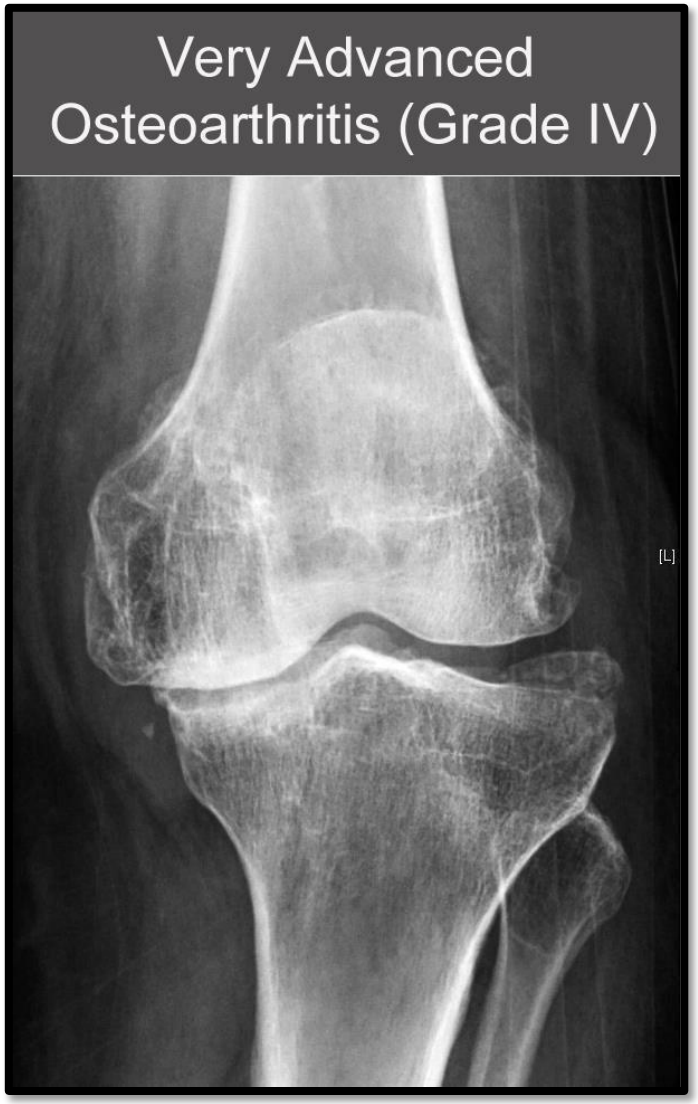


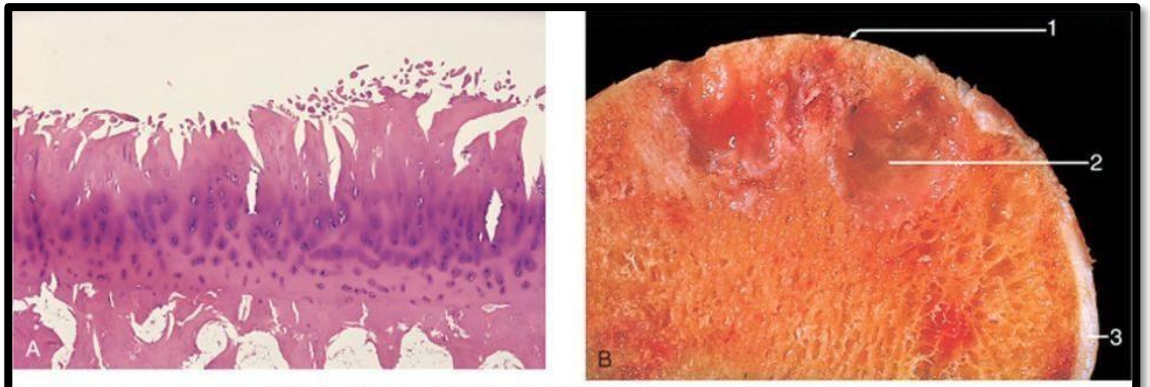
Schematic view of osteoarthritis (OA). OA is thought to be initiat











- 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

OA (DJD) CLINICALLY:

- **Joint pain worsens with use, morning stiffness, crepitus & range limitation, radicular pain, osteophytes impingement on vertebrae, muscle spasm & atrophy**
- **No magic preventive strategies (wt loss?)**
- **Trx: pain control, decrease inflammation (NSAIDs), intra-articular steroids, or joint replacement for severe cases**
- **Large health cost on countries**

RHEUMATOID ARTHRITIS:

- **Chronic inflammatory disease; autoimmune in nature; attacks joints with nonsuppurative proliferative and inflammatory synovitis; leading to destruction of joints and adhesions (ankylosis); systemic disease (skin, heart, vessels & lungs).**
- **1% prevalence in USA; F:M = 3:1; 4^{th}-5^{th} decade**
- **Genetic predisposition + environmental factors plays a role in the development, progression and chronocity of the disease**

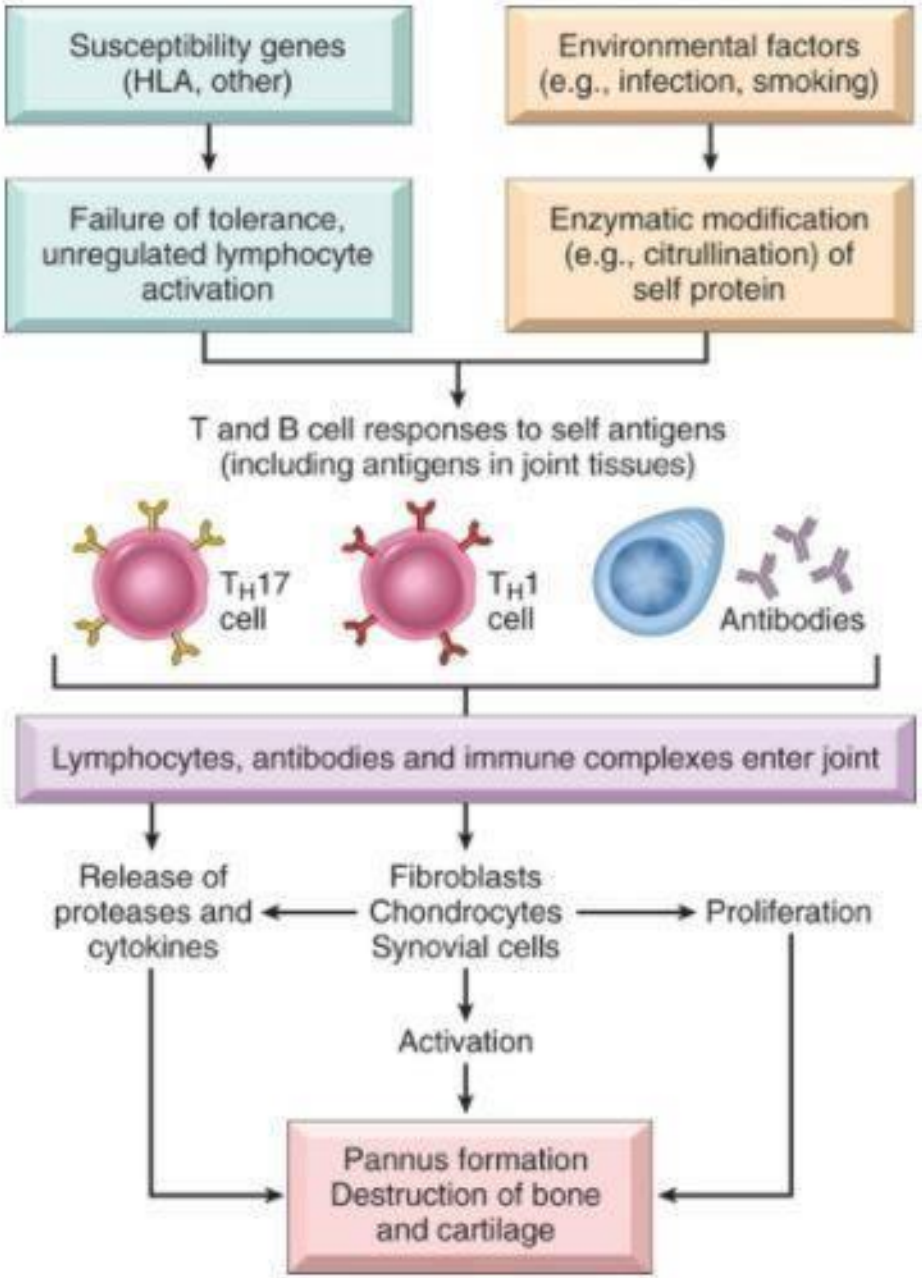


FIG. 21.36 Major processes involved in the pathogenesis of rheumatoid arthritis.

PATHOGENESIS:

IFN-γ from T_H1	**Activates macrophages & synovial cells**
IL-17 from T_H 17	**Recruits neutrophils and monocytes**
RANKL from T cells	**Stimulates osteoclasts & bone resorption**
TNF & IL-1 from macrophages	**Stimulates residents synoviocytes to secrete proteases that destroy hyaline cartilage**

80% of patients with RA have autoantibodies IgG & IgM against the Fc portion of their own IgG [Rheumatoid factor]

70% of patients with RA have Anti-Citrulliniated Protein Antibodies (ACPA)

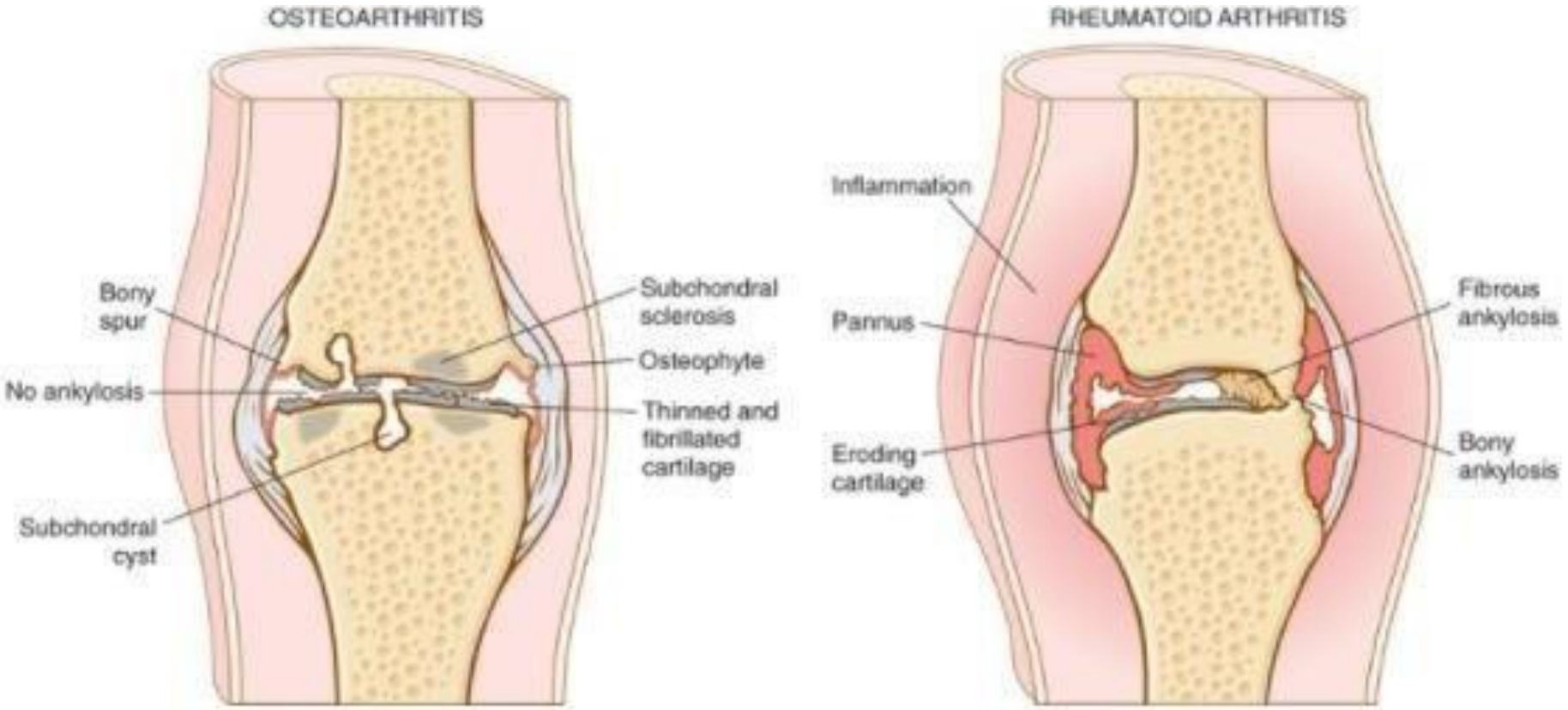
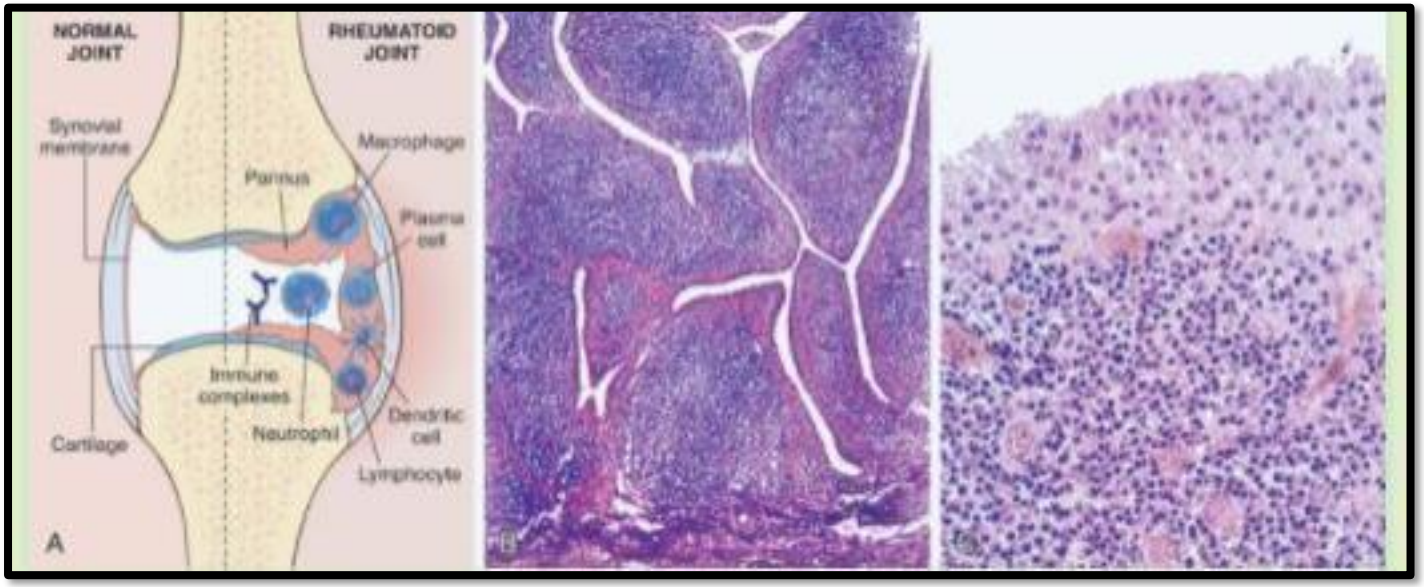
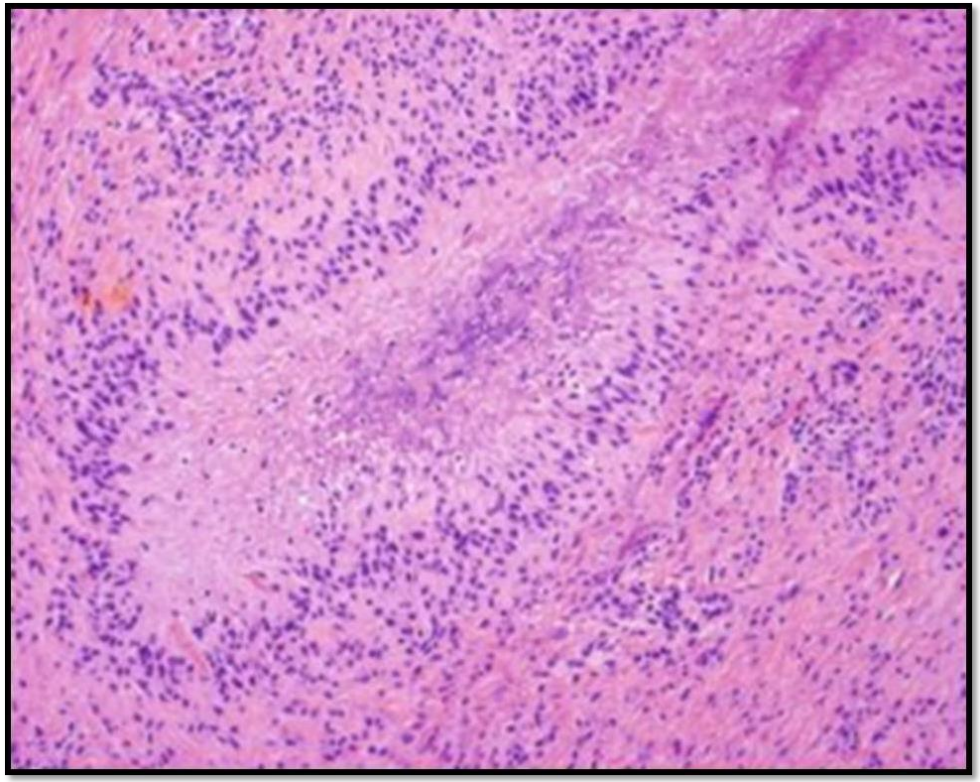


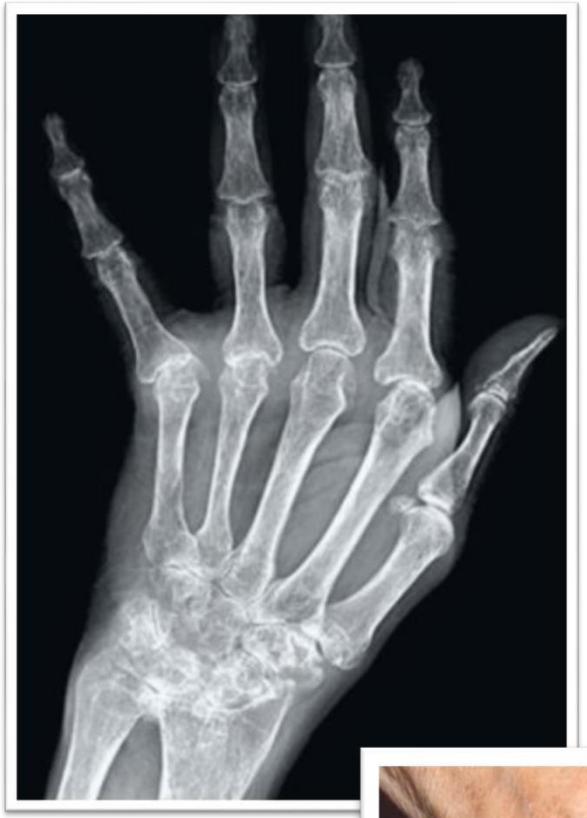
FIG. 21.35 Comparison of the morphologic features of rheumatoid arthritis and osteoa...

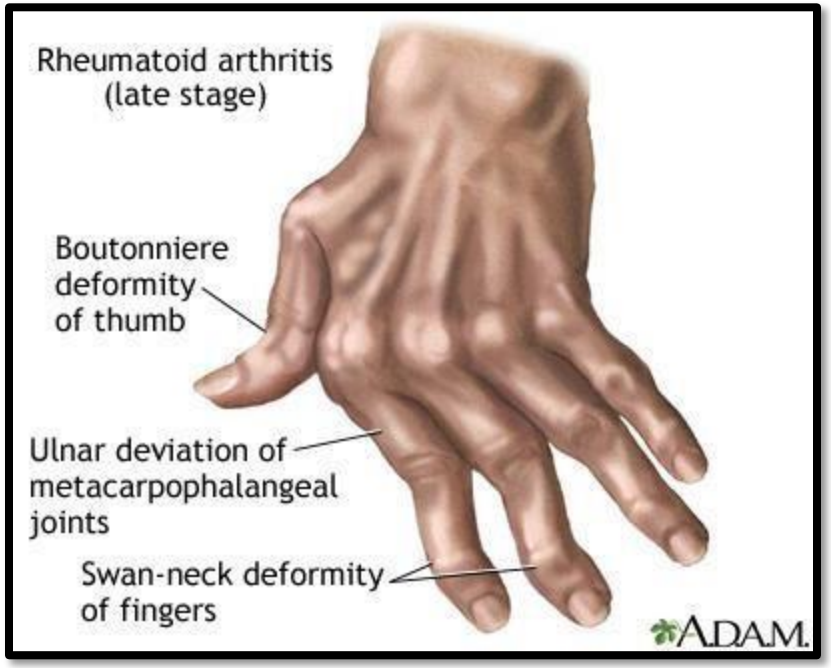

NORMAL JOINT
RHEUMATOID JOINT
Synovial membrane
Pannus
Macrophage
Plasma cell
Immune complexes
Neutrophil
Dendritic cell
Lymphocyte
Cartilage
A

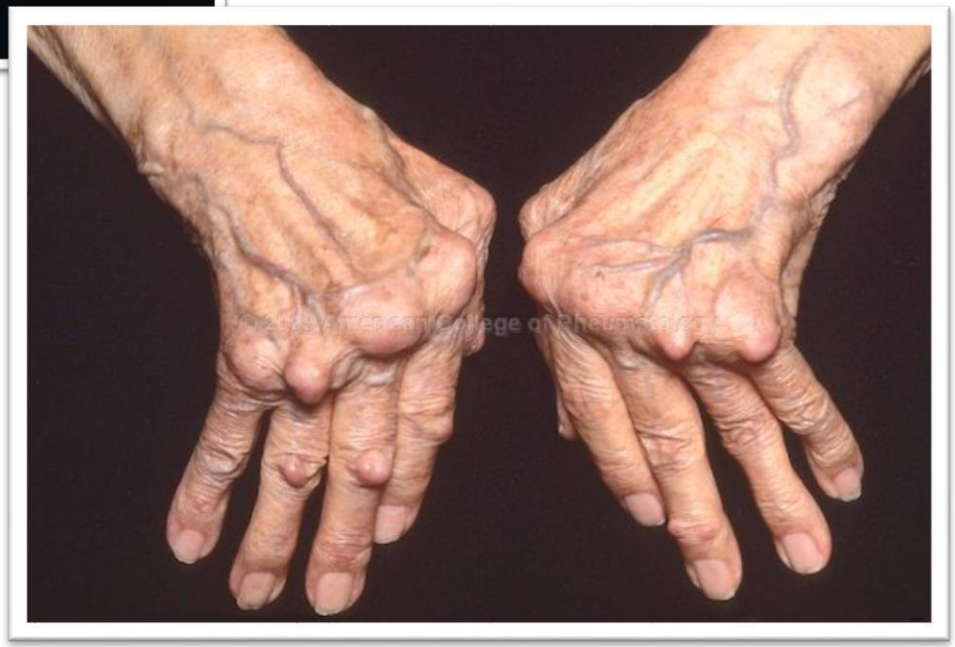


CLINICAL COURSE OF RA:

- **Begins slowly and insidiously, polyarthritis**
- **Symmetrical joints: hands, feet, wrists, ankle, MCP and proximal IPJ are commonly affected**
- **Joints: warm, swollen & painful**
- **Stiffness when inactive and in the morning**
- **Waxing and waning chronic**
- **Ulnar deviation**




Rheumatoid arthritis
(late stage)
Boutonniere
deformity
of thumb
Ulnar deviation of
metacarpophalangeal
joints
Swan-neck deformity
of fingers
A.D.A.M.



JUVENILE IDIOPATHIC ARTHRITIS (JIA):

- **Heterogeneous group; arthritis of unknown cause ; <16 years for at least 6 weeks**
- **Pathogenesis is similar to adult RA**
- **Prognosis variable; only 10% will have serious functional disability**

IN CONTRAST TO ADULTS RA; JIA IS CHARACTERIZED BY:
Oligoarthritis is more common
Systemic disease is more common
Large joints are affected more than small joints
Rheumatoid nodules and Rheum Factor are usually absent
Anti Nuclear Antibody seropositivity is common

SERONEGATIVE

Autoimmune T cell response to unidentified antigen (possibly infectious agent) that cross react with self musculoskeletal antigens

HETEROGENOUS GROUP THAT SHARE THE FOLLOWING FEATURES:
Absence of rheumatoid factor
Ligaments pathology rather than synovium
Sacroiliac joints mainly
Association with HLA-B27
Bony ankylosis (fusion)

- **Ankylosing spondylitis: most common prototype.**
- **Destructive arthritis and bony damage and ankylosis of sacroiliac joint, main joint involved.**
- **90% HLA-B27**
- **Anti IL-17 has shown some efficacy as treatment**

SERONEGATIVE SPONDYLOARTHROPATHIES:

- **Ankylosing Spondylitis:**
  - Adolescent boys, HLA B27, axial joints (sacroiliac)
- **Reiter Syndrome:**
  - Triad of arthritis, urethritis/cervicits & conjuctivitis
  - Autoimmune but initiated by bacterial infection.
- **Enteropathic Arthritis:**
  - Secondary to bowel infections (salmonella, shigella)
  - HLA B27 positive
- **Psoriatic Arthritis:**
  - 5% of patients, starts in DIP joints, similar to RA.

Spondyloarthropathies: Subtype Classification

Ankylosing Spondylitis	Psoriatic Arthritis	Enteropathic (IBD-associated)	Reactive Arthritis	Undifferentiated SpA
Most common subtype along with uSpa 2.5:1 male:female Gradual onset of IBP Acute anterior uveitis most common extra-articular manifestation Can lead to sacroiliac fusion and spinal syndesmophyte formation	Between 10% and 40% of patients with psoriasis develop PsA, depending on study population and psoriasis severity Most phenotypically diverse SpA with 5 subtypes Skin disease precedes joint disease in approximately 70% of cases	5% to 29% of patients with IBD develop arthritis Peripheral arthritis (not axial) can parallel bowel inflammation and can occur in up to 20% of patients Spondylitis occurs in 3% to 6%	Typical acute asymmetric oligoarticular (<4 joints) arthritis 1-3 months after gastrointestinal and genitourinary infection Characteristic triad of urethritis, conjunctivitis, and arthritis seen in < 35% of patients Keratoderma blennorrhagica and circinate balanitis	Most common subtype along with AS Typically used to describe patients not fulfilling criteria of any one SpA but presenting with IBP and other extra-articular SpA manifestations Up to 50% of uSpA will develop into AS

uSpA = undifferentiated SpA; IBP = inflammatory back pain; PsA = psoriatic arthritis; IBD = inflammatory bowel disease; AS = ankylosing spondylitis

Lecture 8

SUPPURATIVE ARTHRITIS:

- **Bacterial infection**
- **Hematogenous spread**
- **< 2 years: *H. influenza;* older children & adults *S. aureus;* gonococcus young adults**
- **Sickle cell disease: salmonella**
- **Clinically: sudden acute pain, swollen and warm joints, mainly knee with systemic manifestation (fever, leukocytosis, elevated ESR)**
- **Dx & Rx: aspiration of joint; antibiotics**

LYME ARTHRITIS

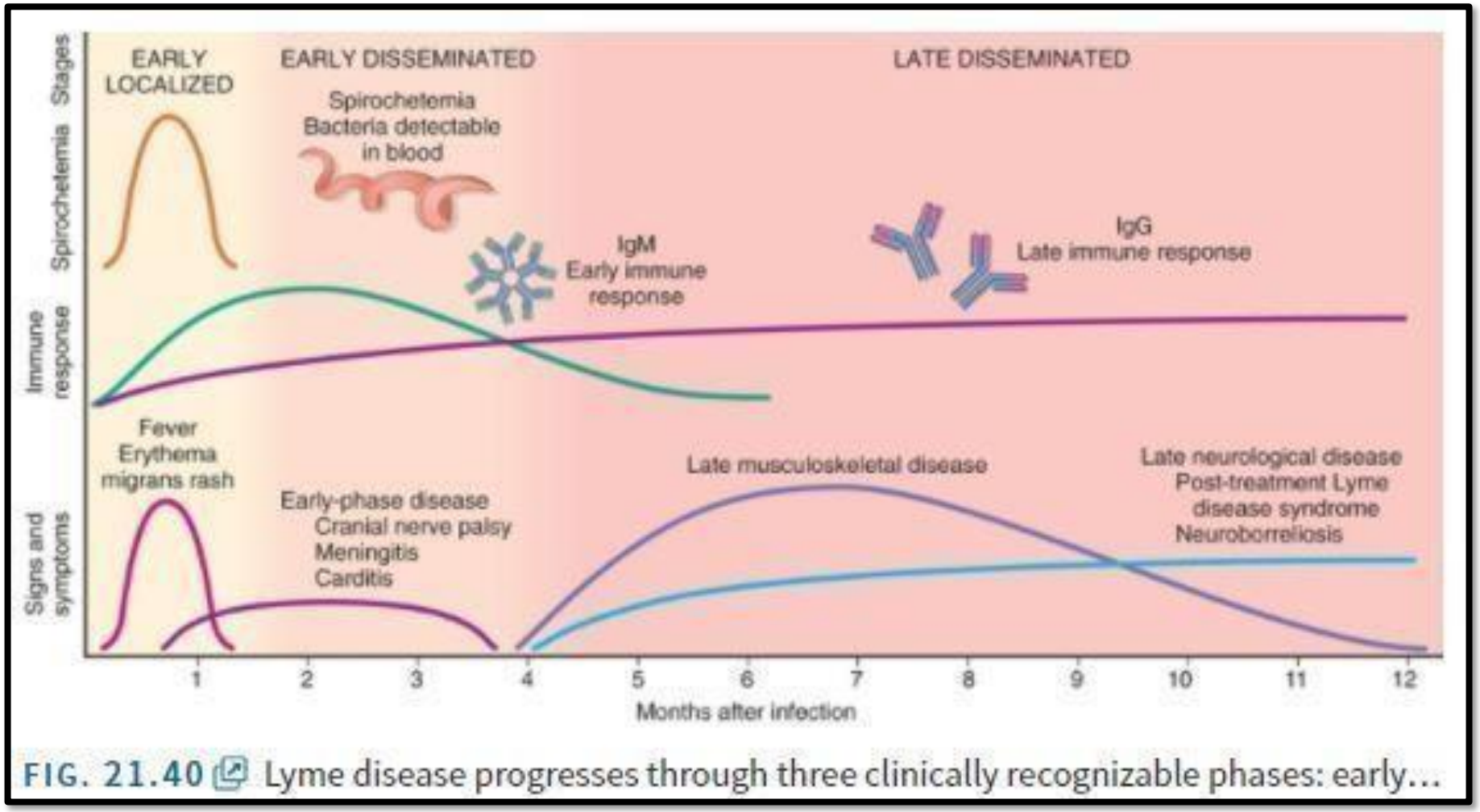


FIG. 21.40 Lyme disease progresses through three clinically recognizable phases: early…

CRYSTAL-INDUCED ARTHRITIS:

- **Crystals deposited in joints causing disease**
- **Crystals triggers inflammatory reaction that destroys cartilage**
- **Endogenous crystals:**
  - **Monosodium urate, MSU (GOUT)**

    Calcium pyrophosphate dehydrogenase, CPPD (PSEUDOGOUT)

GOUT: لڤوس

- **Transient attacks of arthritis, mainly big toe, triggered by deposition of MSU crystals**
- **Uric acid: purine metabolite; increased production or decreased excretion from kidney**
- **With hyperuricemia, risk increases with: 20-30 years of age, obesity, alcohol, genetic predisposition, drugs (thiazides)**

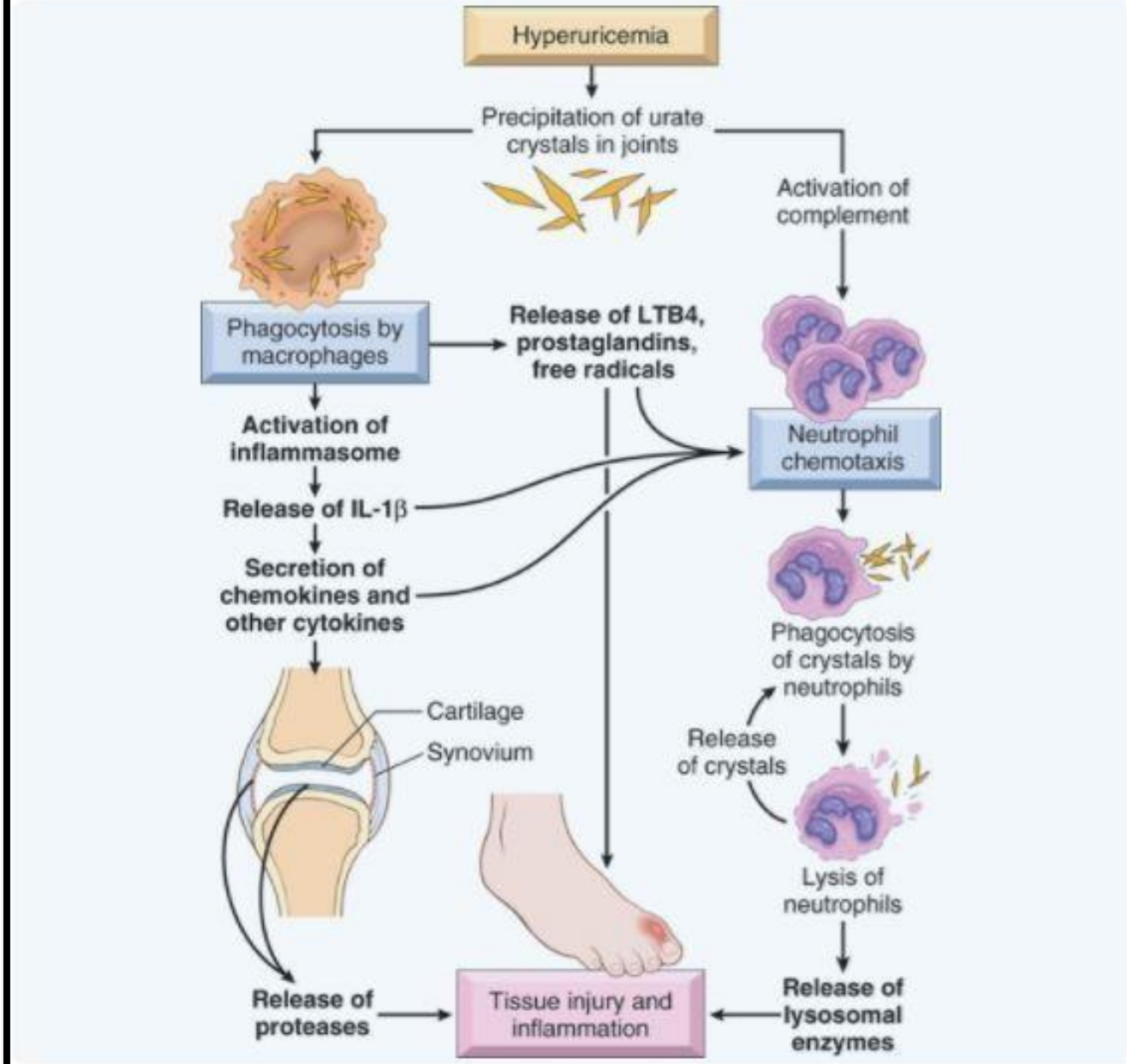
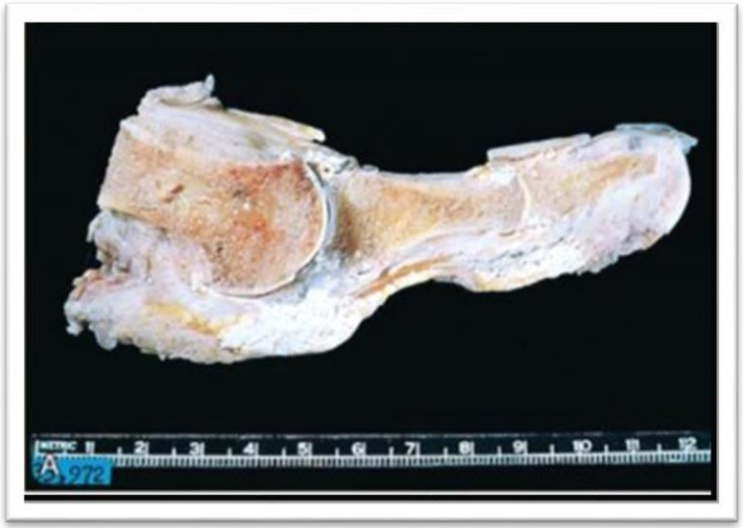
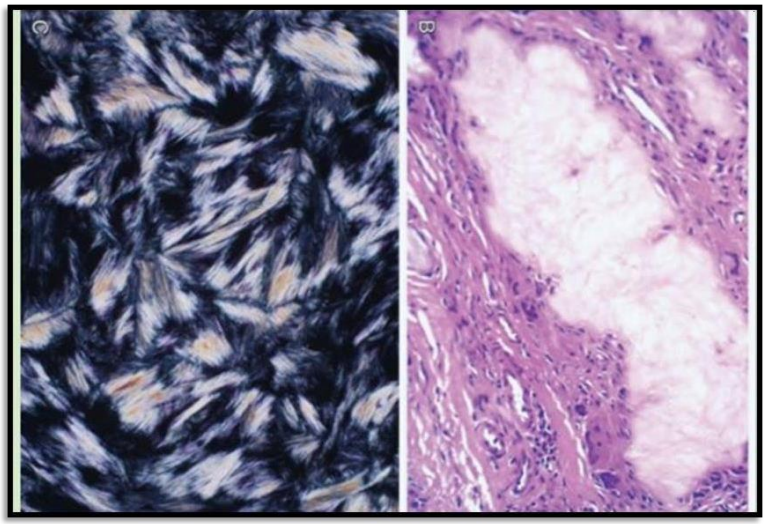


FIG. 21.41 Pathogenesis of acute gouty arthritis. Urate crystals are phagocytosed by m…

MORPHOLOGIC CHANGES OF GOUT:

Acute arthritis	**Dense inflammation of synovium, MSU crystals in neutrophils, -ve birefringent**
Chronic tophaceous arthritis	**Repetitive attacks & crystals deposition in the joint; thick synovium, pannus**
Tophi in various sites	**Cartilage, ligaments, bursae and tendons**
Gouty nephropathy	**MSU crystals deposition in kidney; nephrolithiaisis & pyelonephritis**

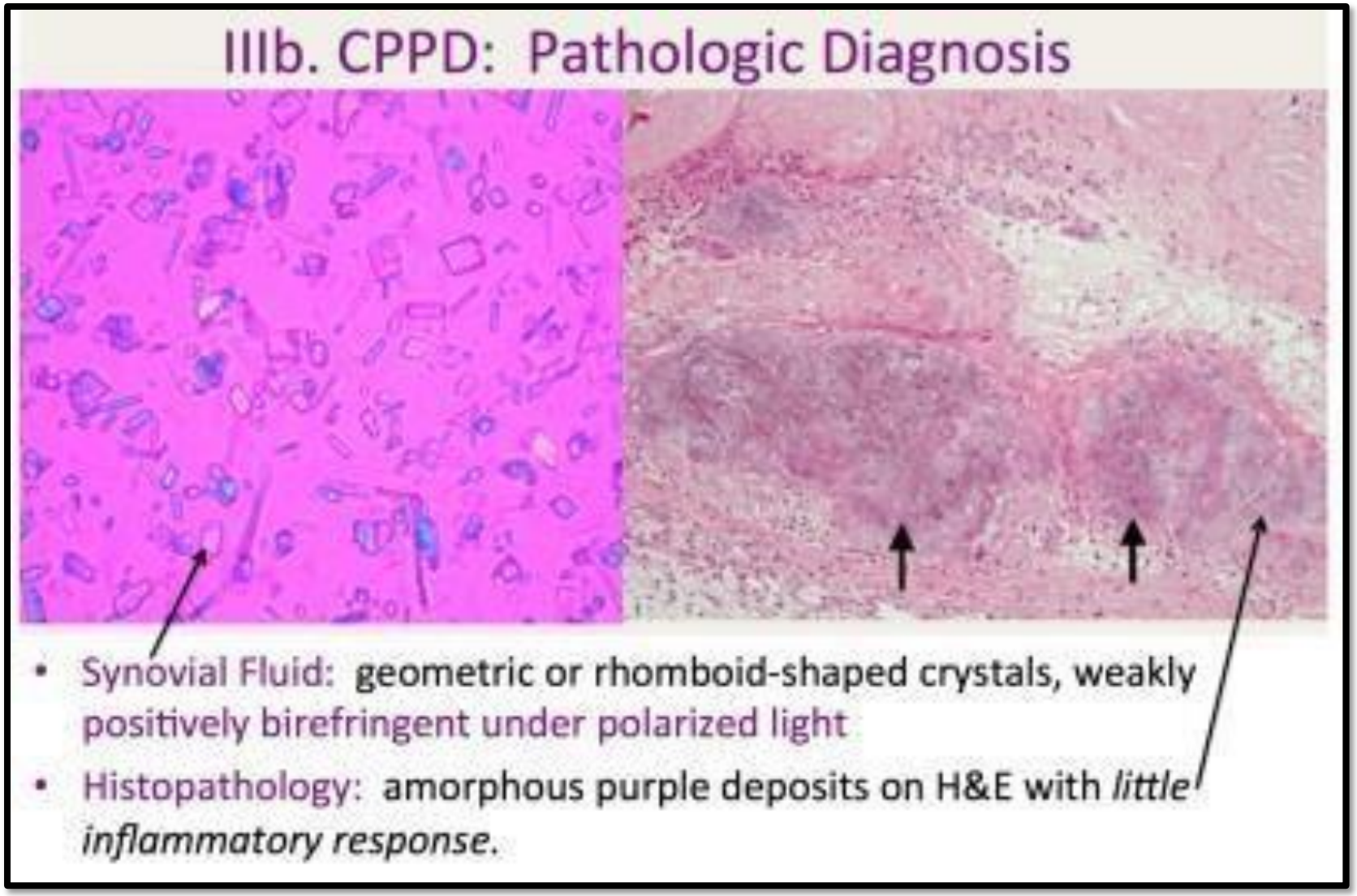




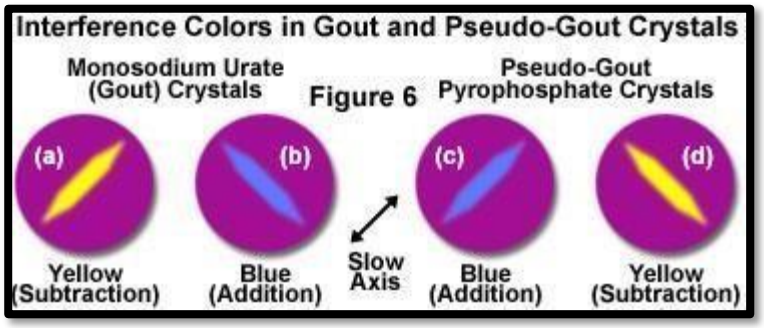
PSEUDOGOUT:

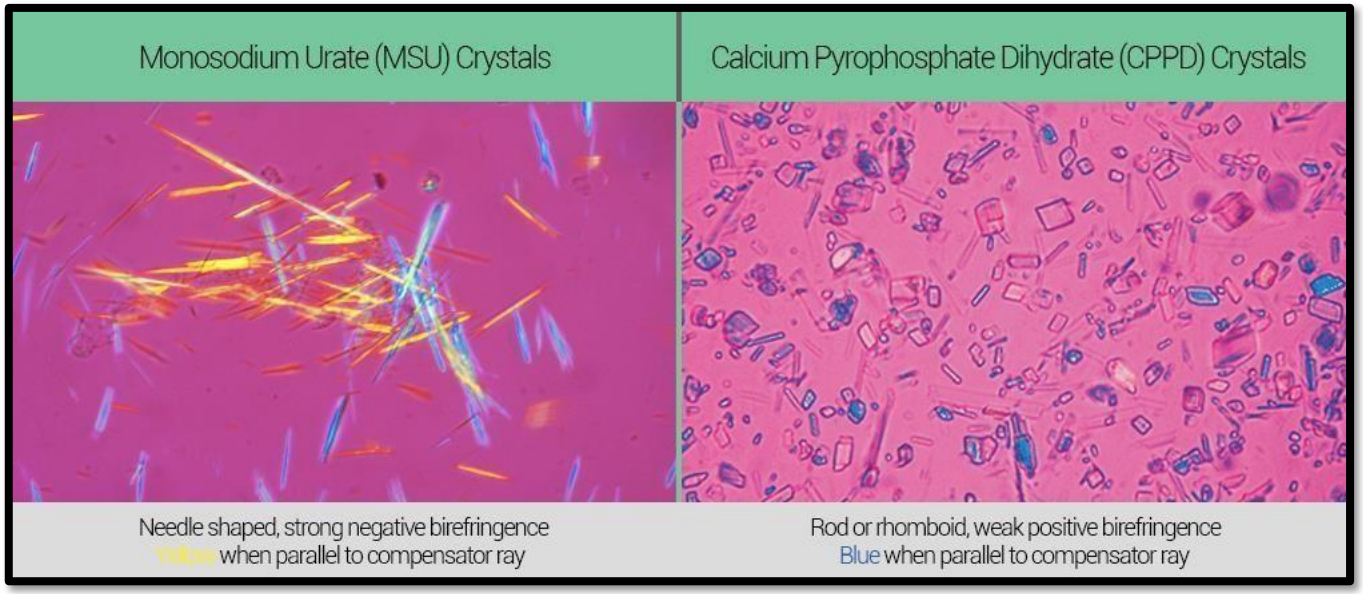
- **> 50 years; increase with age**
- **Idiopathic (genetic) or secondary**
- **CPPD crystal induced arthritis via triggering inflammatory reaction**
- **Secondary: DM, previous joint damage, HPTH, hemochromatosis**
- **Acute, subacute and chronic forms**
- **Trx: supportive, no preventive measures so far**

PSEUDOGOUT:


IIIb. CPPD: Pathologic Diagnosis
• Synovial Fluid: geometric or rhomboid-shaped crystals, weakly positively birefringent under polarized light
• Histopathology: amorphous purple deposits on H&E with *little inflammatory response*.

NEGATIVE VS POSITIVE BIERFRINGENCE





Summary

Arthritis

- **Osteoarthritis (OA, degenerative joint disease)**, the most common disease of joints, is a degenerative process of articular cartilage in which matrix breakdown exceeds synthesis. Inflammation is minimal and typically secondary. Local production of inflammatory cytokines may contribute to the progression of joint degeneration.
- **Rheumatoid arthritis (RA)** is a chronic autoimmune inflammatory disease that affects mainly small joints, but can be systemic. RA is caused by a cellular and humoral immune response against self-antigens, particularly citrullinated proteins. TNF plays a central role and antagonists against TNF are of clinical benefit.
- **Seronegative spondyloarthropathies** are a heterogeneous group of likely autoimmune arthritides that preferentially involve the sacroiliac and vertebral joints and are associated with HLA-B27.
- **Suppurative arthritis** describes direct infection of a joint space by bacterial organisms.
- **Lyme disease** is a systemic infection by *Borrelia burgdorferi*, which manifests, in part, as an infectious arthritis, possibly with an autoimmune component in chronic stages.
- **Gout and pseudogout** result from inflammatory responses triggered by precipitation of urate or calcium pyrophosphate, respectively.

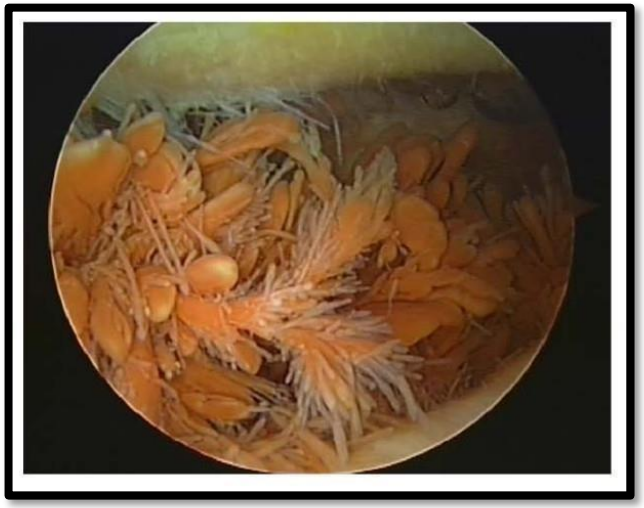
Lecture 9

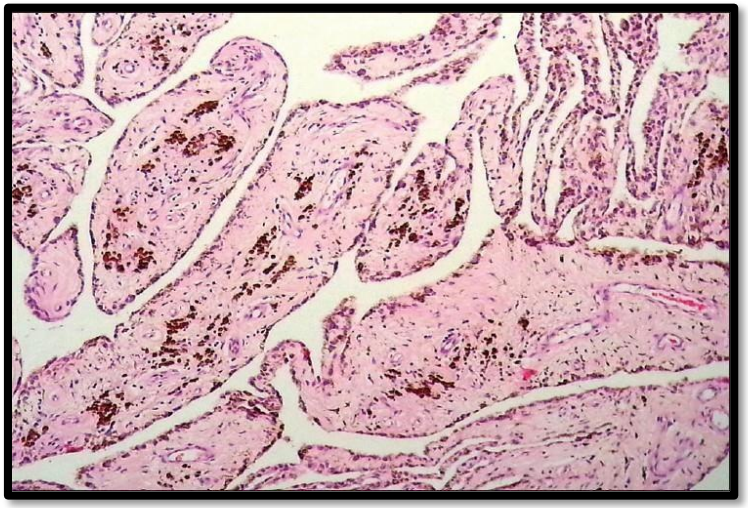
JOINT TUMORS & TUMORLIKE CONDITIONS:

- **Joint tumors are rare**
- **Ganglion cyst and tenosynovial giant cell tumor are the most frequent**
- **Ganglion cyst: common condition; close to a joint, dorsum of wrist; not true cyst, no communication with synovial joint; may cause pressure pain; treated by surgical removal**
- **True synovial cyst (Baker cyst around the knee): herniation process**

TENOSYNOVIAL GIANT CELL TUMOR:

- **Benign neoplasm of synovium**
- **Diffuse (pigmented villonodular synovitis, PVNS, large joints) or localized small hands tendons**
- **T(1;2)(p13q;37); affecting type IV collagen α-3**



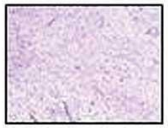
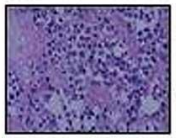
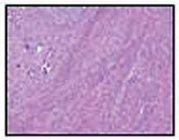
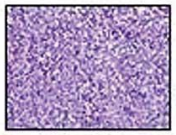


SOFT TISSUE TUMORS:

- **Benign >>>>>>malignant**
- **Incidence: 1% and cause 2% cancer death**
- **Sarcomas are aggressive and metastasize mainly to lungs, hematogenous spread**
- **Most are in extremities (thigh)**
- **Most are sporadic; very few arise from tumor suppressor gene mutations (NF1, Gardner syndrome, Li-Fraumeni syndrome, Osler-Webber-Rendu Syndrome)**
- **Few occur after exposure to radiation, burns &**

SOFT TISSUE TUMORS:

- **No precursor lesions; theory that they arise from pluripotent mesenchymal stem cell which acquire somatic mutation**
- **15-20% simple karyotype, single signature mutation (Ewing and synovial sarcoma)**
- **80-85% complex karyotype (genomic instability), LMS and pleomor. Sarcoma**
- **Wide range (benign-highly malignant)**
- **Diagnosis, grade and stage are all important**

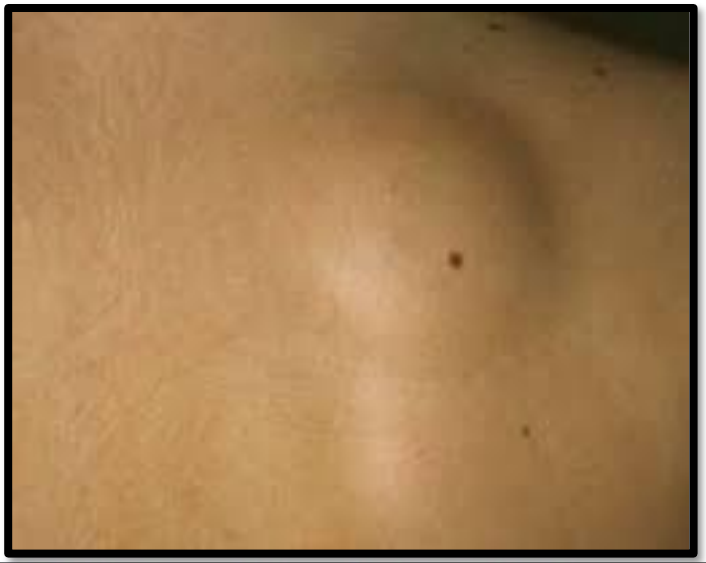
DIFFERENTATION	Subtypes	Chromosomal traslocations	Fusion trascripts
 ADIPOCYTIC TUMORS	*Lipoblastoma*:	t(7;8)(q31;q13); t(8;8)(q24;q13)	PLAG1-COL1A2;PLAG1-HAS2
	Myxoid liposarcoma	t(12;16)(q13;p11); t(12;22)(q13;q12)	CHOP-TLS; CHOP-EWS
 FRIBLOBLASTIC/ MYOFIBROBL.TUMORS	*Inflammatory myofibroblastic tumor*	t(1;2)(q25;p23); t(2;19)(p23;q13); t(2;17)(p23;q23)	TPM3-ALK; ALK-TPM4; ALK-CLTC
	Infantile fibrosarcoma	t(12;15)(p13;q25)	ETV6-NTRK3
	Dermatofibrosarcoma protuberans/ Giant cell fibroblastoma	t(17;22)(q22;q13)	COL1A1-PDGFB
 SKELETAL MUSCLE TUMORS	*Alveolar rhabdomyosarcoma*	t(2;13)(q35;q14); t(1;13)(p36;q14)	PAX3-FKHR; PAX7-FKHR
 TUMORS OF UNCERTAIN DIFFERENTIATION	*Angiomatoid fibrous histiocytoma*	t(12;22)(q13;q12); t(12;16)(q13;p11)	
	Synovial sarcoma	t(X;18)(p11.2;q11.2)	SYT-SSX1/2/4
	Alveolar soft part sarcoma	t(X;17)(p11;q25)	TFE3/ASPL
	Clear cell sarcoma	t(12;22)(q13;q12)	EWS-ATF1
	Extraskeletal myxoid chrondrosarcoma	t(9;22)(q22;q12); t(9;15)(q22;q21)	EWS-TEC; CHN-TFC12
	Desmoplastic small round cell tumor	t(11;22)(p13;q12)	EWS-WT1
 EWING SARCOMA		t(11;22)(q24;q12);t(21;22)(q22;q12); t(17;22)(q12;q12); t(7;22)(p22;q12);	FLI1-EWS; ERG-EWS E1AF-EWS; ETV1-EWS

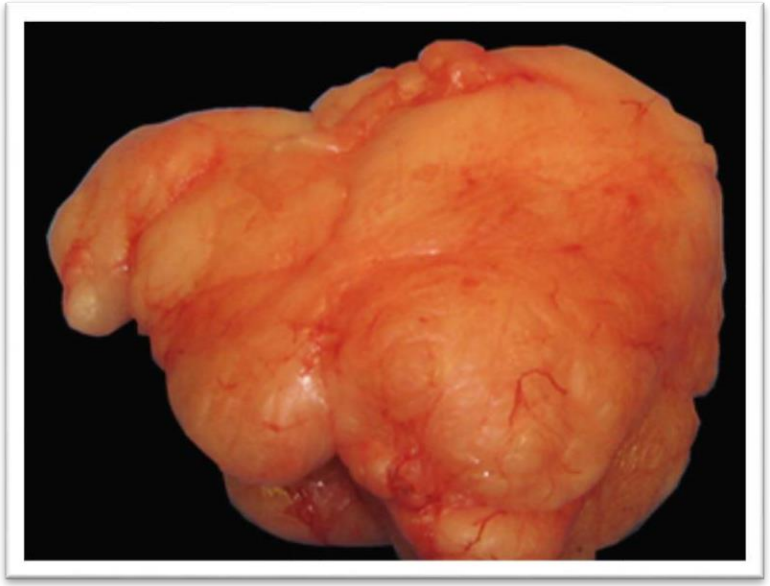
ADIPOSE TISSUE TUMORS:

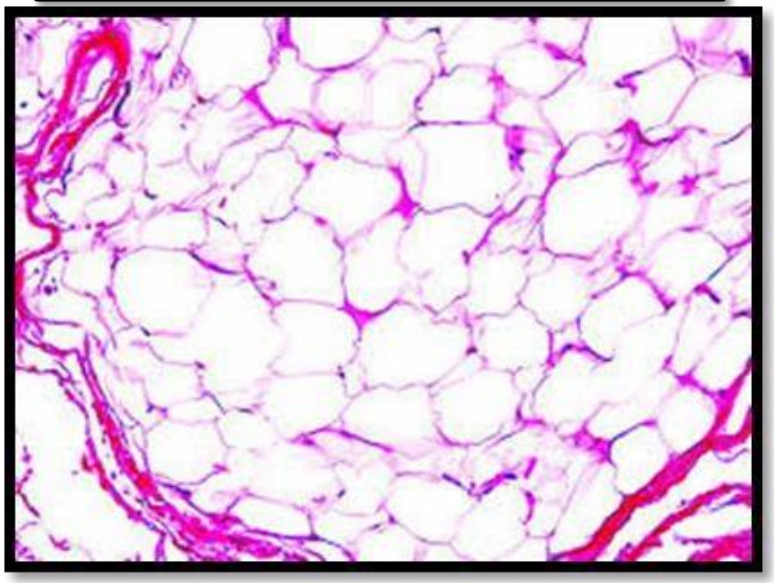
- **Most common soft T tumor**
- **Well-encapsulated, subcutis**
- **Mature fat cells**
- **Trx: excision**

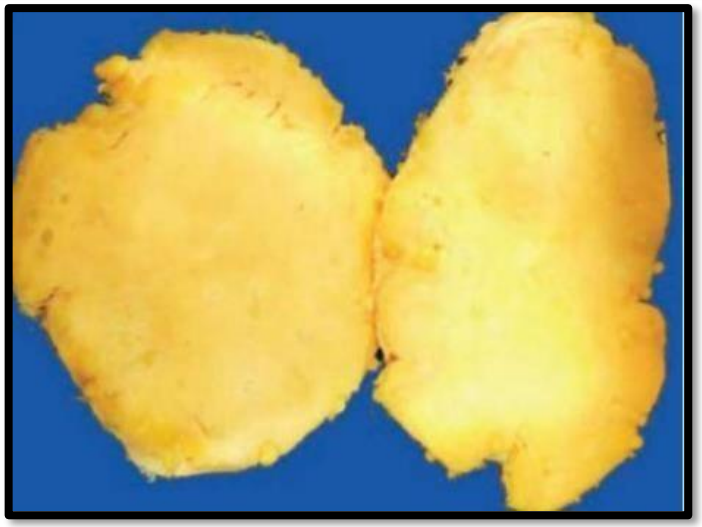
- **Most common sarcomas in adults. >50 years**
- **Extremities and retroperitoneum**
- **3 types:**
  - **WD (MDM2 gene chr 12)**
  - **Myxoid, t(12,16)**
  - **Pleomorphic (aggressive**

LIPOMA PATHOLOGIC FEATURES:

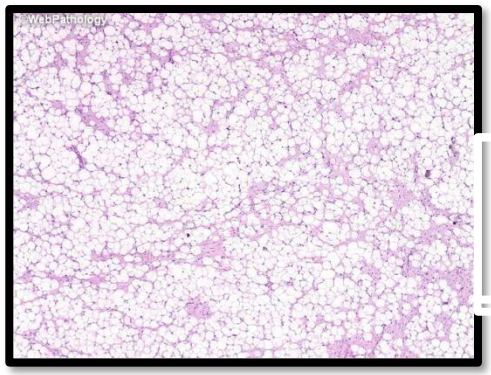




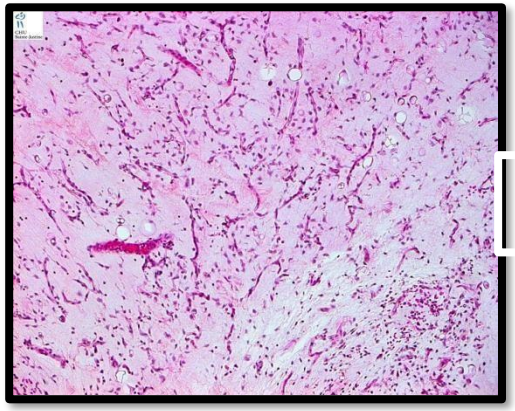




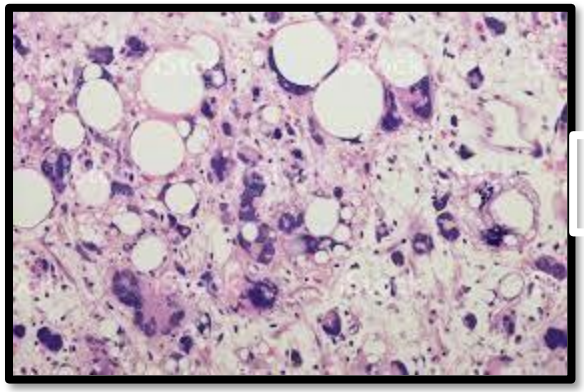
LIPOSARCOMA FEATURES:



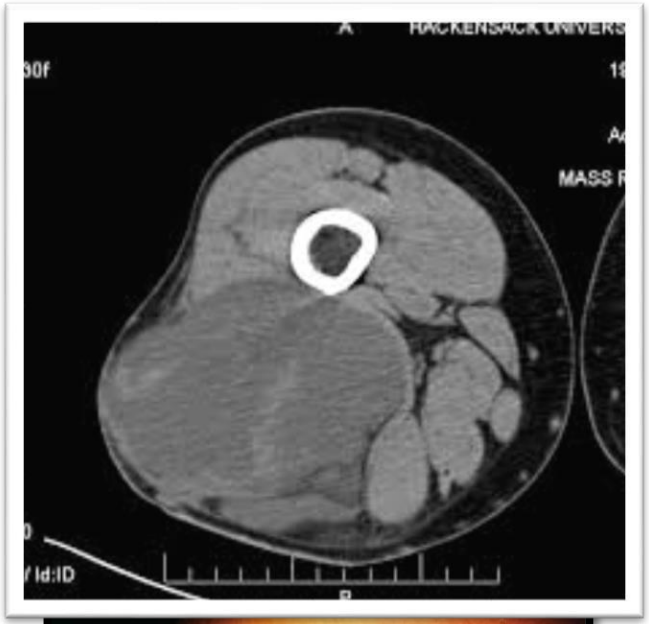
Well-differentiated

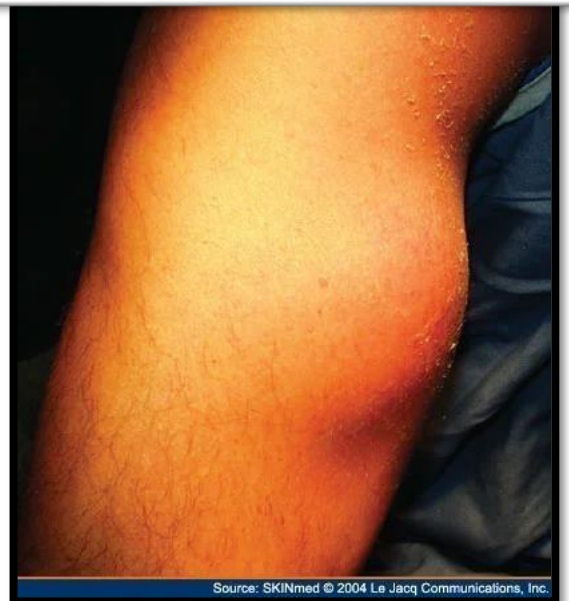


Myxoid



Pleomorphic





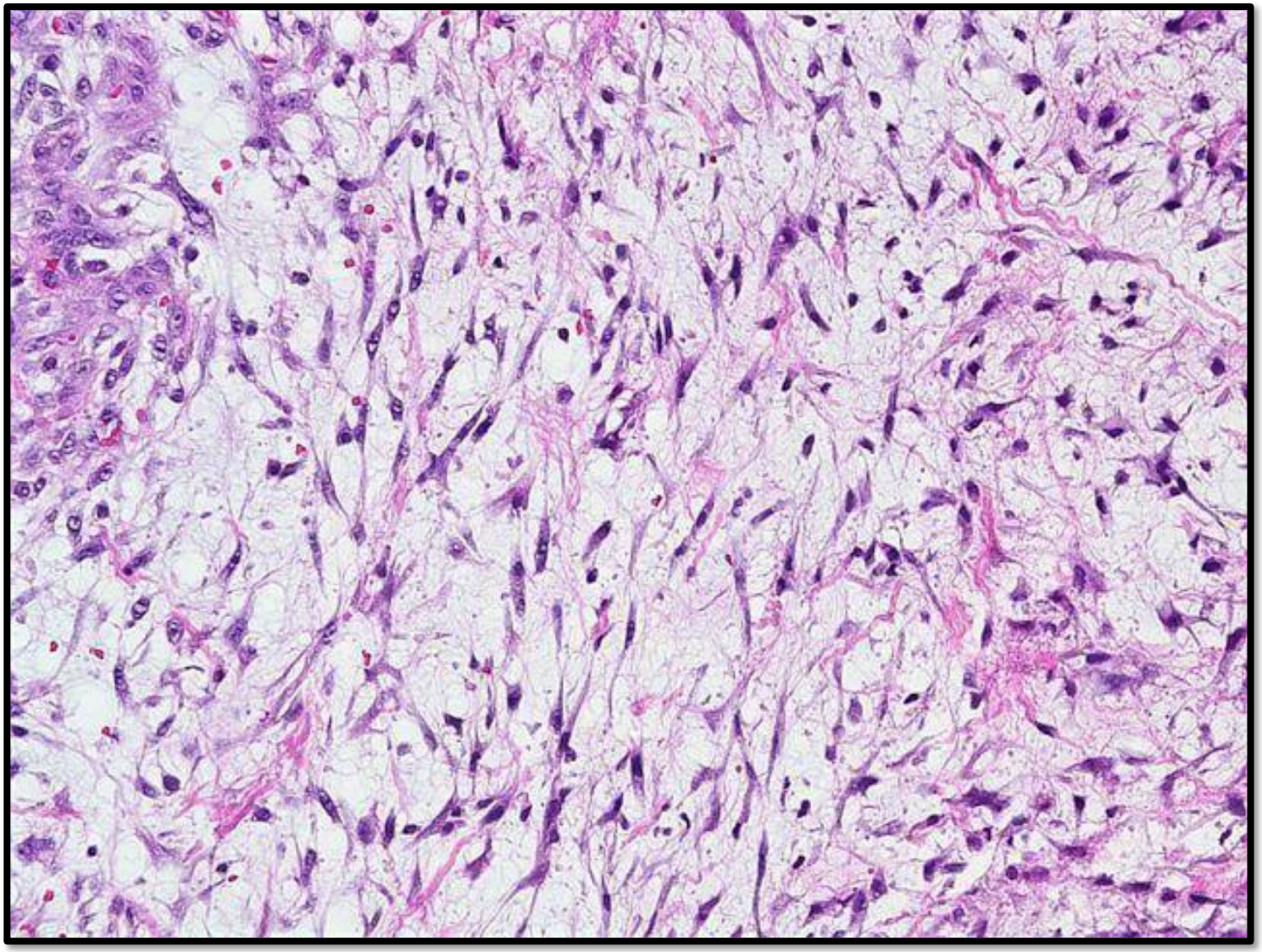
FIBROUS **TUMORS:**

- **Fibromas and Fibrosarcoma**
- **Fibromatoses:**
  - **Superficial**
  - **Deep (Desmoid tumor)**

NODULAR FASCIITIS:

- **Nodular fasciitis: thought to be reactive process**
- **Now, clonal, t(17;22) producing *MYH9-USP6* fusion gene**
- **Trauma history, recent rapid size increase**
- **Maybe self-limiting**
- **IMPORTANT: not to diagnose it malignant**
- **Culture-like histology**

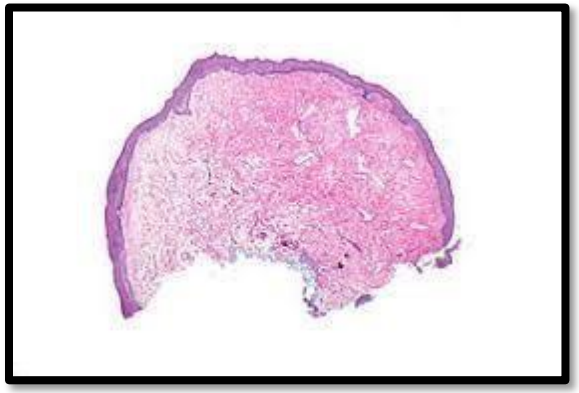
NODULAR FASCIITIS:

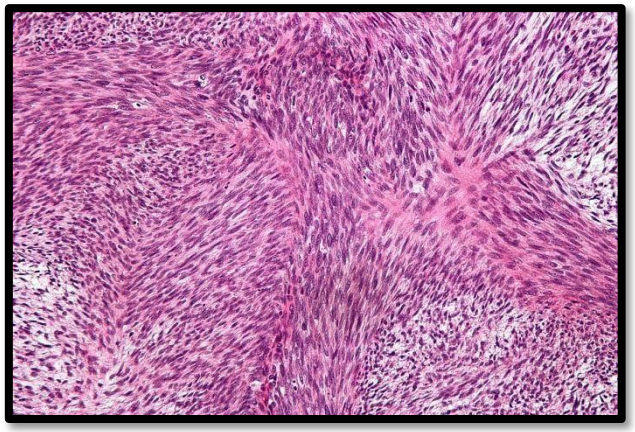


Lecture 10

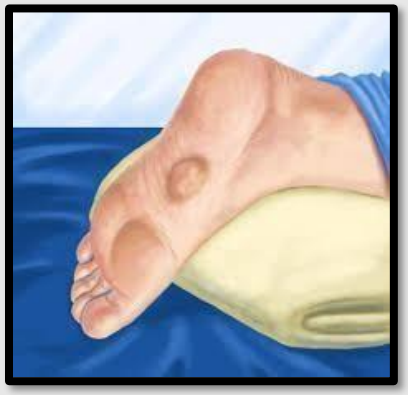
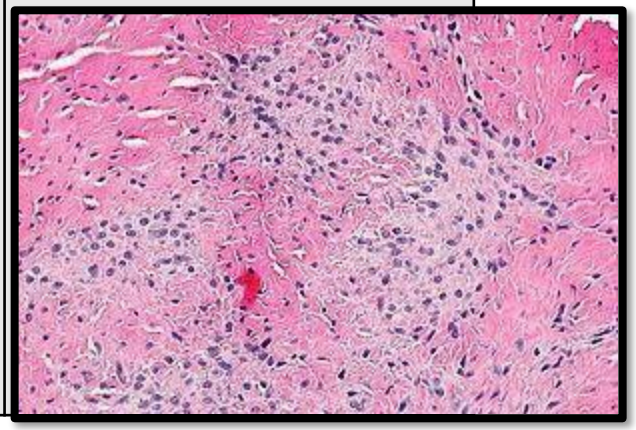
FIBROMAS AND FIBROSARCOMAS:

- **Fibromas: benign proliferation of fibroblasts, very common, skin and subcutaneous tissue**
- **Fibrosarcoma: malignant counterpart; usually superficial cutaneous tumors of fibroblasts, cellular, storiform pattern with increased mitosis**





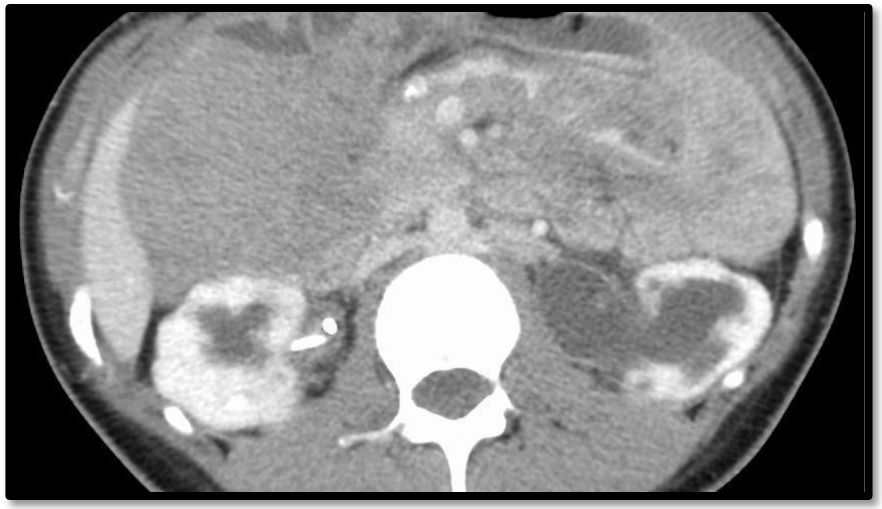
SUPERFICIAL FIBROMATOSES:

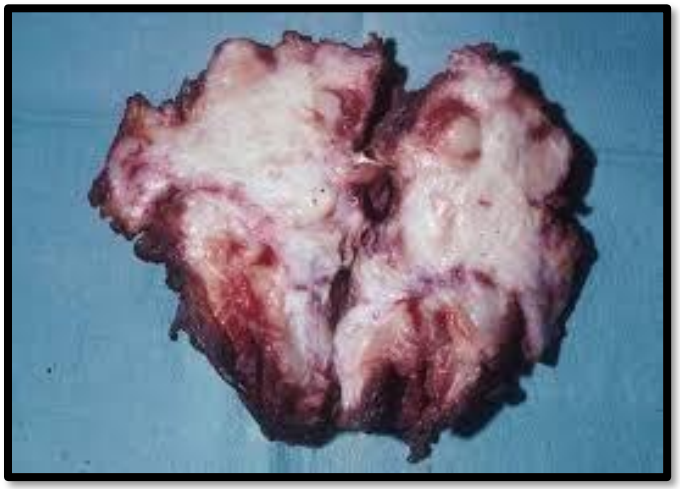
PALMAR (DUPUYTREN CONTRACTURE)	PLANTAR FIBROMATOSES	PENILE (PEYRONIE DISEASE)
Palmar fascia	Sole of foot	Dorsolateral aspect of the penis
		

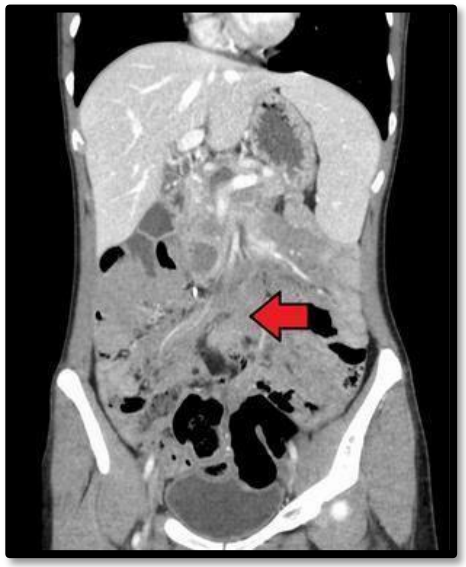
DEEP FIBROMATOSES (DESMOID TUMOR):

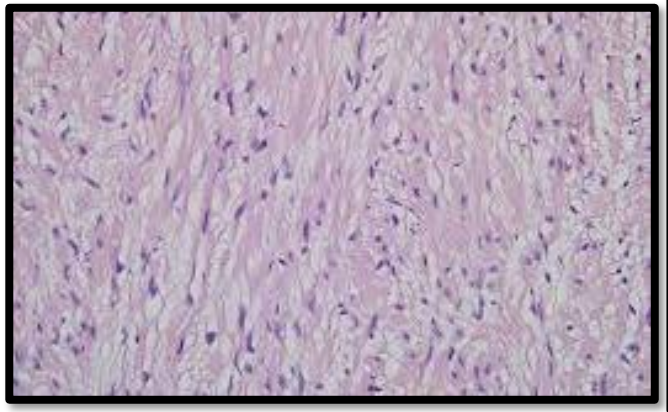
- **Deep infiltrative but bland fibroblastic proliferation; doesn't metastasize but recur**
- **20-30years, females more common**
- **Abdominal wall, mesentery and limbs**
- **Mutations in *CTNNB1* (β-catenin) or *APC* genes leading to increased Wnt signaling**
- **Mostly are sporadic; but patients with Gardner (FAP) syndrome are susceptible**
- **Complete excision is needed to prevent recurrence which is very common**
- **These tumors kill by local infiltration NOT metastasis**

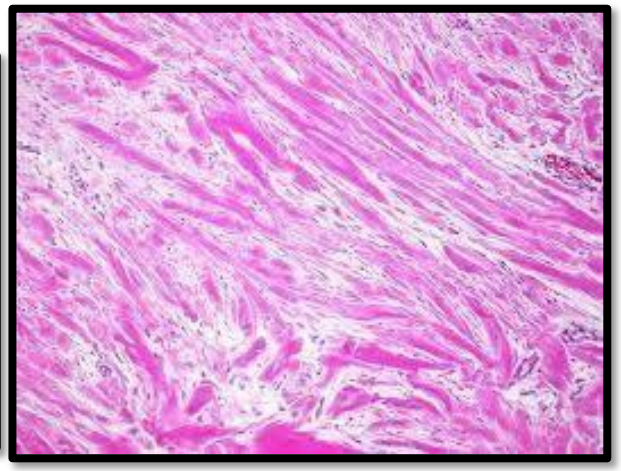
DEEP FIBROMATOSES (DESMOID TUMOR):





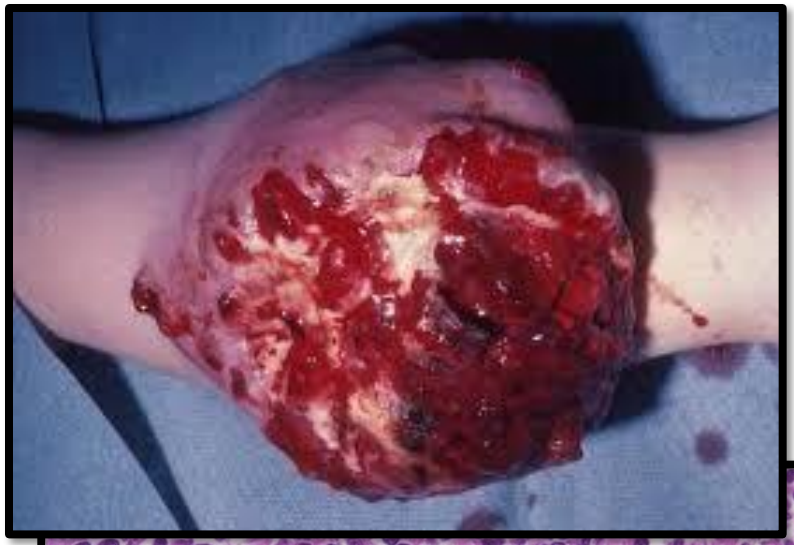


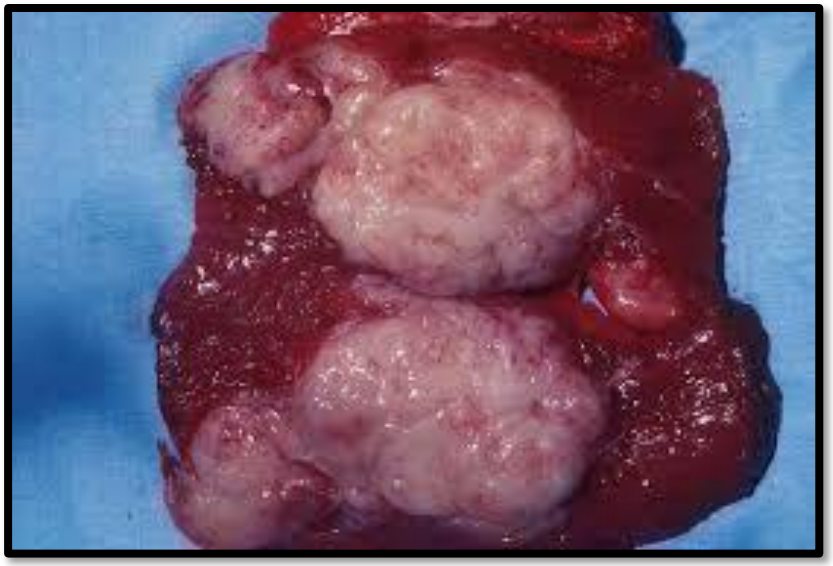


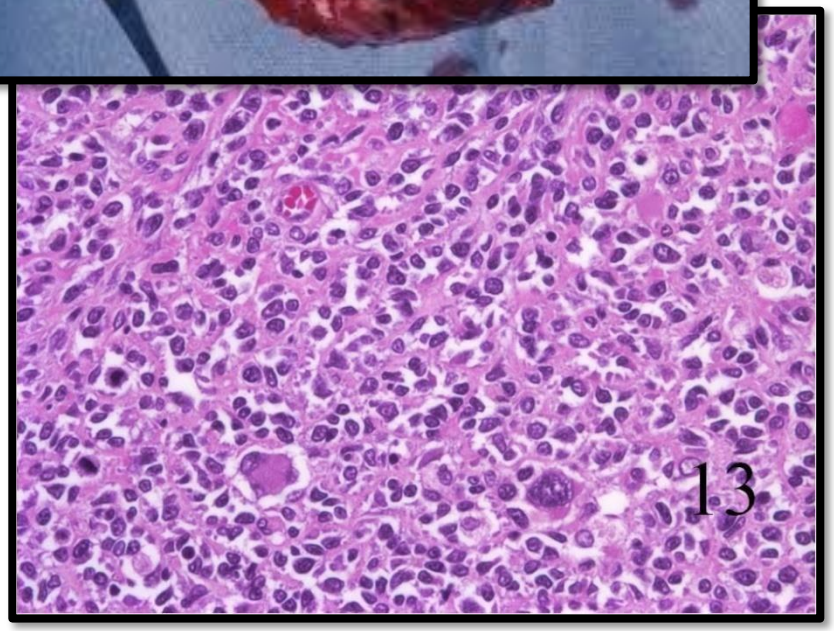


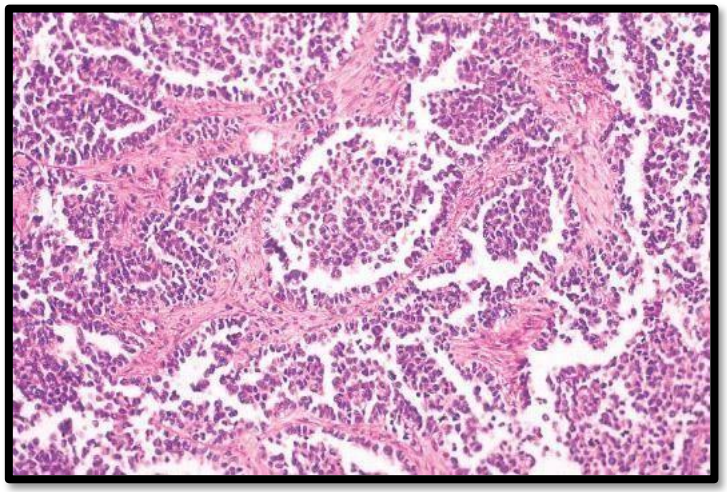
SKELETAL MUSCLE TUMORS:

- **Almost all malignant; except rhabdomyoma which is benign, rare, occurs with tuberous sclerosis**
- **Rhabdomyosarcoma (RMS) is the malignant prototype; most common child sarcoma**
- **3 types (embryonal 60%; alveolar 20%; pleomorphic 20%)**
- **Specific mutations are common**
- **Aggressive tumors; treated by surgery, CT +/-**





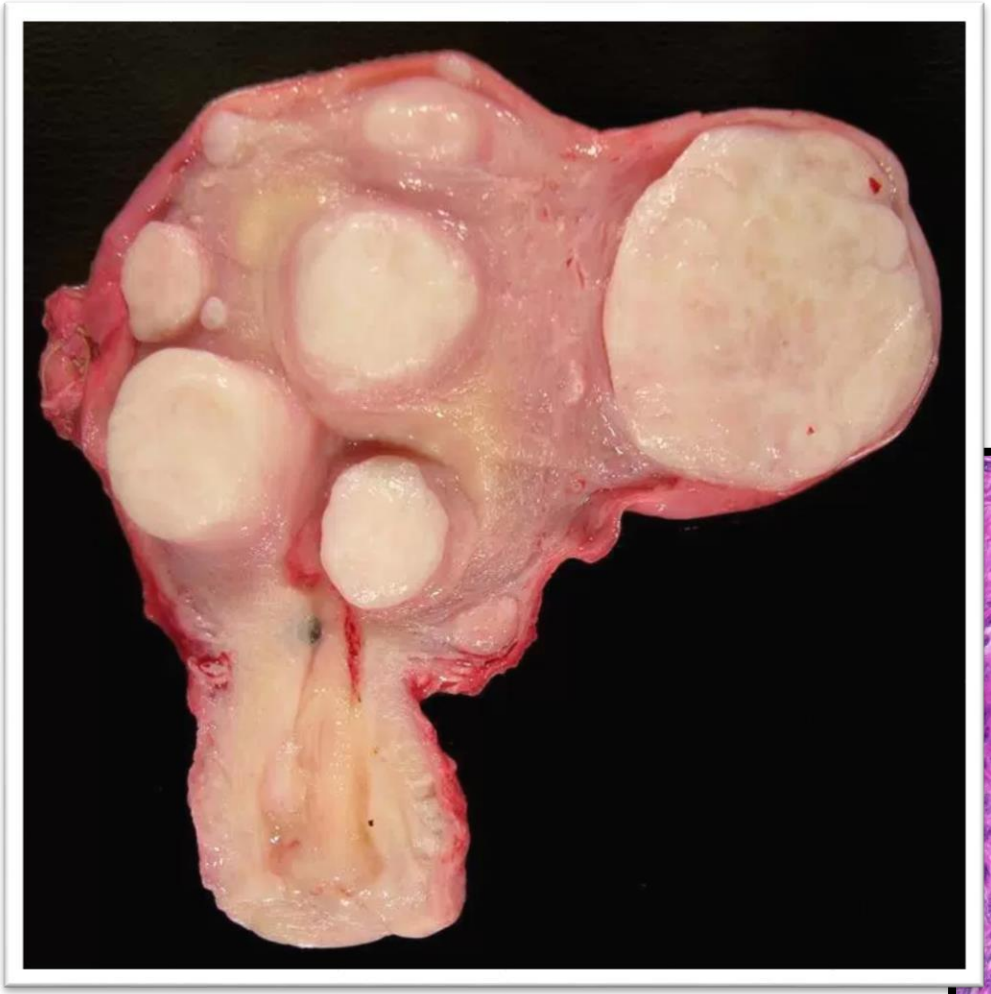


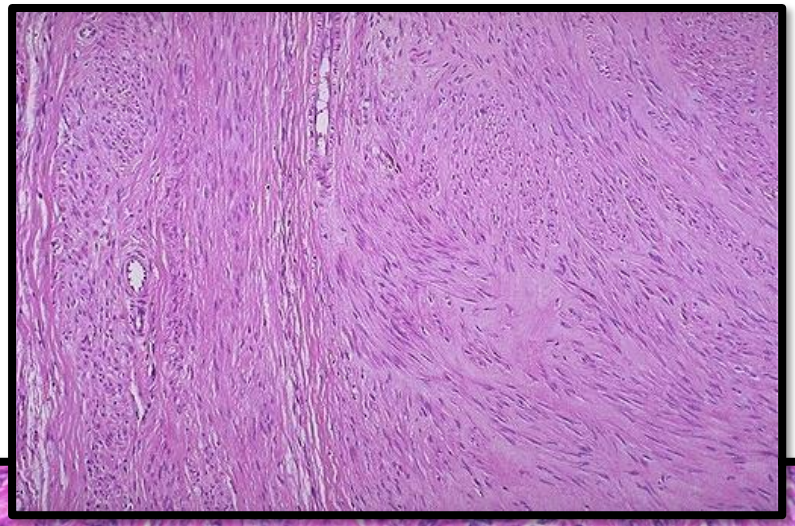


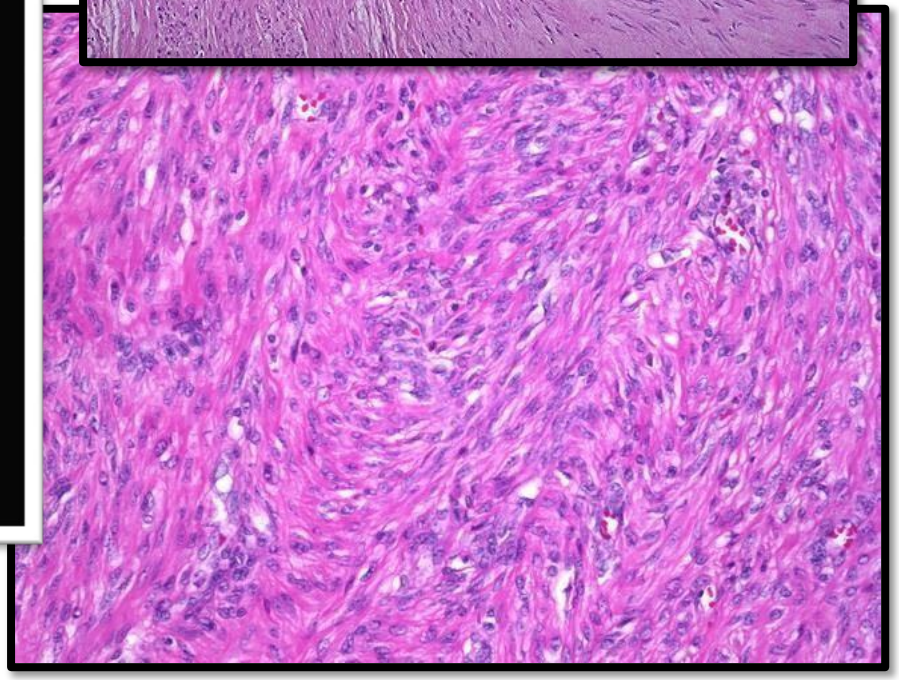
SMOOTH MUSCLE TUMORS:

- **Leiomyoma (benign) and leiomyosarcoma (malignant)**
- **Leiomyoma (LYM): very common; any site but mostly uterus (fibroid)…menorrhagia and infertility**
- **LYM vary in size and location**
- **Few can have specific mutations (Fumarate hydratase on chromosome 1q42.3)**

LEIOMYOMA FEATURES:



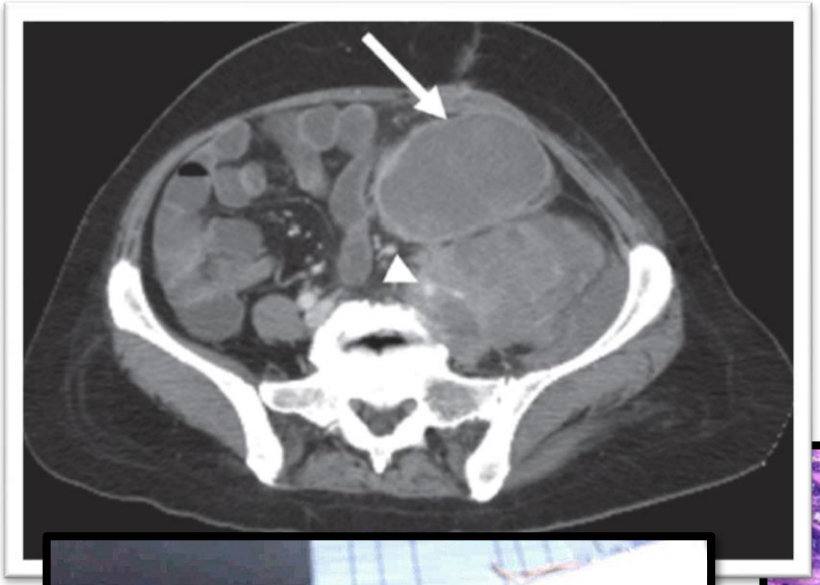


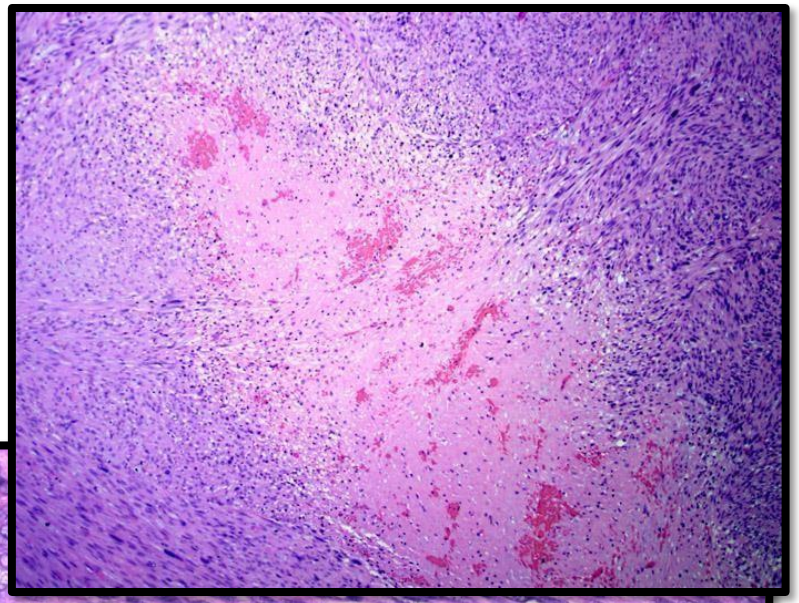


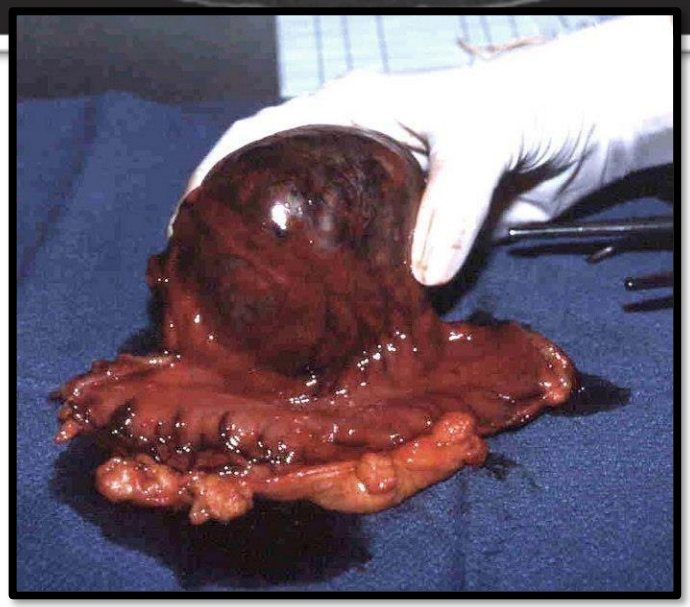
LEIOMYOSARCOMA:

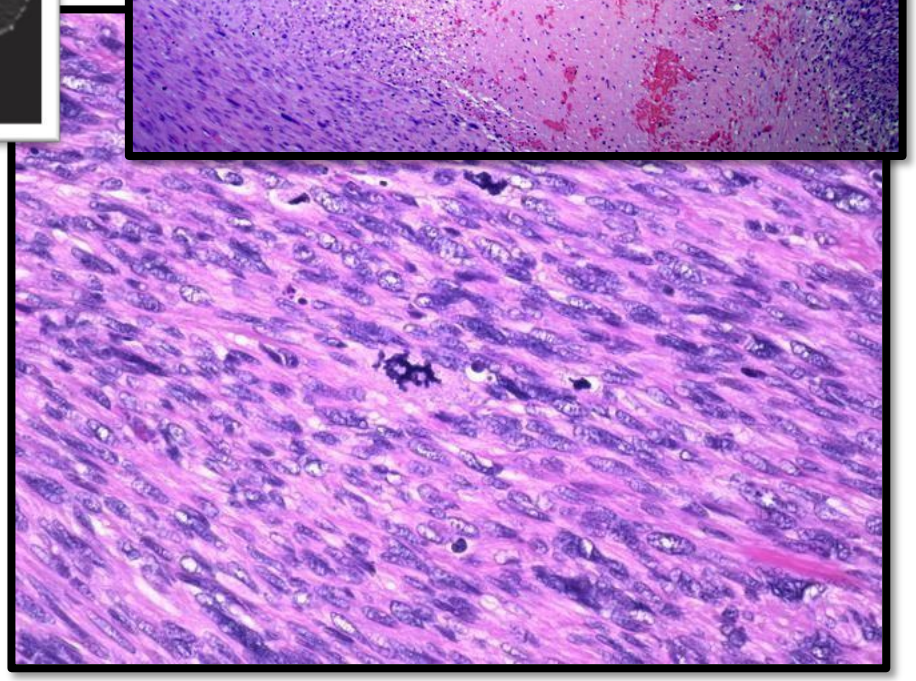
- **10-20% of soft tissue sarcomas**
- **Adults; more in females**
- **Deep soft tissue, extremities and retroperitoneum or from great vessels**
- **Complex genotypes**
- **Hemorrhage, necrosis, increased mitosis and infiltration of surrounding tissue**
- **Trx: depends on location, size and grade**

LEIOMYOSARCOMA FEATYURES:









TUMORS OF UNCERTAIN ORIGIN:

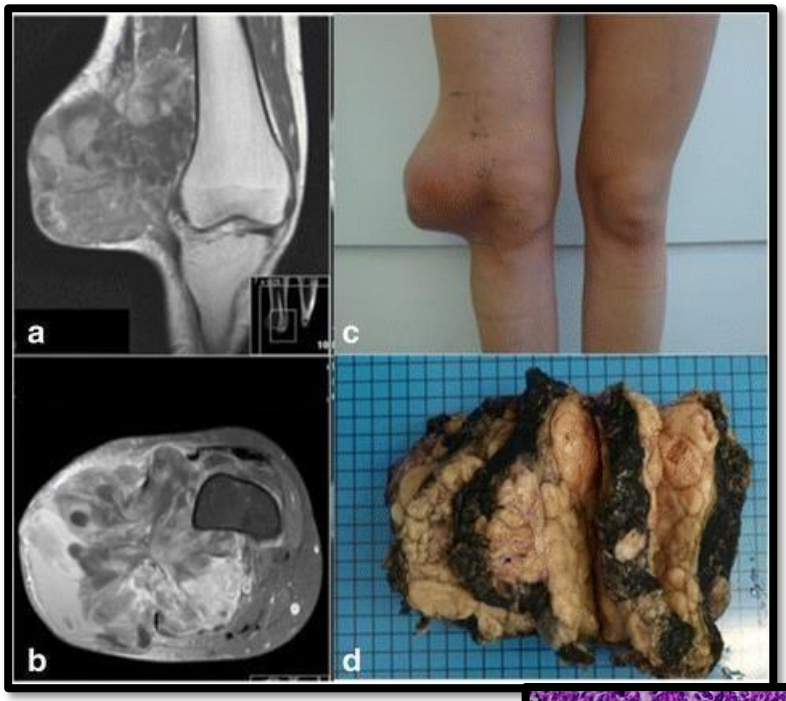
- **Uncertain mesenchymal lineage**
- **Synovial sarcoma**
- **Undifferentiated pleomorphic sarcoma**

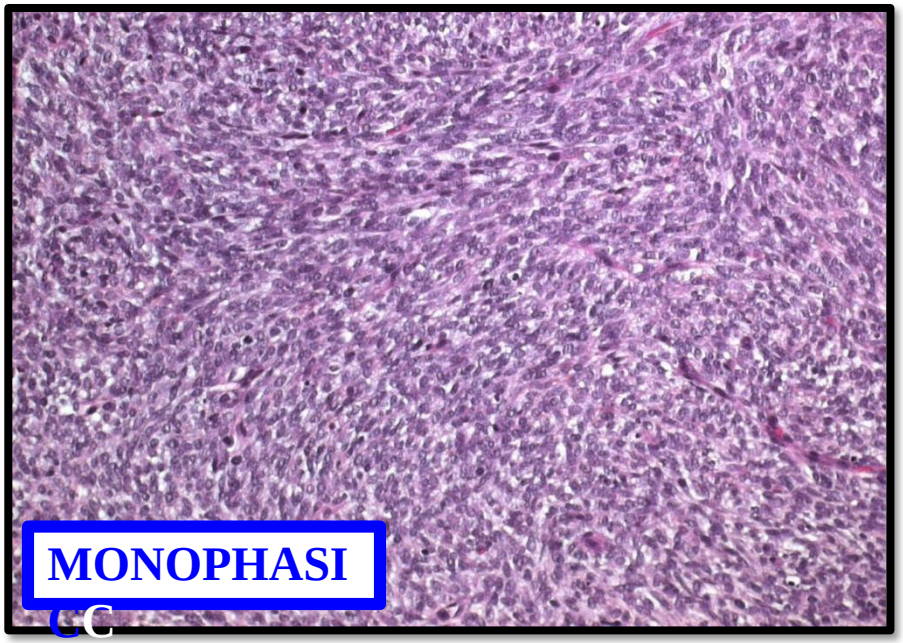
SYNOVIAL SARCOMA:

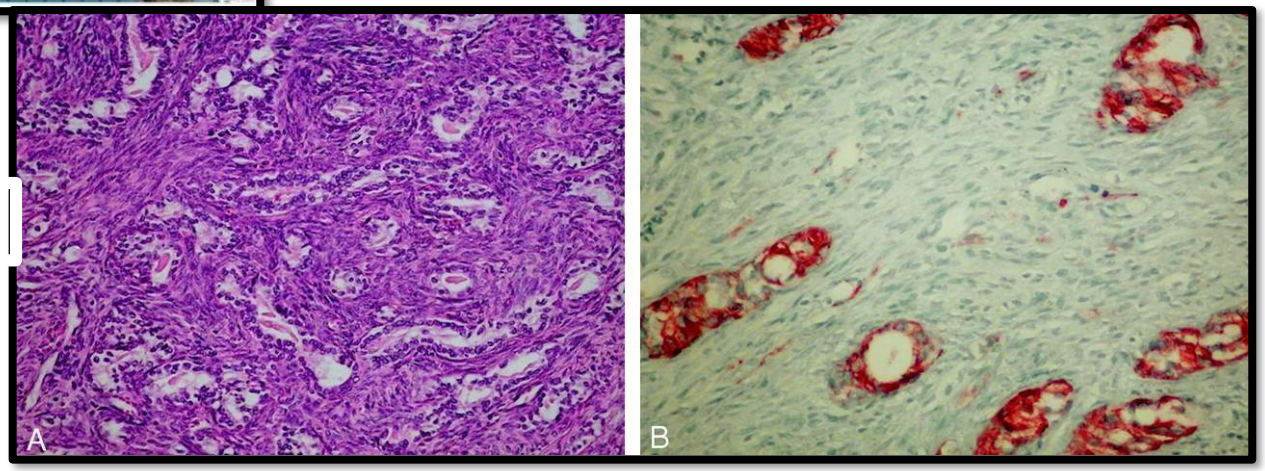
- Name is misnomer
- 10% of all soft tissue sarcomas; 20-40s age
- Deep seated mass of long history

- **T(X;18)(p11;q11 → fusion genes *SS18***
- **Monophasic (only spindle cells) or biphasic (spindle cells and glands)**
- **Trx: aggressive with limb sparing excision + CT**
- **5 year survival 25-65% depending on stage**
- **Metastasis: lung and lymph nodes**

SYN. SA. FEATURES:



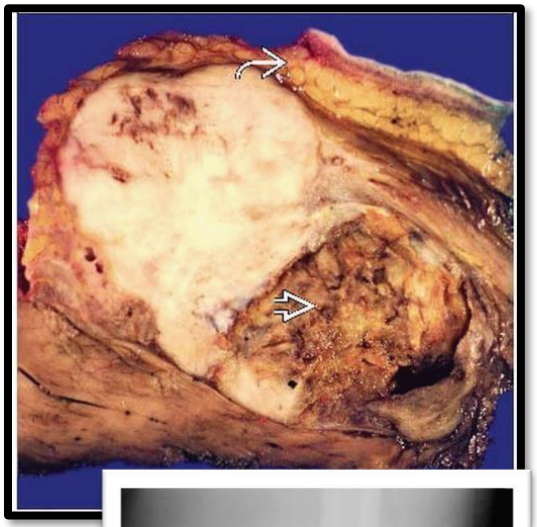


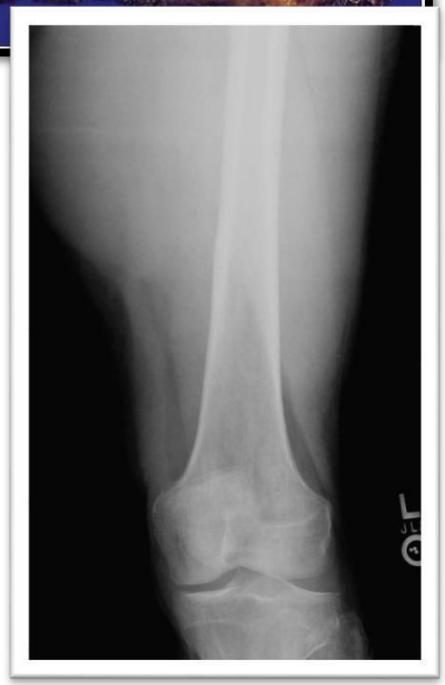


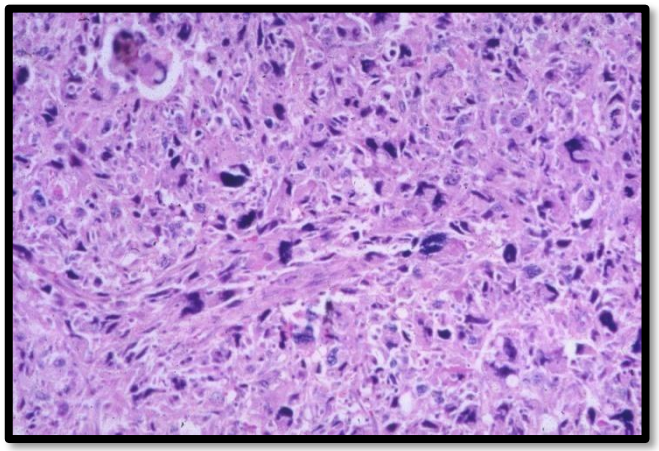
UNDIFFERENTIATED PLEOMORPHIC SARCOMA (UPS):

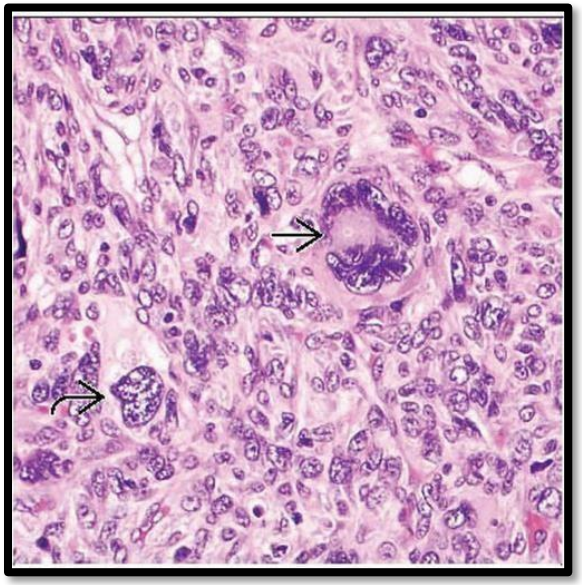
- **High grade mesenchymal sarcomas of pleomorphic cells that lack cell lineage**
- **Deep soft tissue and extremities**
- **Old terminology: malignant fibrous histiocytoma (MFH)…not anymore**
- **Aneuploid and complex genetic abnormalities**
- **Large tumors; anaplastic and pleomorphic cells, abnormal mitoses, necrosis**
- **Trx: aggressive with surgery and adjuvant CT +/- RT; poor prognosis**

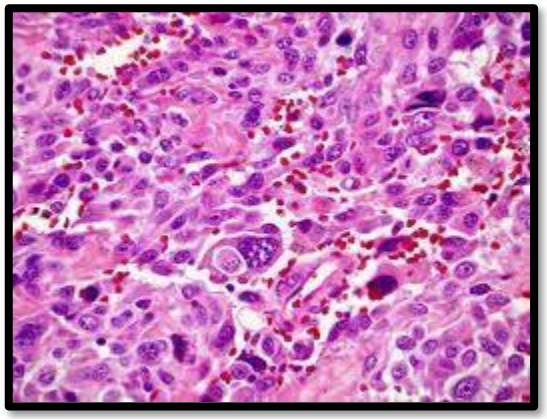
UPS FEATURES:











Summary

Soft Tissue Tumors

- The category of soft tissue neoplasia describes tumors that arise from non-epithelial tissues, excluding the skeleton, joints, central nervous system, and hematopoietic and lymphoid tissues. A sarcoma is a malignant mesenchymal tumor.
- Although all soft tissue tumors probably arise from pluripotent mesenchymal stem cells, rather than mature cells, they can be classified as
  - Tumors that recapitulate a mature mesenchymal tissue (e.g., fat). These can be further subdivided into benign and malignant forms.
  - Tumors composed of cells for which there is no normal counterpart (e.g., synovial sarcoma, UPS).
- Sarcomas with simple karyotypes demonstrate reproducible, chromosomal, and molecular abnormalities that contribute to pathogenesis and are sufficiently specific to have diagnostic use.
- Most adult sarcomas have complex karyotypes, tend to be pleomorphic, and are genetically heterogeneous with a poor prognosis.

GOOD

LUCK