MSS

PATHOLOGY

#8
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About the last lecture, the doctor mentioned about Rheumatoid factor:

Rheumatoid factor: it's a serum test, in the old days they used to give titers(The concentration of a solution as determined by titration) ex: 1:18, if the measured number is above it, will test positive, nowadays they give a whole number (14) above it positive bellow it negative.

Now we will talk about crystal-induced joint disease.

GOUT: النقرس

• Transient attacks of arthritis can affect any joint, but the major affected site is the big toe (swollen painful big toe) triggered by the deposition of MSU (MONOSODIUM URATE) crystals in the joints.

• Uric acid: purine metabolite; increased production or decreased excretion from the kidney (duo to kidney disease) Those patients will be characterized with hyperuricemia the major risk factor for gout)

• risk increases with 20-30 years of age (but it can occur at any age), obesity, alcohol, genetic predisposition, drugs (thiazides: which increase uric acid levels).

About this picture the doctor said:

Precipitation of urate crystals in joints will activate all the cascade of inflammatory cells and mediators (complement, phagocytosis, lymphocyte) leading to release of many lysosomal enzymes and proteases that will damage your joint including the synovial, the ligament and the soft tissue around it.

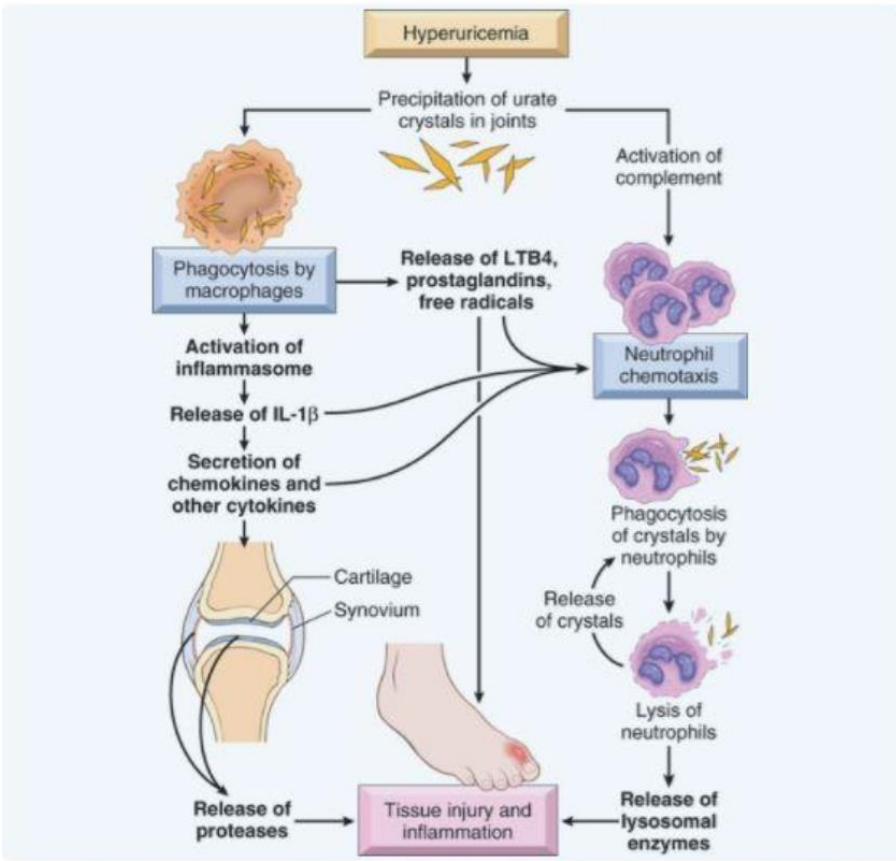


FIG. 21.41 Pathogenesis of acute gouty arthritis. Urate crystals are phagocytosed by m…

MORPHOLOGIC CHANGES OF GOUT

• **Acute arthritis: Dense inflammation of the synovium** **(the patient will come to you with a big warm toe and very painful, and if you take a biopsy from the synovial fluid you will see MSU crystals in neutrophils, -ve birefringent**

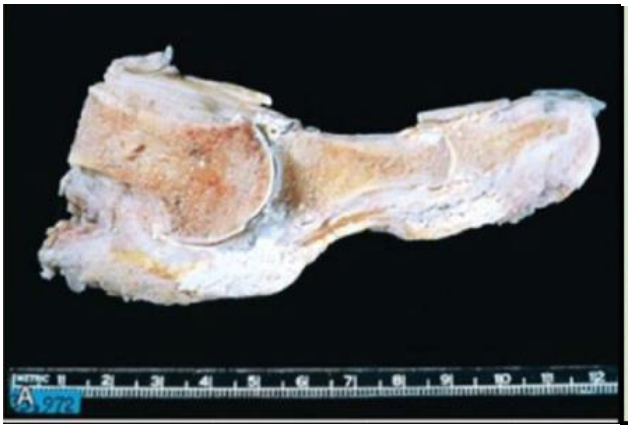
• **Chronic tophaceous arthritis: Repetitive attacks** **(they may remove the big toe because of it)** **& crystals deposition in the joint; thick synovium, formation of pannus**

Side note: pannus is a type of extra growth in your joints that can cause pain, swelling, and damage to your bones, cartilage, and other tissue.

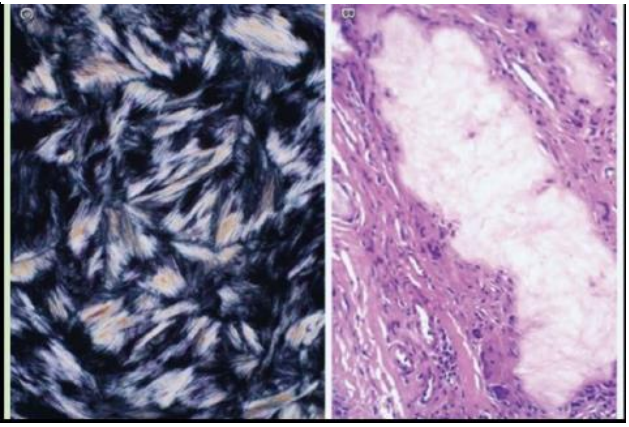
• **Tophi (crystals induce inflammatory reaction)** **in various sites: Cartilage, ligaments, bursae, and Tendons**

• **Gouty nephropathy: MSU crystals deposition in the kidney; nephrolithiaisis & pyelonephritis**

• **Treatment: lifestyle modifications, NSAIDs & Colchicine in acute gout, Xanthine oxidase inhibitors (Allopurinol) in chronic and prevention**



Chronic



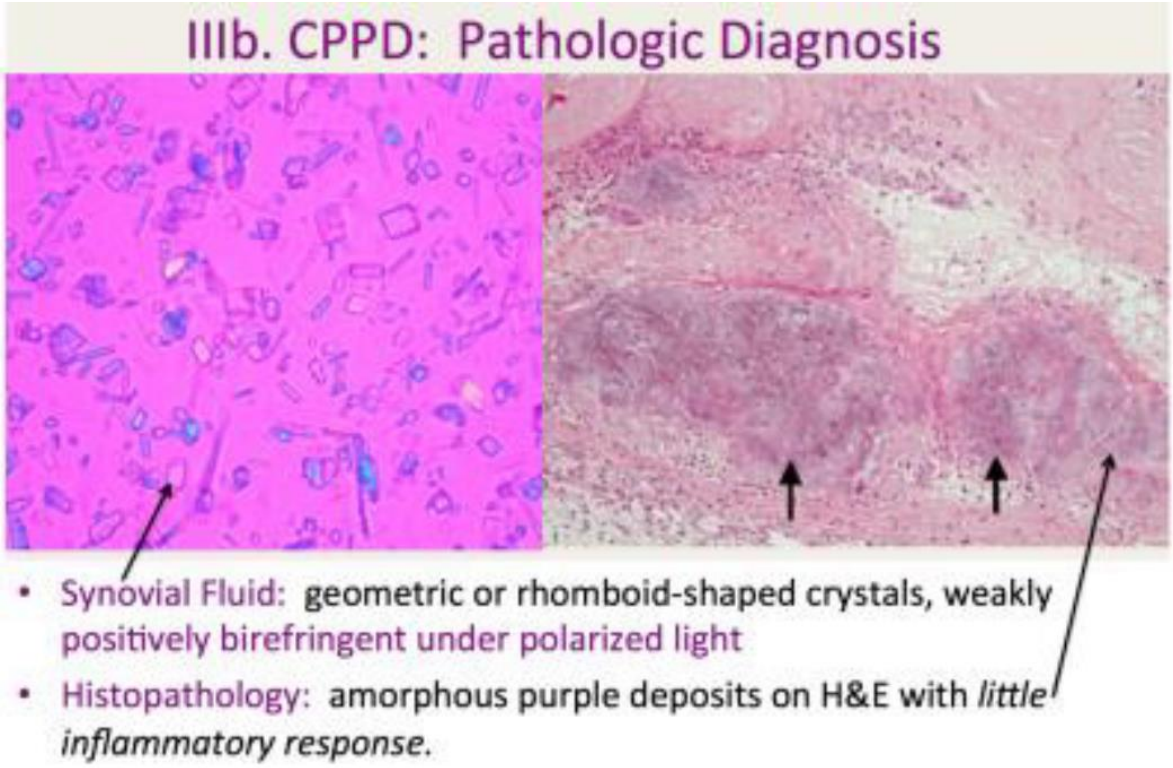
deposition

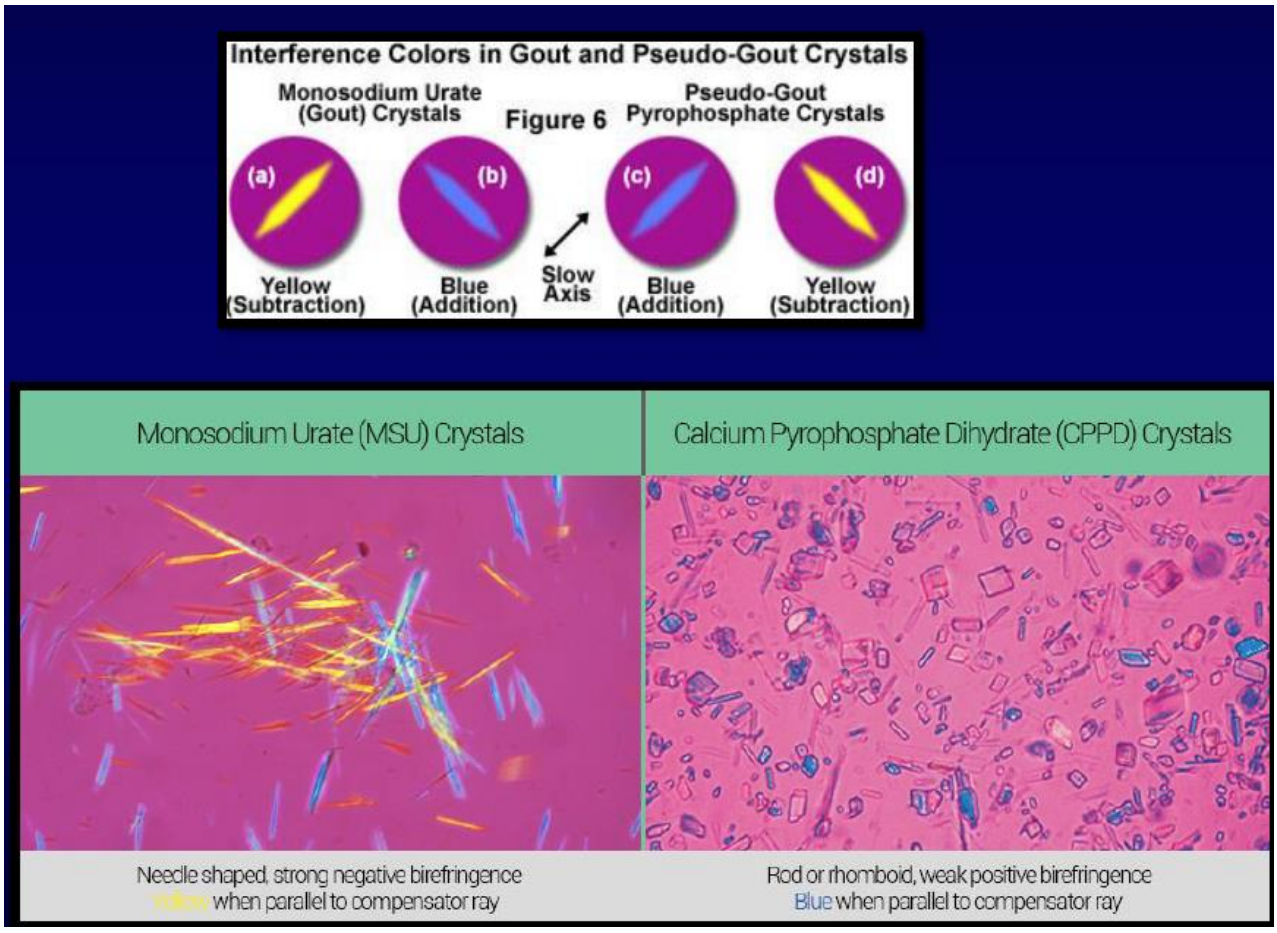
PSEUDOGOUT

Same mechanism same pathogenesis of gout but the crystals are different.

> 50 years; increase with age.
• Idiopathic (genetic) or secondary
• CPPD (Calcium pyrophosphate deposition) crystal-induced arthritis via triggering an inflammatory reaction
• Secondary: DM, previous joint damage, HPTH, hemochromatosis

• **Acute (acute gout is more painful than acute pseudogout), subacute and chronic forms**
• **Treatment: supportive, no preventive measures so far**





GOUT **PSEUDOGOUT**

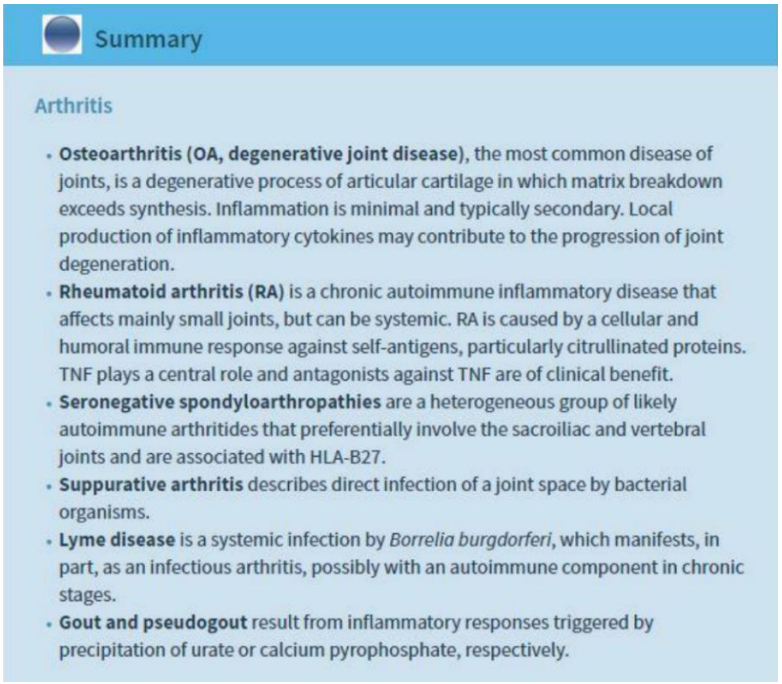
- About the slide above the doctor said:

The polarizing microscope is a special microscope have a polarizing lens.

When we put the biopsy on the polarizing microscope if it appeared:

- yellow, parallel, needle-like, -ve birefringent then It's gout

- parallel, blue, rhomboid, +ve birefringent then its pseudogout



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 (less than bone and soft tissue tumors)

• Ganglion cysts and tenosynovial giant cell tumors are the most frequent joint tumor

• Ganglion cyst: common condition; close to a joint, dorsum of the wrist; not true cyst (doesn't have a specific epithelial lining), no communication with a synovial joint; may cause pressure pain; treated by surgical removal

*** pathology of the ganglion cyst is unknown but there is some accepted theory say's it is a herniation of the synovial membrane**

• True synovial cyst (have a specific lining) (Baker cyst around the knee posterior of the knee on the popliteal fossa comes with severe pain and sometimes gets bigger causing deep venous thrombosis of the lower limb): herniation process.

TENOSYNOVIAL GIANT CELL TUMOR:

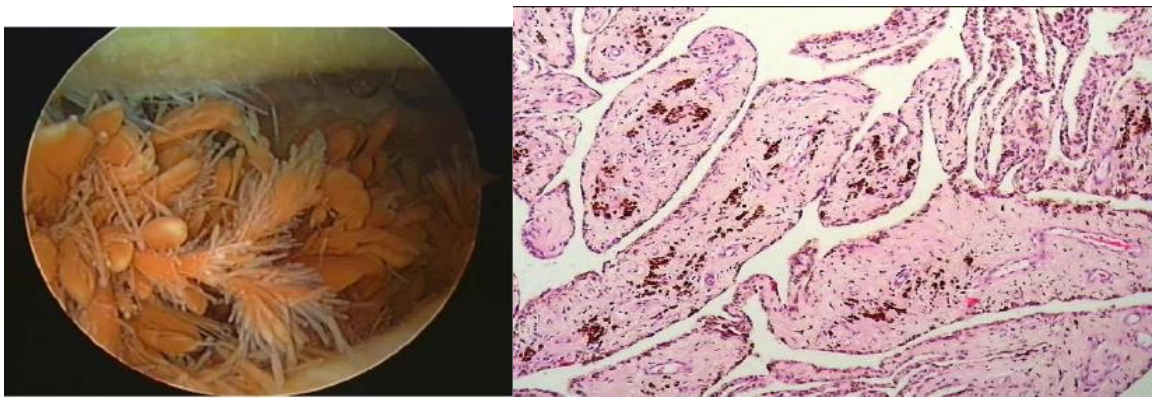
It's a tumor that is composed of multiple giant cells in addition to synovial proliferation.

- **Benign neoplasm of synovium**
- **Diffuse (in many cases it gets pigmented so we call it pigmented villonodular (it's finger like) synovitis, PVNS, mainly large joints common in the knee) it can cause severe pain and lock of joint or localized small hands, tendons**

- hemosiderin is the pigment that gives the PVNS its brown color.

- brown pigment is previous bleeding, the iron gets into the macrophages so we do an iron stain to confirm if it's iron or not.

- **T(1;2) (p13q;37); affecting type VI collagen α-3**



SOFT TISSUE TUMORS

-like (skeletal muscle, adipose tissue, and mesenchymal cells)

- **Benign is much more common than malignant**
- **Incidence: in general, 1% and cause 2% of cancer death**
- **Sarcomas are aggressive and metastasize by hematogenous spread mainly to the lungs.**
- **Most are in the extremities (the thigh is the most common site then the retroperitoneum)**

• **Most are sporadic** (without a family history or genetic predisposition) **very few syndromes characterized by an increased risk of certain sarcomas arise (tumor suppressor gene mutations) (NF1**(Neurofibromatosis type 1)**, Gardner syndrome, Li-Fraumeni syndrome, Osler-Webber-Rendu Syndrome)**

***The doctor said he doesn't like to ask about these syndromes because they are very rare**

• **Few occur after exposure to radiation** (for psoriasis and cancer, the area which gets radiated will have a higher risk to develop secondary sarcoma), **burns & toxins.**

• **No precursor lesions** (de novo)**; the theory that they arise from pluripotent** (A cell that can develop into many different types of cells or tissues in the body) **mesenchymal stem cells which acquire somatic mutation** (not genetic)

• **15-20% simple karyotype (**single mutation or single translocation which makes it easy to diagnose by FISH or next-generation sequencing)**, single signature mutation (Ewing and synovial sarcoma)**

- in certain situations in sarcoma we need to do molecular test and check the mutation

• **80-85% complex karyotype (genomic instability), LMS** (leiomyosarcoma), **and pleomorphic Sarcoma**

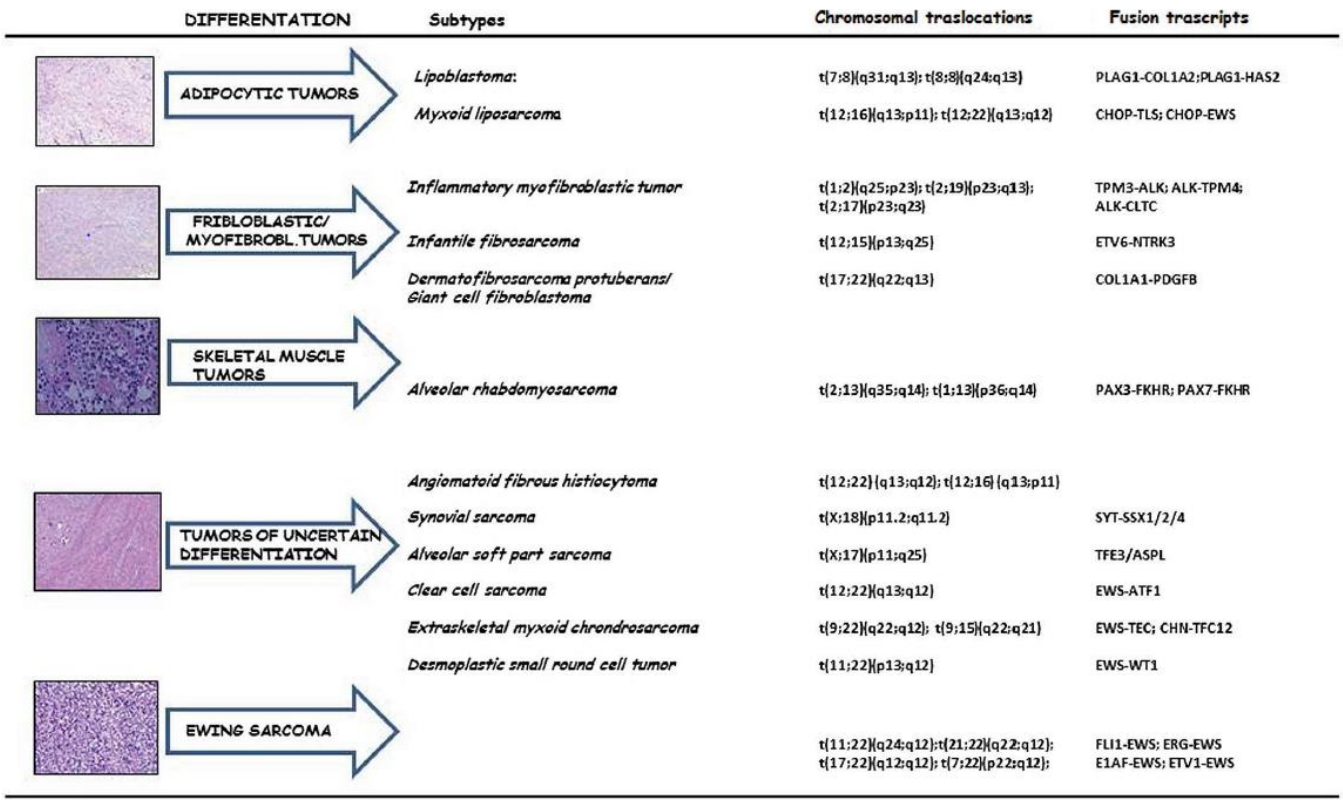
• **Wide range (benign-highly malignant)**

-benign: well-circumscribed, not infiltrative, small in size, close to skin not deep, no hemorrhage, no necrosis, no increased mitosis.

- malignant: infiltrative, large in size, necrosis, hemorrhage, anaplasia, increase in normal and abnormal mitosis.

• **Diagnosis, grade, and stage are all important**

*** The doctor said we don't need to memorize the table below:**



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

LIPOMA:

- **Most common soft T tumor**
- **Usually Well-encapsulated, subcutis (close to skin most common location subcutaneous tissue but it can occur at any site)**
- **easily removable**
- **Histologically: Mature fat cells**
- **Treatment: excision (one of the reasons for excision is to distinguish between malignant and benign especially if it is big and deep).**

LIPOSARCOMA:

-the malignant counterpart of lipoma.

- there is no malignant transformation of lipoma to liposarcoma

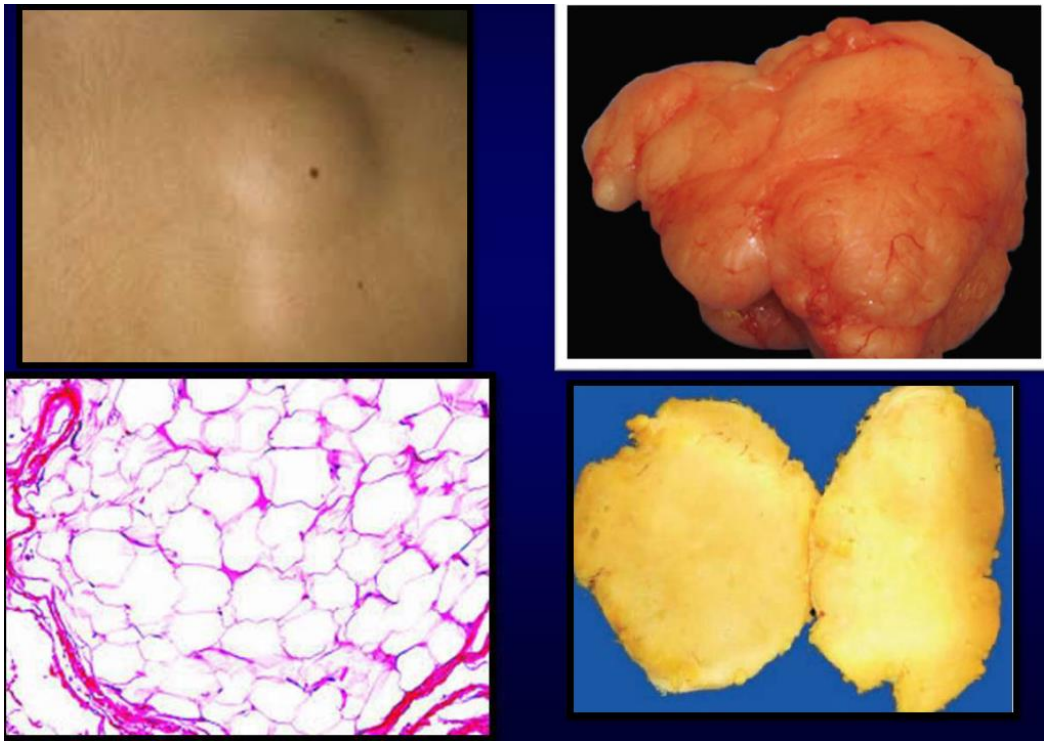
- **Most common sarcomas in adults. >50 years (in children Rhabdomyosarcoma)**
- **Extremities and retroperitoneum**
- **3 types:**

– **WD (Well-Differentiated) (MDM2 gene chr 12 by FISH, positive WD negative lipoma) (not easy to diagnose) we can also use immunohistochemistry instead of FISH**

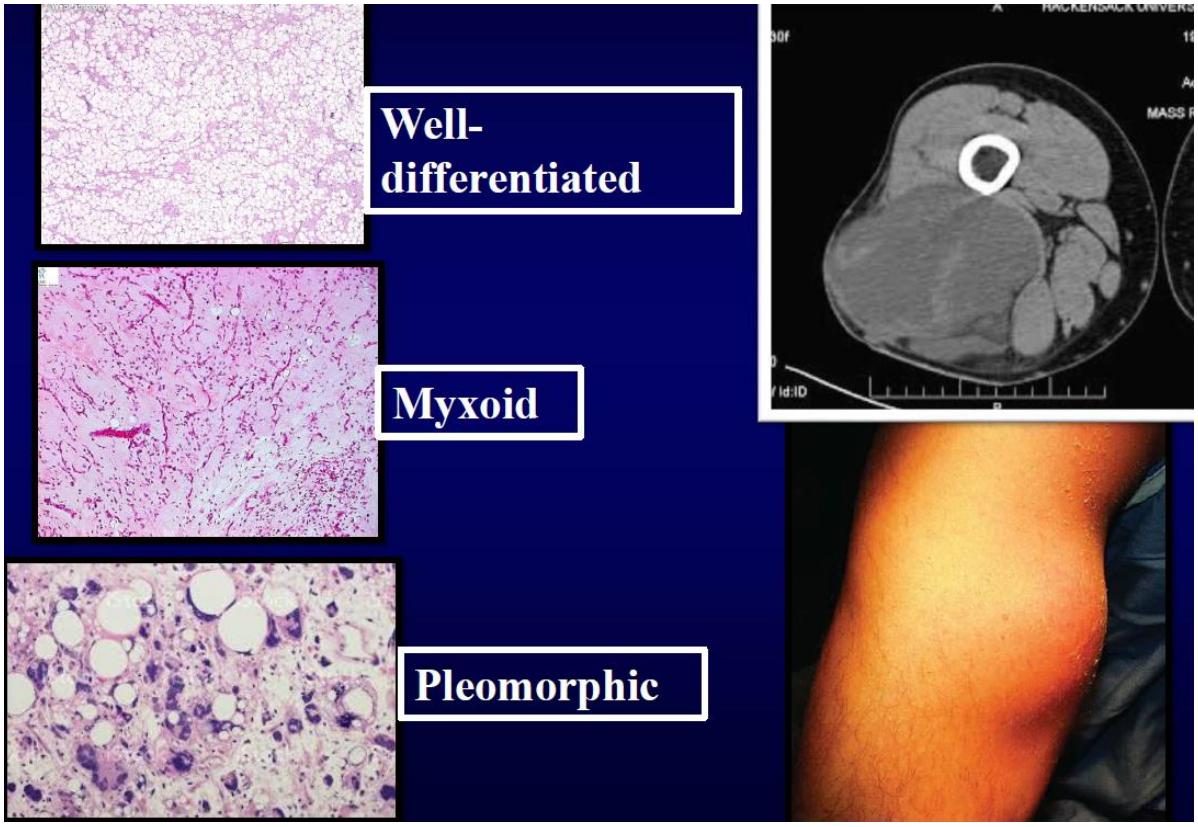
– **Myxoid, t (12,16) (malignant appearing) (easy to diagnose)**

– **Pleomorphic (aggressive) (the difficulty is to find the cell of origin) very aggressive, lethal, large thigh mass, ugly looking.**

LIPOMA PATHOLOGIC FEATURES:



LIPOSARCOMA FEATURES:



GOOD LUCK

V2

On page 5 (hemosiderin is the pigment that gives the PVNS its brown color)

On page 6 (sporadic: without a family history or genetic predisposition)

On page 7 (Adipose tissue tumor instead of Soft tissue tumor)

On page 8 (myxoid: malignant appearing) (pleomorphic: ugly looking)

V3

On page 4 (we added the slide about gout and pseudogout under microscope)

V4

On page 6 (collagen type VI instead of type IV)