Lecture 8

MSU crystals

GOUT: النقرس

- 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)

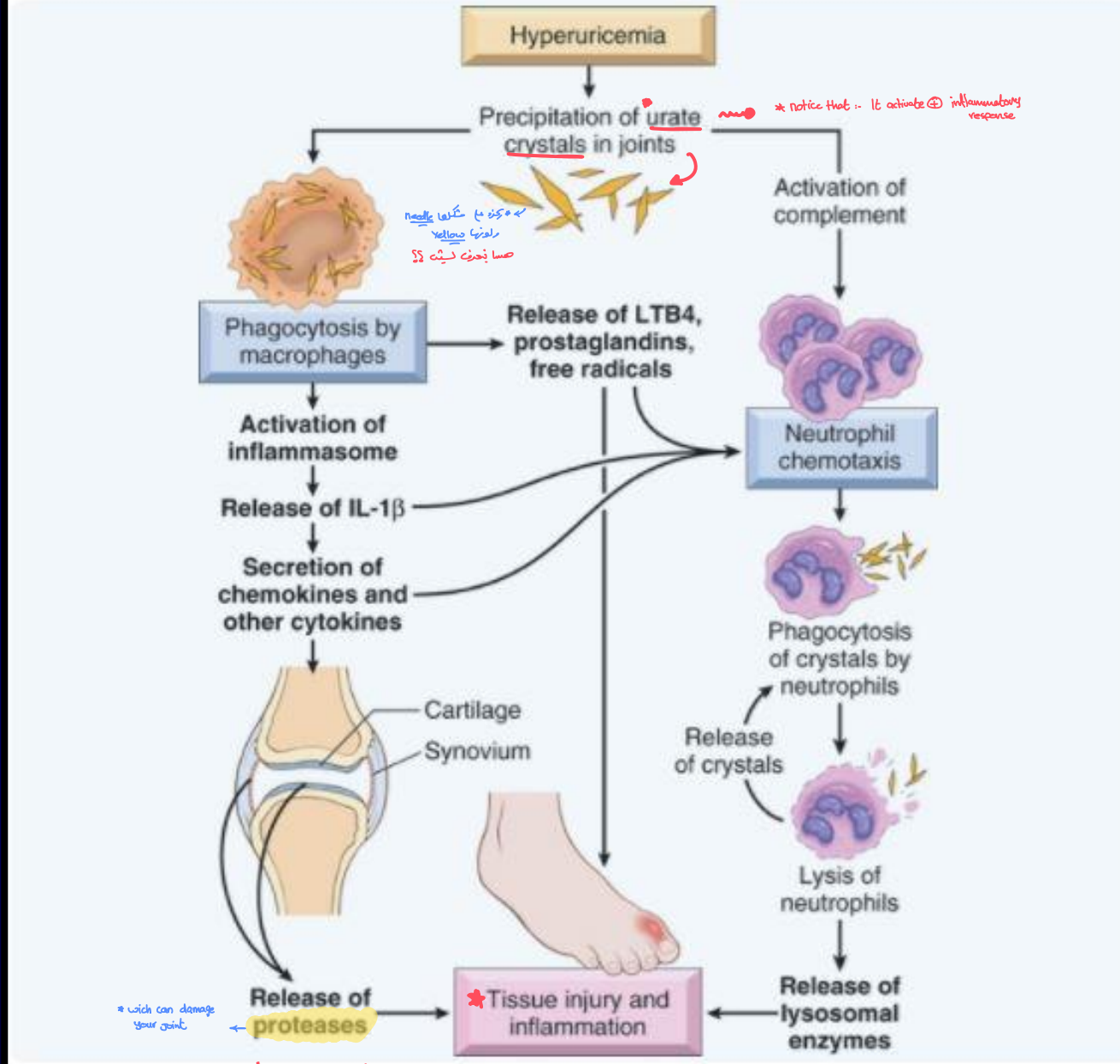
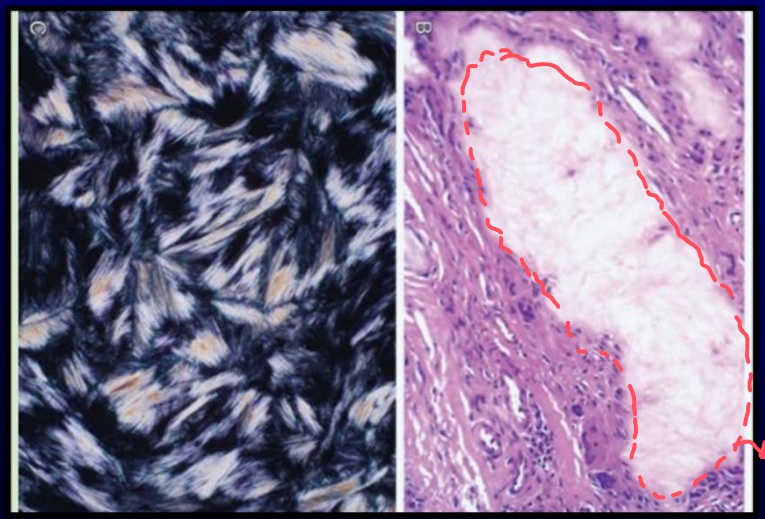


FIG. 21.41 Pathogenesis of acute gouty arthritis. Urate crystals are phagocytosed by m…

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 [around the joints]
Gouty nephropathy	MSU crystals deposition in kidney; nephrolithiaisis & pyelonephritis

Trx: life style modifications, NSAIDS & Colchicine in acute gout, Xanthine oxidase inhibitors (Allupurinol) in chronic and prevention

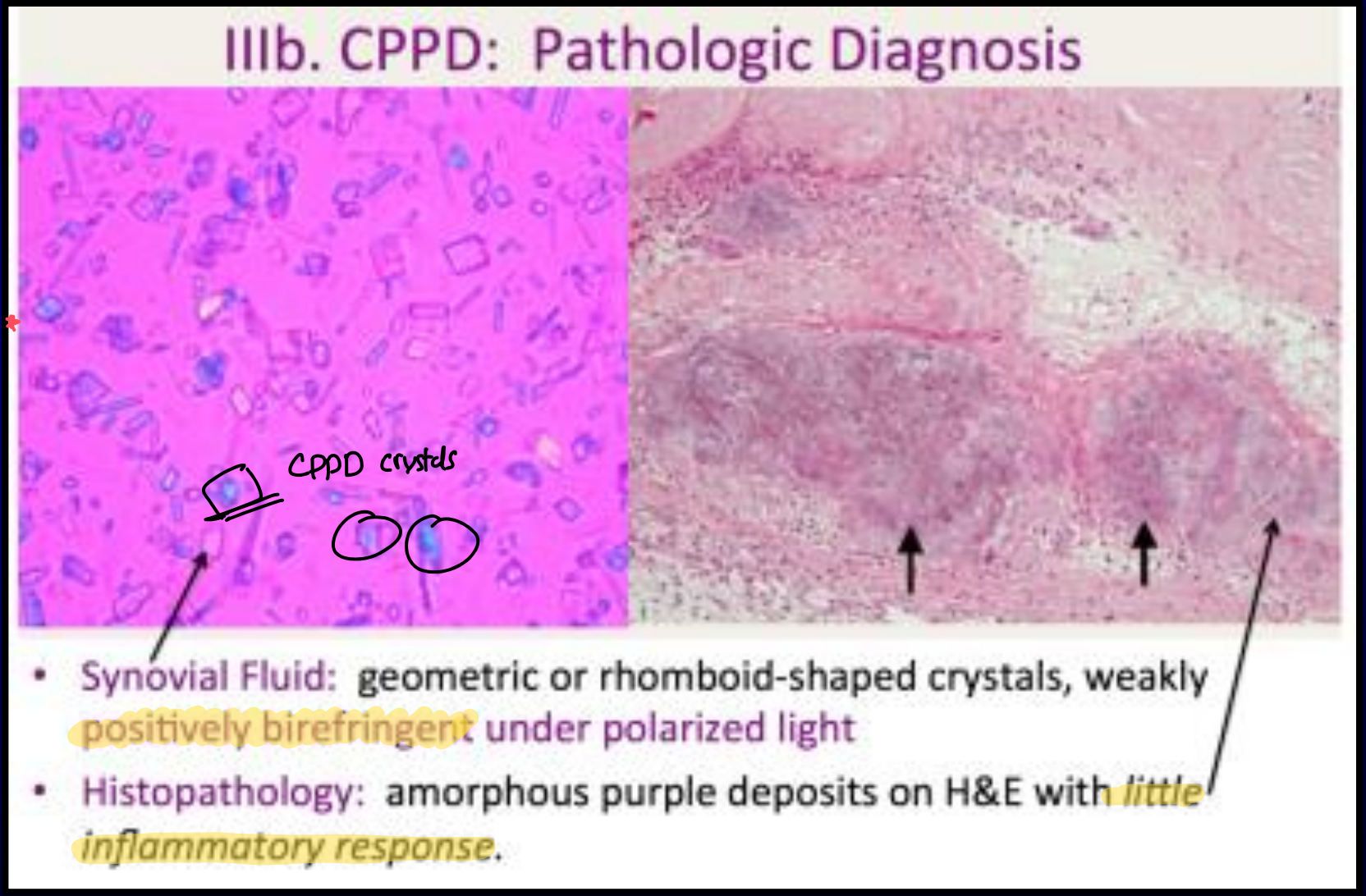


PSEUDOGOUT:

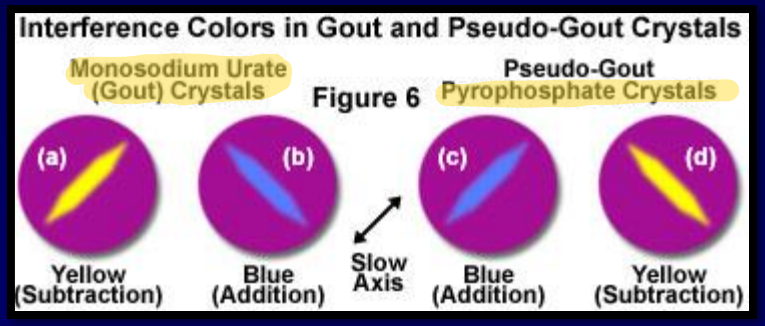
CPPD Crystals

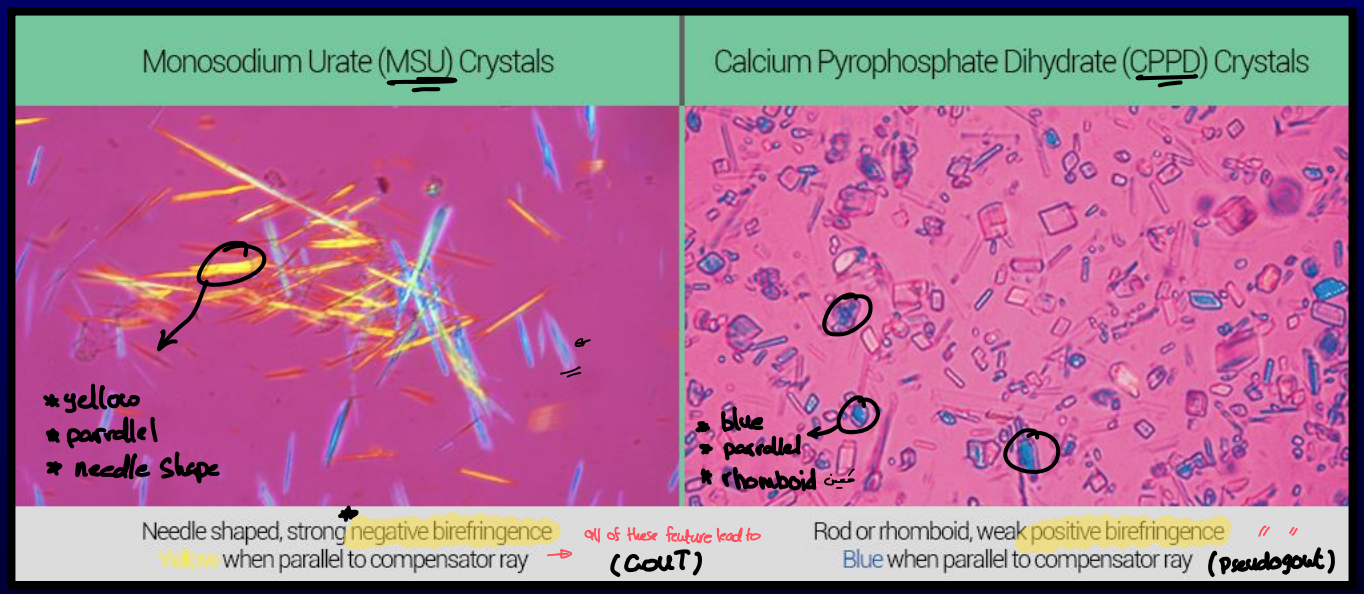
- > 50 years; increase with age
- Idiopathic (genetic) or secondary
- CPPD crystal induced arthritis via triggering inflammatory reaction
- Secondary: DM, previous joint damage, HPTH, hemochromatosis
- Acute, subacute and chronic forms
- Trx: supportive, no preventive measures so far

PSEUDOGOUT:


IIIb. CPPD: Pathologic Diagnosis
CPPD crystals
• 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

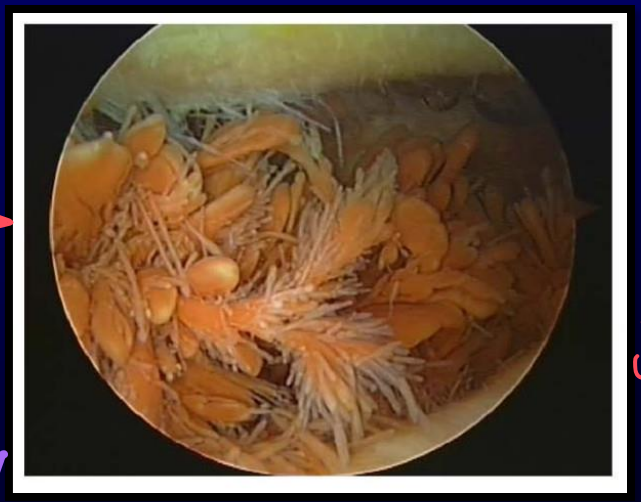
- **Osteoarthritis (OA, degenerative joint disease)**, the most common disease of joints, is a degenerative process of articular cartilage in which matrix breakdown exceeds synthesis. Inflammation is minimal and typically secondary. Local production of inflammatory cytokines may contribute to the progression 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.

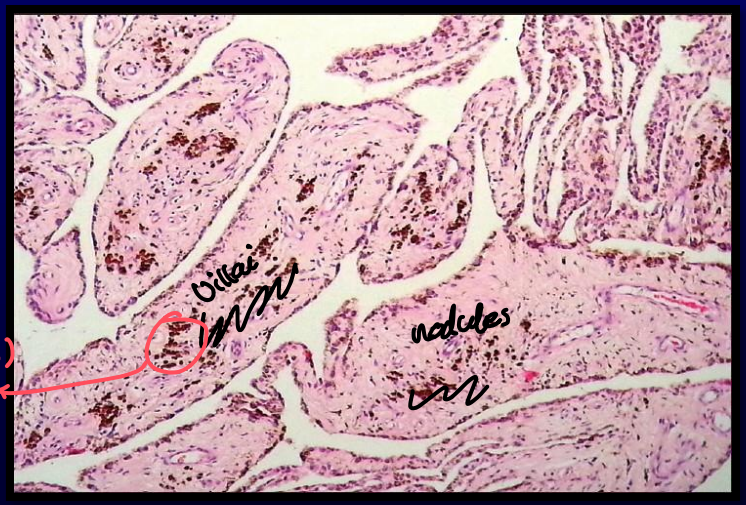
JOINT TUMORS & TUMORLIKE CONDITIONS:

- 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



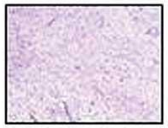
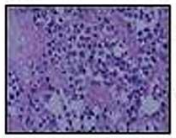
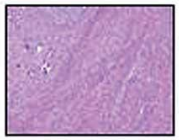
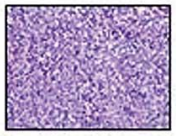


SOFT TISSUE TUMORS:

- 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 & toxins.

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

Examples on ST tumors ?!

ADIPOSE TISSUE TUMORS:

LIPOMA

- Most common soft T tumor (benign)
- Well-encapsulated, subcutis (under the skin)
- Mature fat cells
- Trx: excision

LIPOSARCOMA

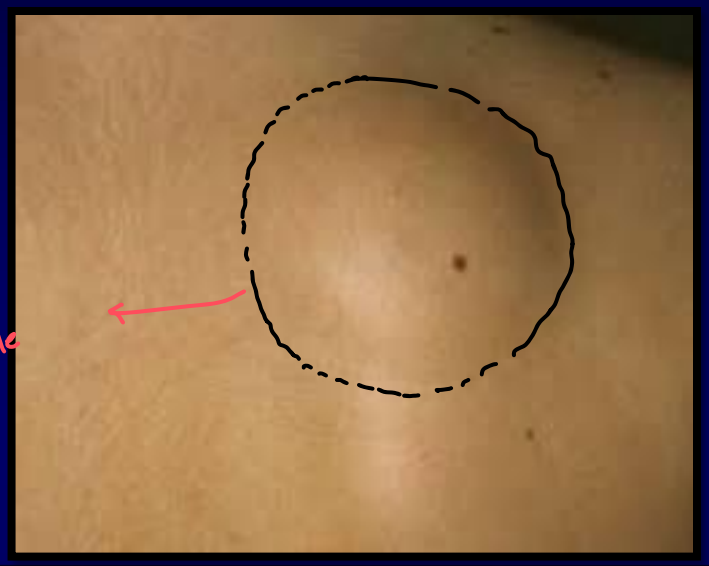
- Most common sarcomas in adults. >50 years
- Extremities and retroperitoneum
- 3 types:
  - WD (MDM2 gene chr 12)
  - Myxoid, t(12,16)
  - Pleomorphic (aggressive)

* Most difficult type to diagnose.
* They usually large in size

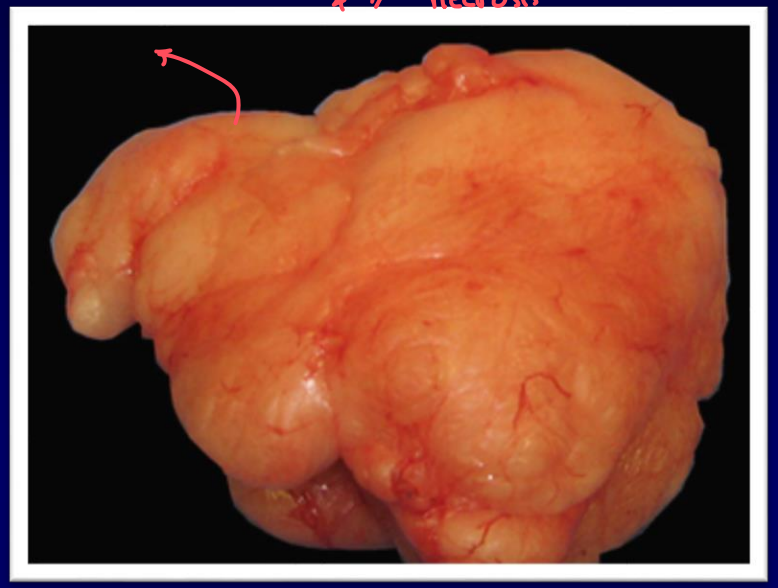
LIPOMA PATHOLOGIC FEATURES:

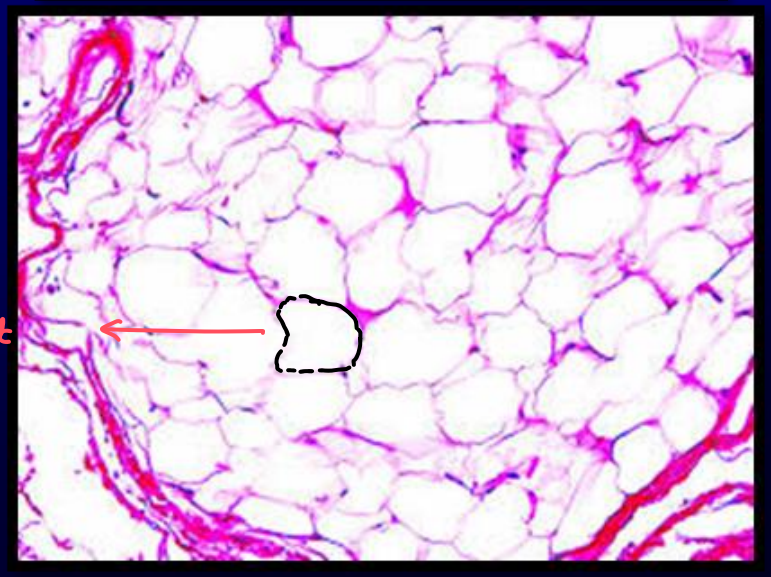
* no invasion
* well circumscribe
* no haemorrhage
* ± necrosis

* benign



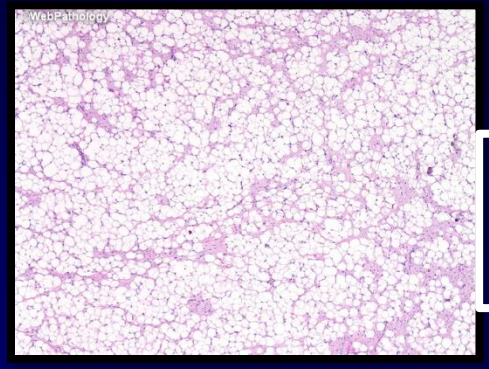
* easy removable



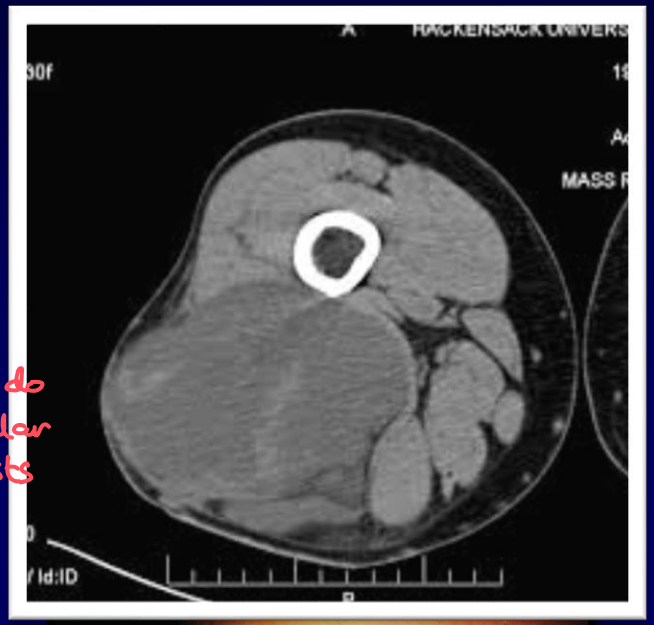


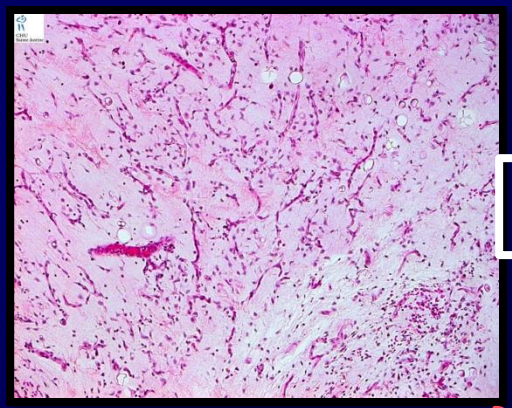
* You see normal fat cell (adipocytes)

LIPOSARCOMA FEATURES:

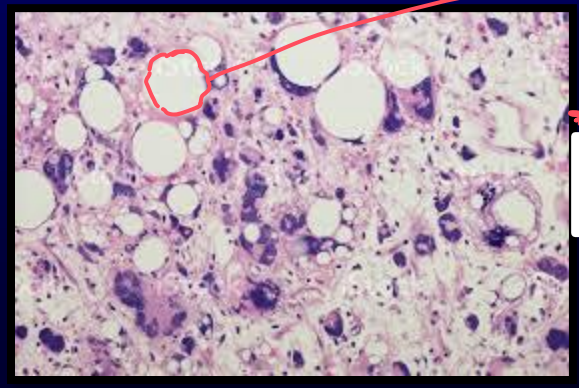


Well-differentiated

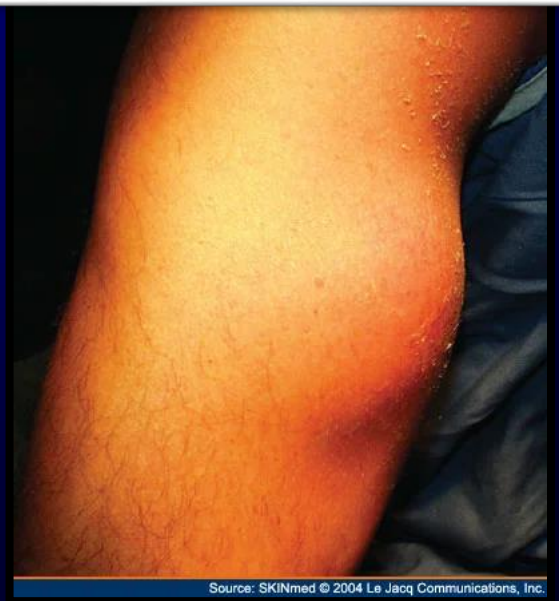




Myxoid



Pleomorphic



Lecture 9

2 **FIBROUS TUMORS:

- **Nodular fasciitis**
- **Fibromas and Fibrosarcoma**
- **Fibromatoses:** *group of diseases, divided into superficial, deep
  - Superficial
  - Deep (Desmoid tumor)

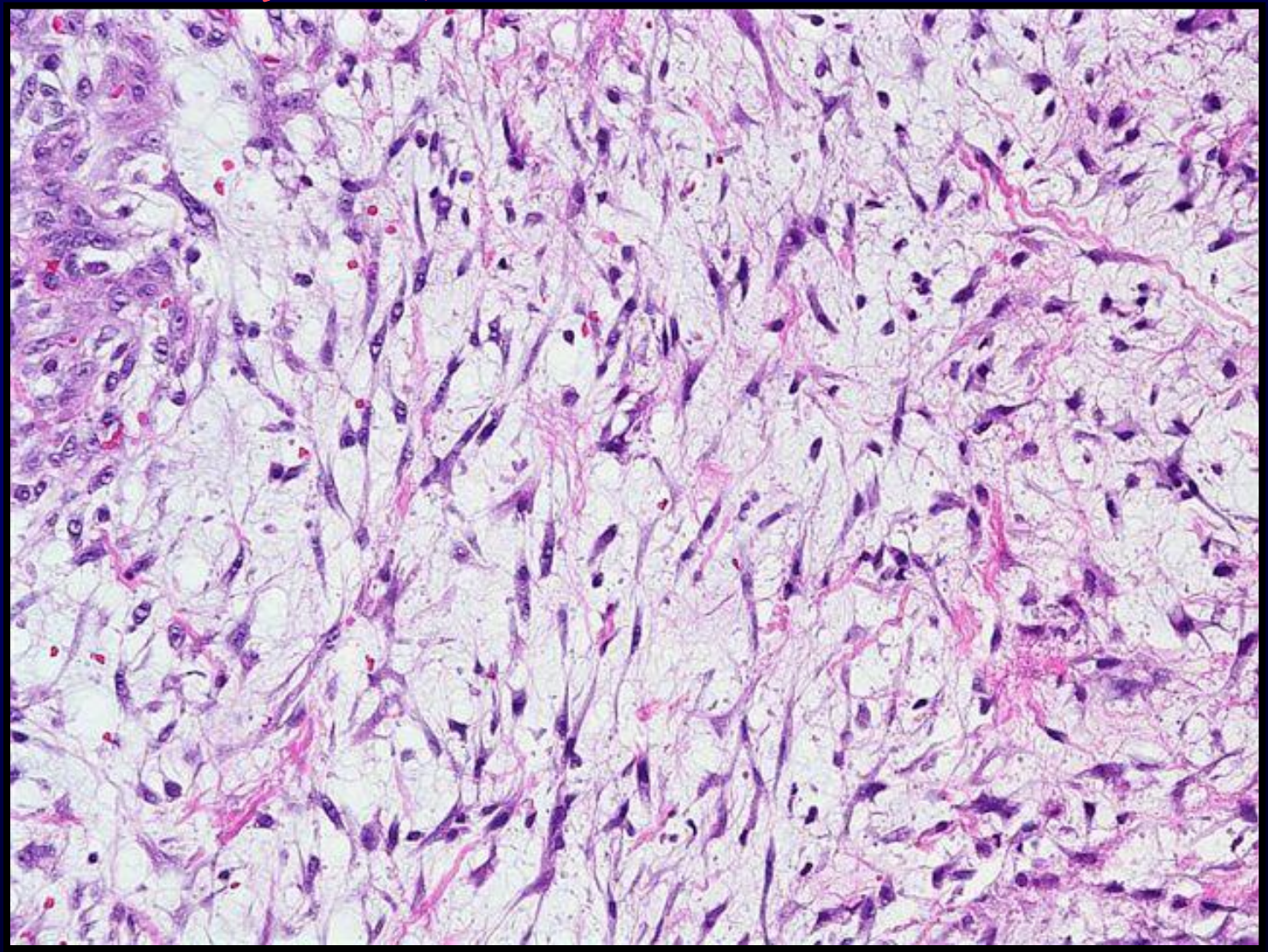
NODULAR FASCIITIS:

- 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:

** benign XX ≠ malignant

inflammation



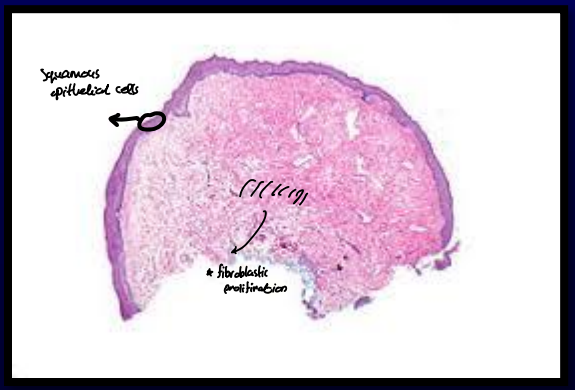
So we can see inflammatory cells

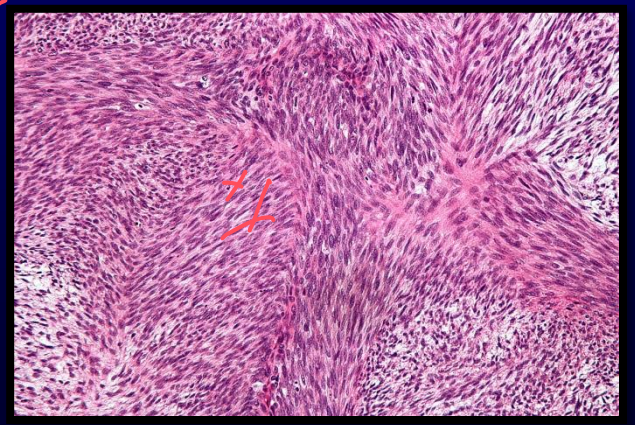
* Lymphocytes, plasma-

* notice the fibroblastic proliferation

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

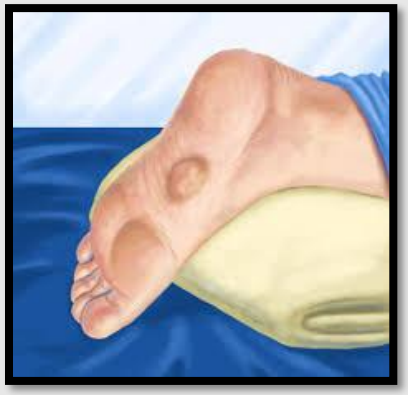
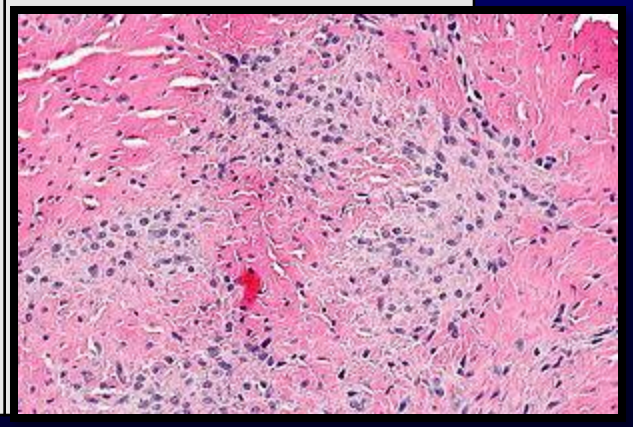




SUPERFICIAL FIBROMATOSES:

* and they don't kill you
لـ بتموتوش عيشك

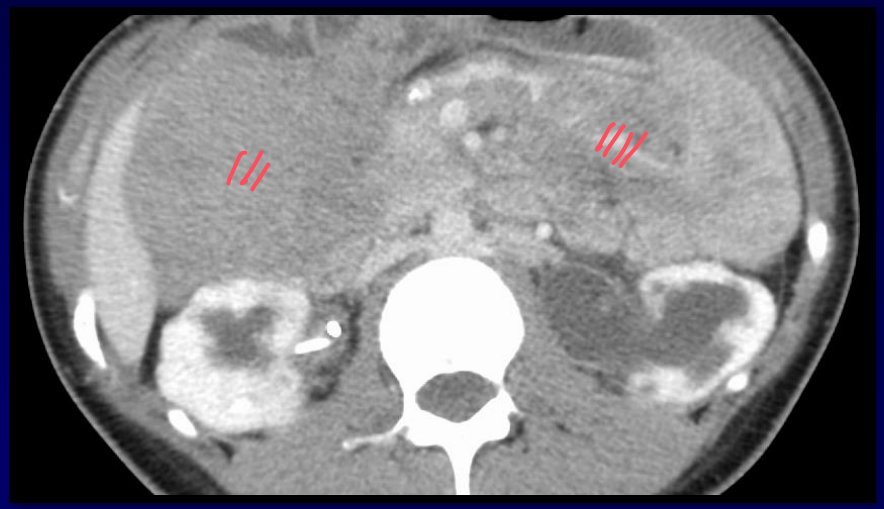
- **Infiltrative benign** fibroblastic proliferation (so ✗ metastasis)
- May run in families; may impact function

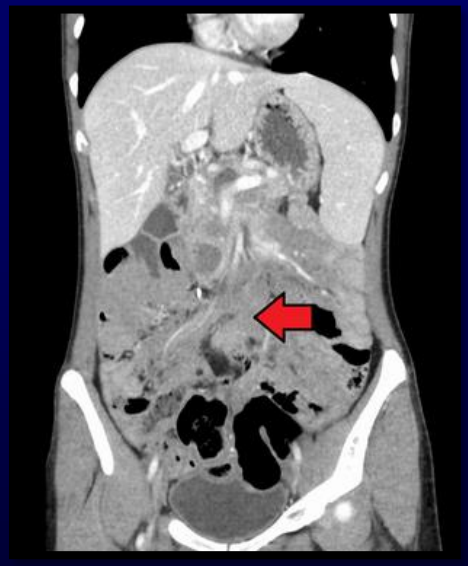
PALMAR (DUPUYTREN CONTRACTURE)	PLANTAR FIBROMATOSES	PENILE (PEYRONIE DISEASE)
Palmar fascia	Sole of foot	Dorsolateral aspect of the penis
		

DEEP FIBROMATOSES (DESMOID TUMOR):

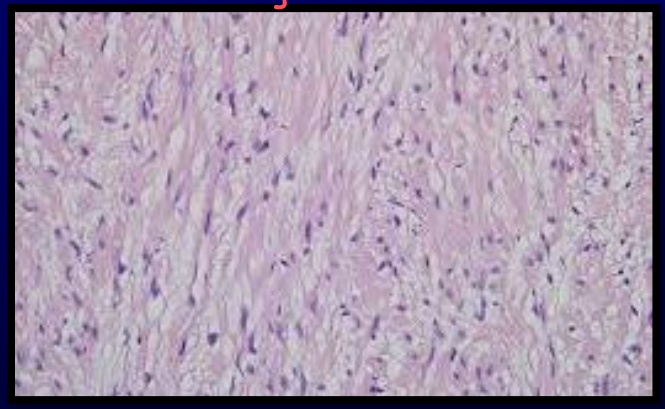
- Deep infiltrative but bland fibroblastic proliferation; doesn't metastasize but recur
- 20-30years, females more common
- Abdominal wall, mesentery and limbs
- Mutations in *CTNNB1* (β-catenin) or *APC* genes leading to increased Wnt signaling
- Mostly are sporadic; but patients with Gardner (FAP) 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):

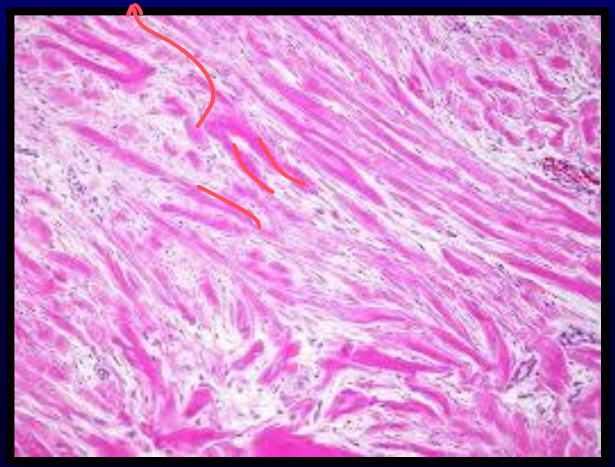




benign



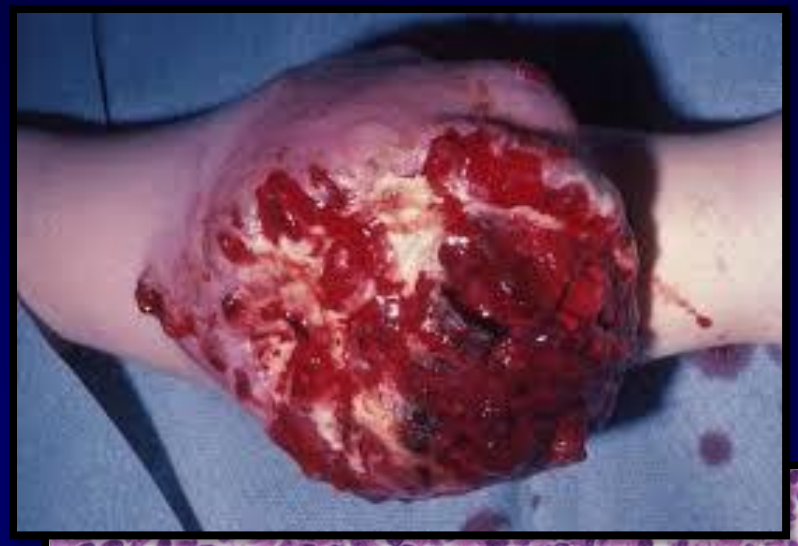
* notice the Fibroblastic infiltration.

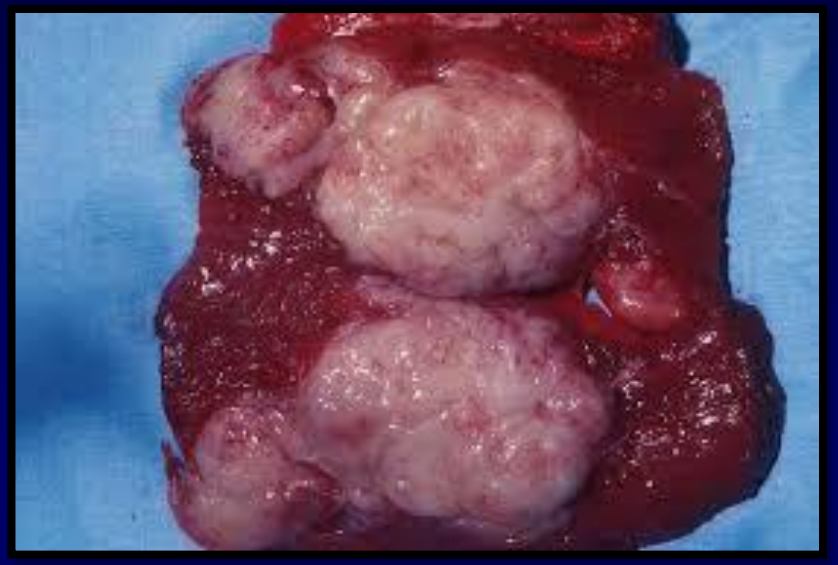


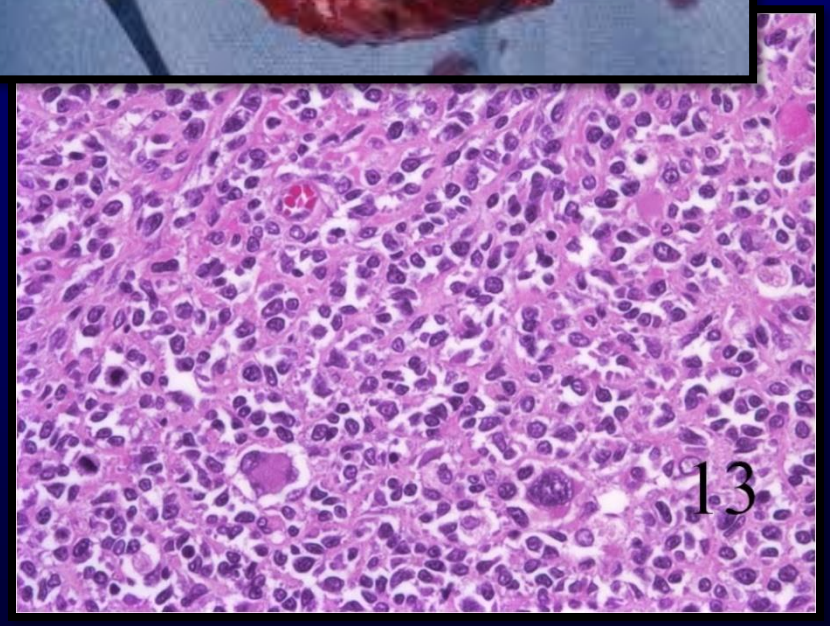
**SKELETAL MUSCLE TUMORS:

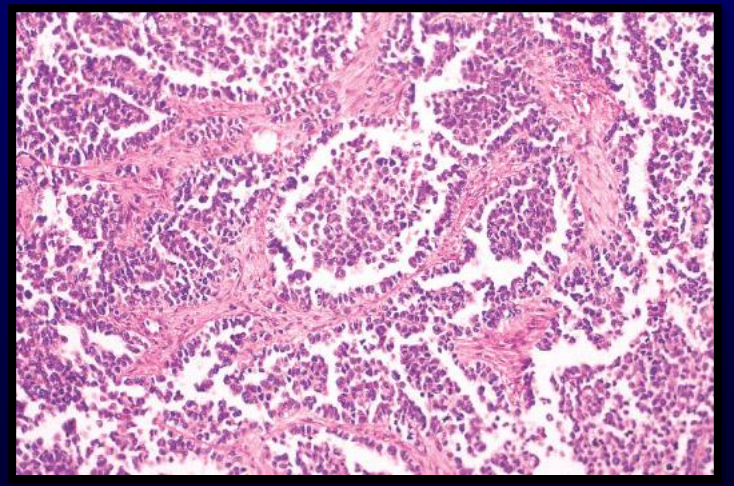
- Almost all malignant; except rhabdomyoma which is benign, rare, occurs with tuberous sclerosis
- Rhabdomyosarcoma (RMS) is the malignant prototype; most common child sarcoma
- 3 types (embryonal 60%; alveolar 20%; pleomorphic 20%)
- Specific mutations are common
- Aggressive tumors; treated by surgery,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

These tumors ⟶
* usually bulk
* rapid protrudation
* Hemorrhage









(Embryonal type) ~ * يدي تشبه الـ embryogenic cells

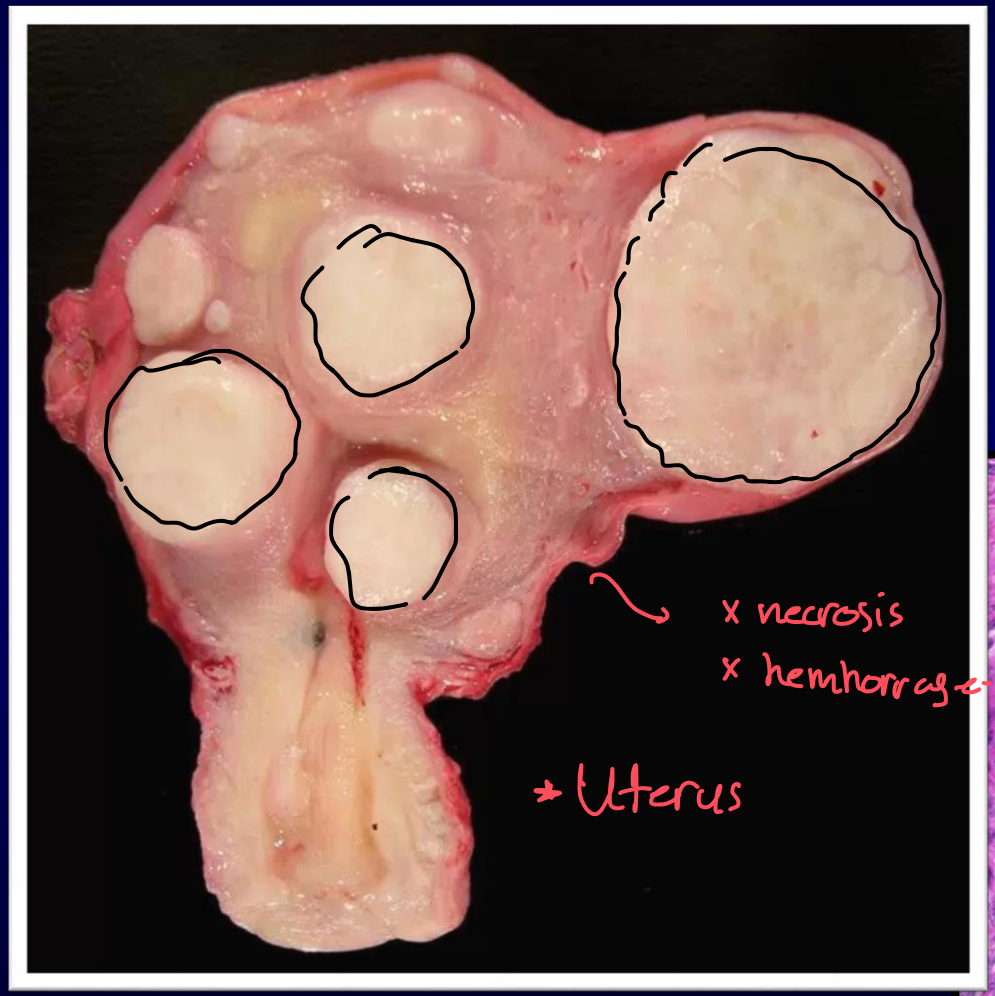
(alveolar type) ← * يدي تشبه alveoli of the lung

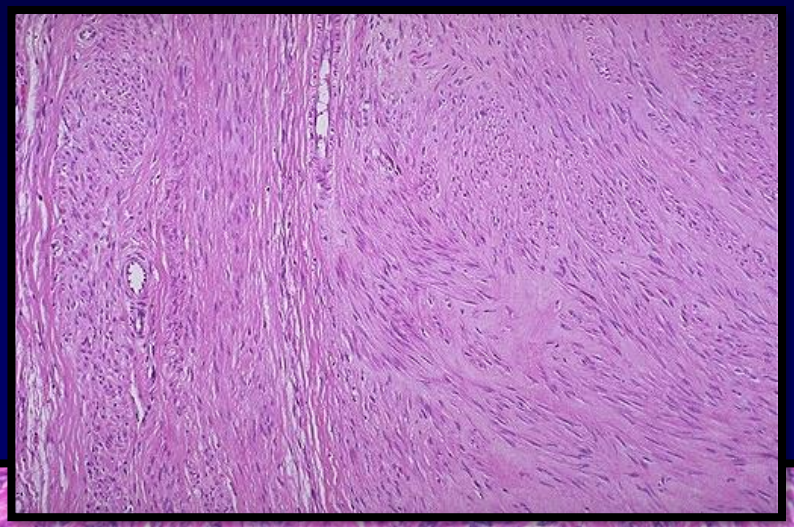
SMOOTH MUSCLE TUMORS:

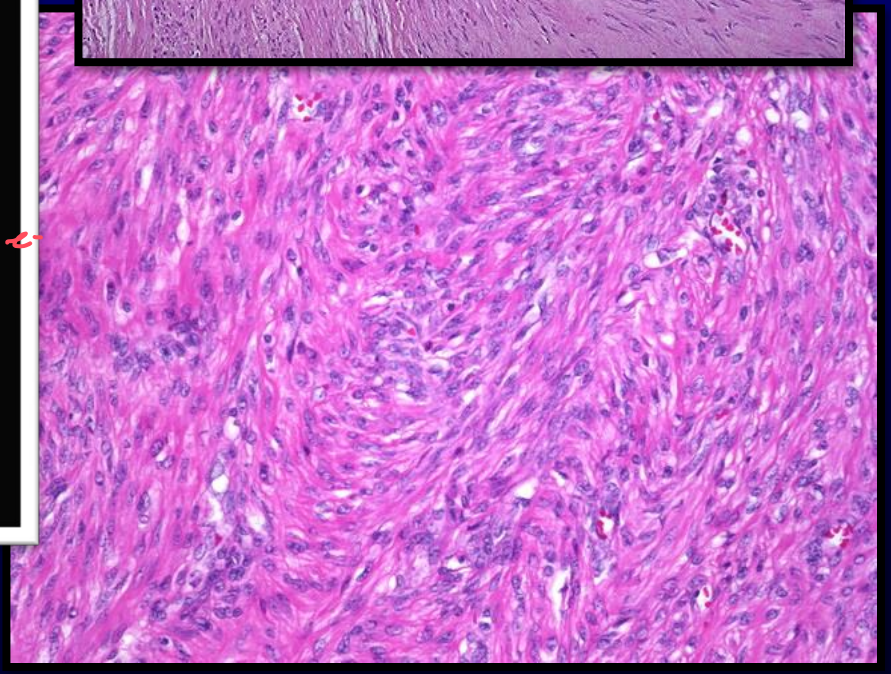
- **Leiomyoma (benign) and leiomyosarcoma (malignant)**
- **Leiomyoma (LYM): very common; any site but mostly uterus (fibroid)…menorrhagia and infertility**
- **LYM vary in size and location**
- **Few can have specific mutations (Fumarate hydratase on chromosome 1q42.3)**

*both are denoba
*we don't need these molecular test for diagnosis

LEIOMYOMA FEATURES:



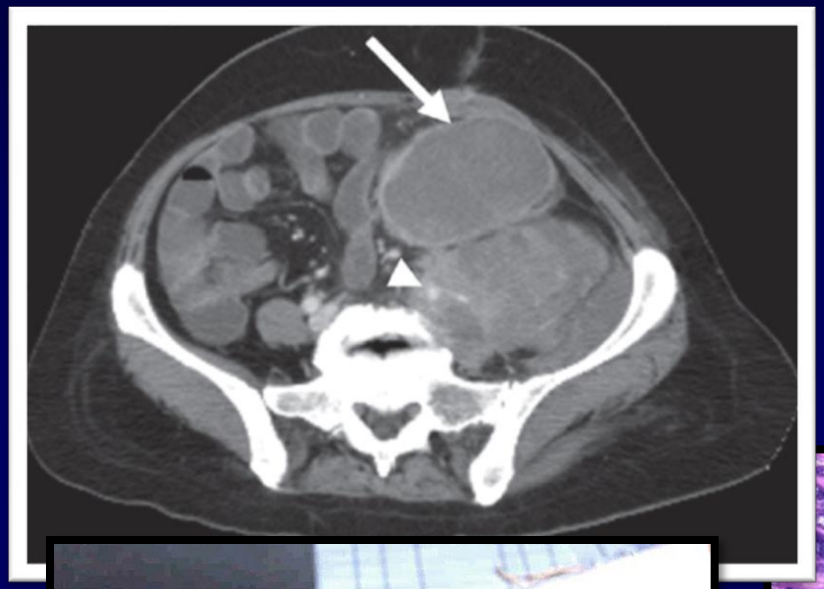


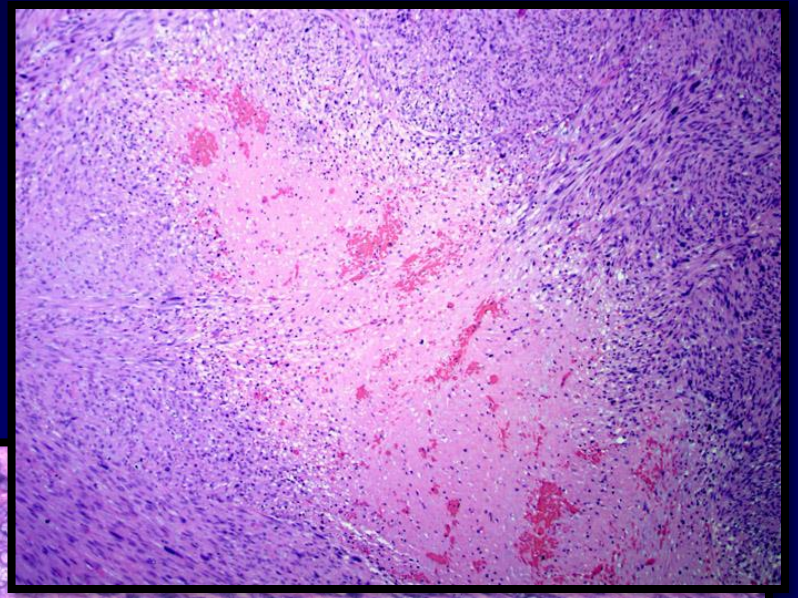


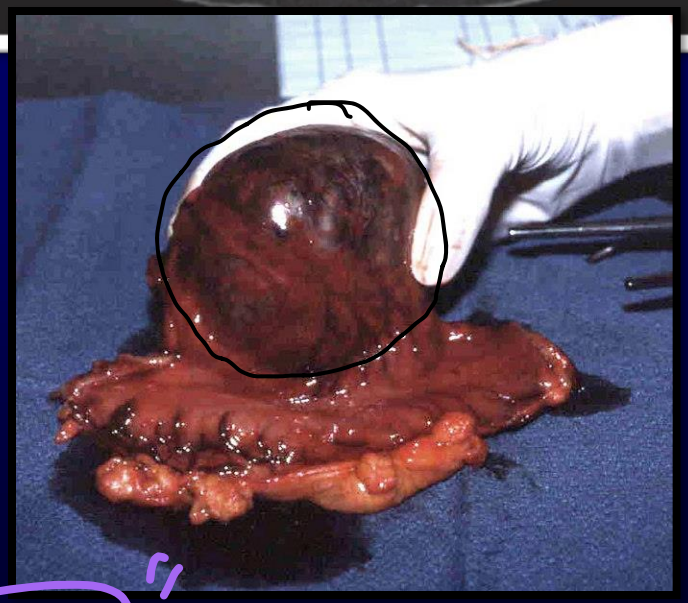
LEIOMYOSARCOMA:

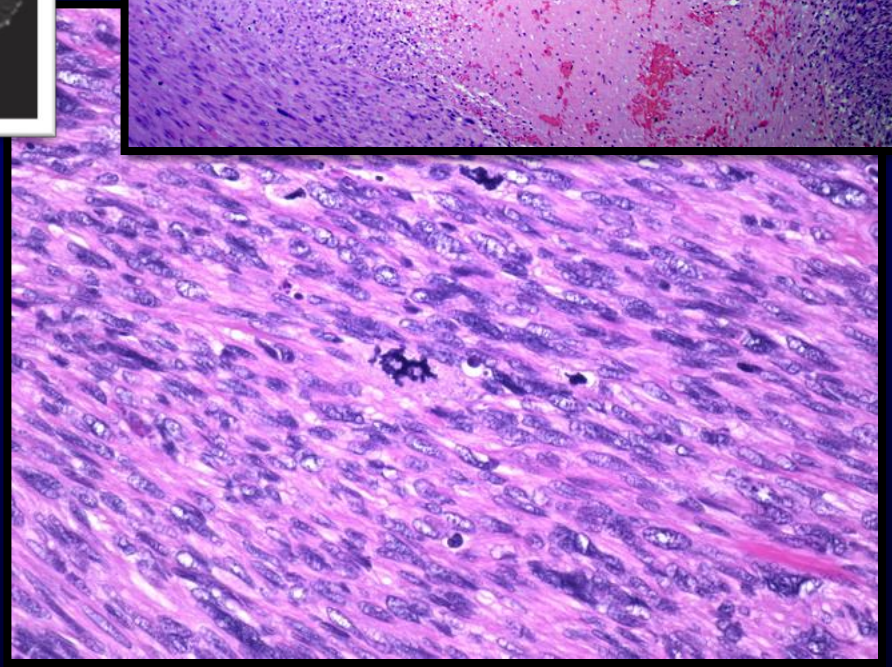
- 10-20% of soft tissue sarcomas
- Adults; more in females
- Deep soft tissue, extremities and retroperitoneum or from great vessels
- Complex genotypes we don't need these tests
- **Hemorrhage, necrosis, increased mitosis and infiltration of surrounding tissue** [malignant]
- Trx: depends on location, size and grade

LEIOMYOSARCOMA FEATYURES:









TUMORS OF UNCERTAIN ORIGIN:

we don't know the cells of origin

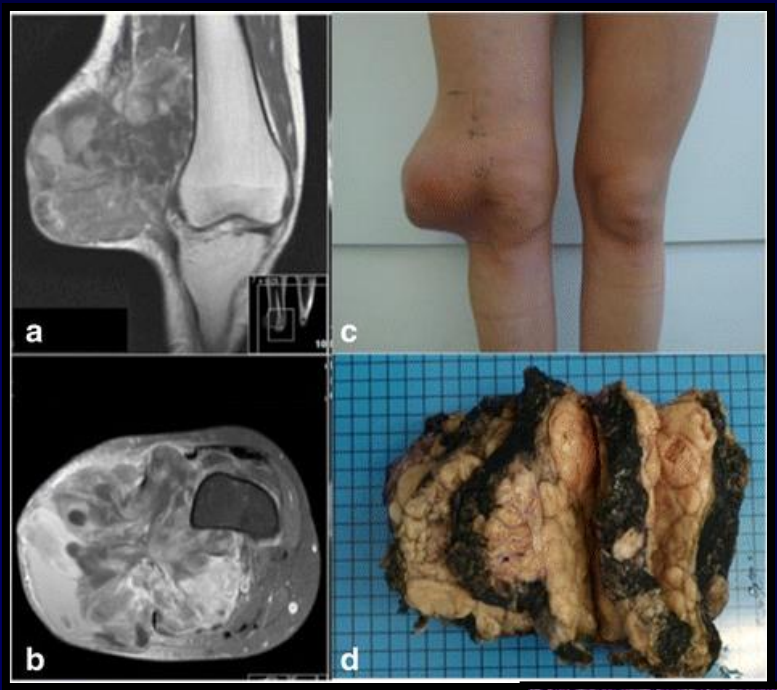
- Uncertain mesenchymal lineage
- Synovial sarcoma
- Undifferentiated pleomorphic sarcoma

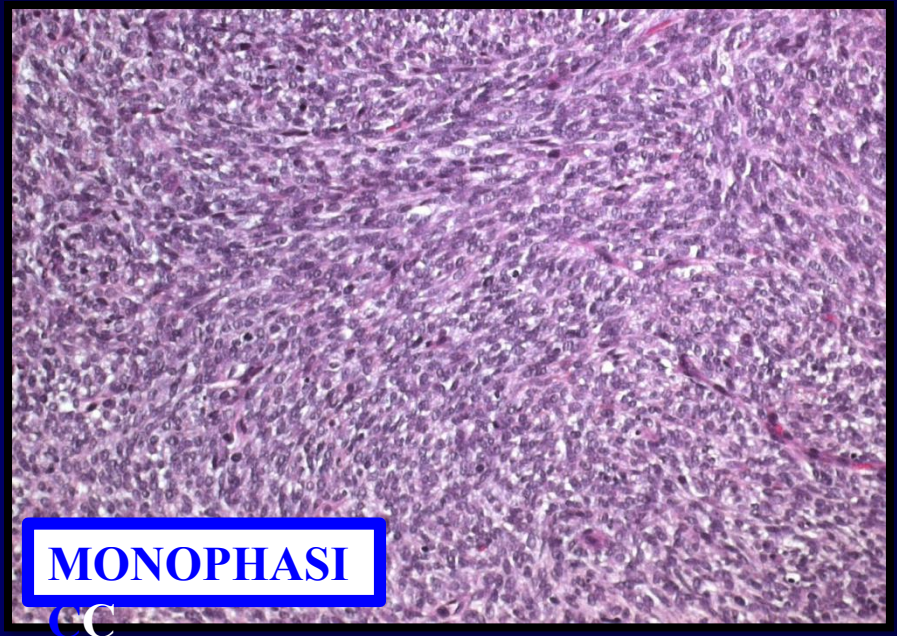
* SYNOVIAL SARCOMA:

- **Name is misnomer** → it doesn't arise from synoviocytes
- **10% of all soft tissue sarcomas; 20-40s age**
- **Deep seated mass of long history**
- **T(X;18)(p11;q11) → fusion genes *SS18*…** → here we need the molecular test for diagnosis
- **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**

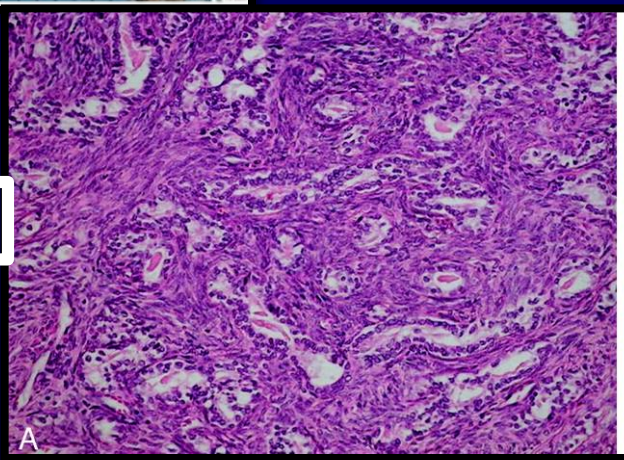
↳ * exception, because we know that sarcomas metastatic to the lung

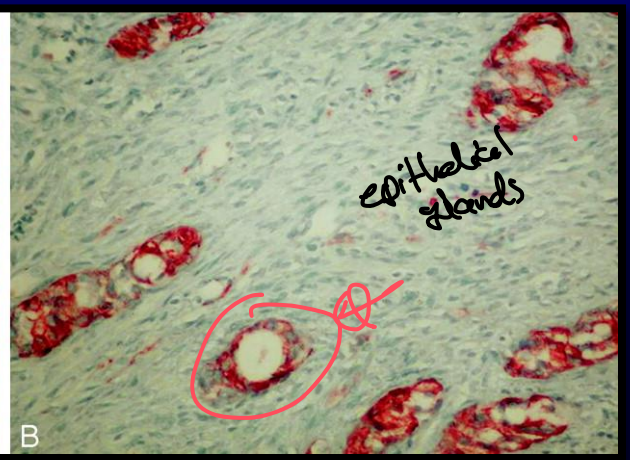
SYN. SA. FEATURES:





BIPHASIC

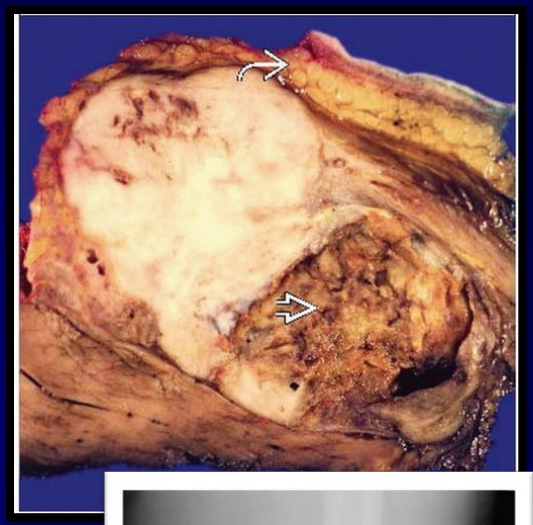


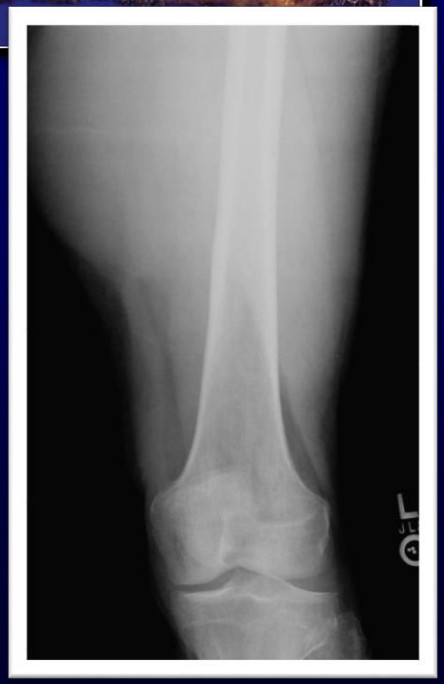


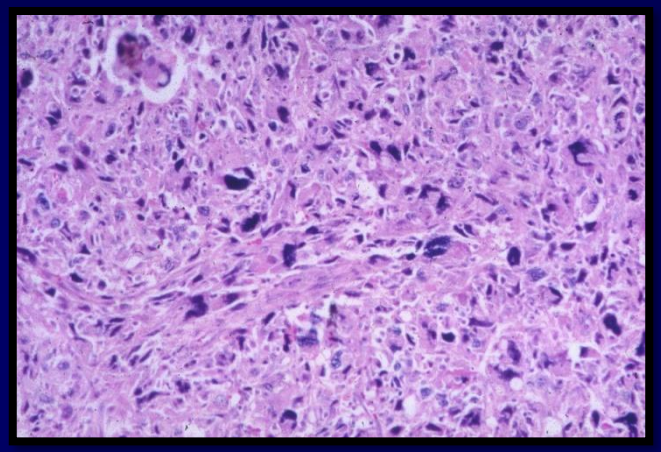
UNDIFFERENTIATED PLEOMORPHIC SARCOMA (UPS):

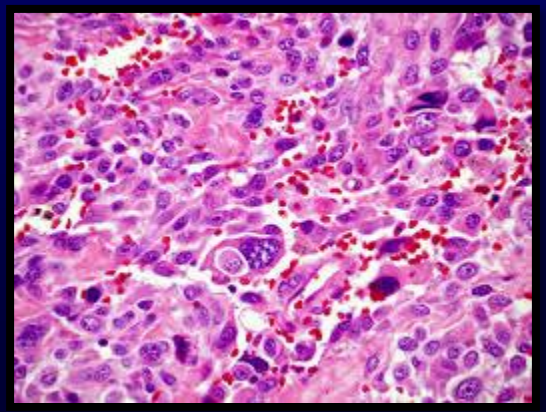
- High grade mesenchymal sarcomas of pleomorphic cells that lack cell lineage
- Deep soft tissue and extremities
- Old terminology: malignant fibrous histiocytoma (MFH)…not anymore
- Aneuploid and complex genetic abnormalities
- Large tumors; anaplastic and pleomorphic cells, abnormal mitoses, necrosis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

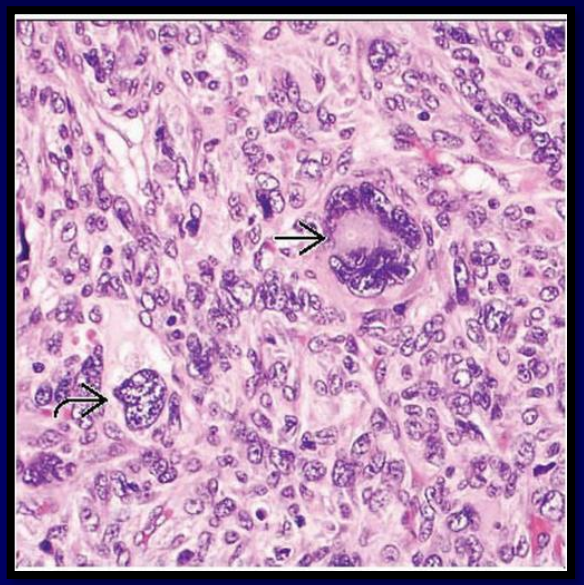
UPS FEATURES:











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.