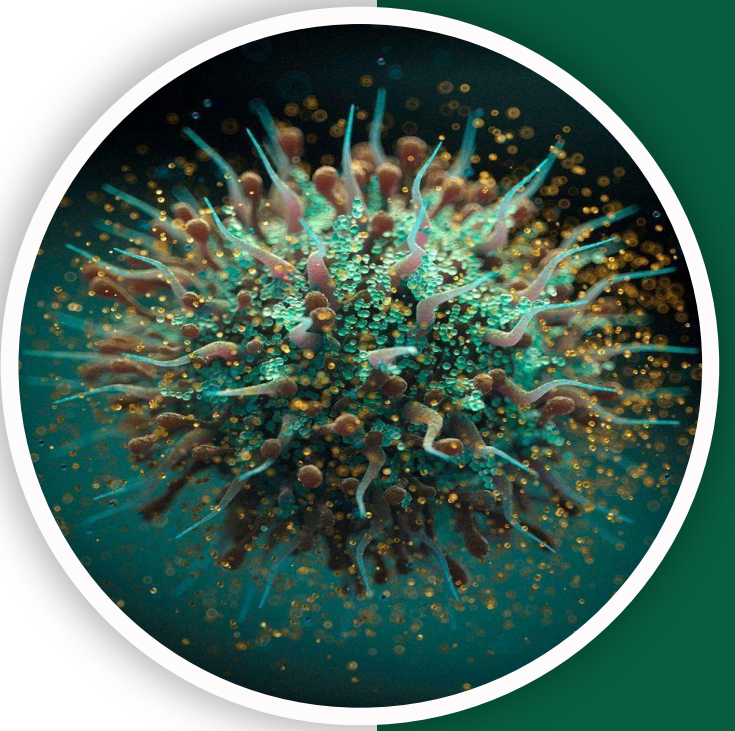
بسم الله الرحمـٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

MSS Pathology | FINAL 2

MSS & Skin Tumors Pt.8



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Gout: النقرس

- Transient attacks of arthritis, mainly big toe (However, it can affect any joint), triggered by deposition of MSU crystals

- Uric acid: purine metabolite; increased production or decreased excretion from kidney

- With hyperuricemia(it doesn't mean that everyone with hyperuricemia will develop gout), risk increases with: 20-30 years of age, obesity, alcohol (for some reasons alcohol induces gouty attacks especially those with known case of gouty arthritis), genetic predisposition, drugs (thiazides; its diuretic given for hypertension & cause hyperuricemia and can induce acute gout arthritis)

GOUT / Diagnosis and Pathogenesis

Diagnosis

If a patient presents with a swollen, painful big toe, gout is the primary suspicion.

✓ In many cases, physicians may diagnose gout clinically (or sometimes using serum uric acid) and start treatment immediately with

- Colchicine for acute attacks
- Allopurinol for long-term maintenance

✓ However, the most accurate diagnostic step is joint aspiration to analyze the synovial fluid under a polarizing microscope.

If needle-shaped, negatively birefringent crystals are seen, this confirms gout.

Pathophysiology & Triggers

✓ Gout results from the metabolism of purines, which break down into uric acid and can precipitate as crystals in the joints.

✓ One of the strongest dietary triggers for acute gout attacks is consuming organ meats (like sheep liver), as they are rich in purines.

✓ Although diet plays a role, gout is multifactorial, influenced by genetics, kidney function, and other metabolic factors

The pathogenesis begins with hyperuricemia, where crystals form and deposit in the joint—most notably the big toe. These crystals initiate a cascade of inflammatory cell activation, releasing mediators like interleukin-1 beta. This, in turn, leads to destruction of both cartilage and synovium. These crystals are injurious, perpetuating the inflammatory reaction

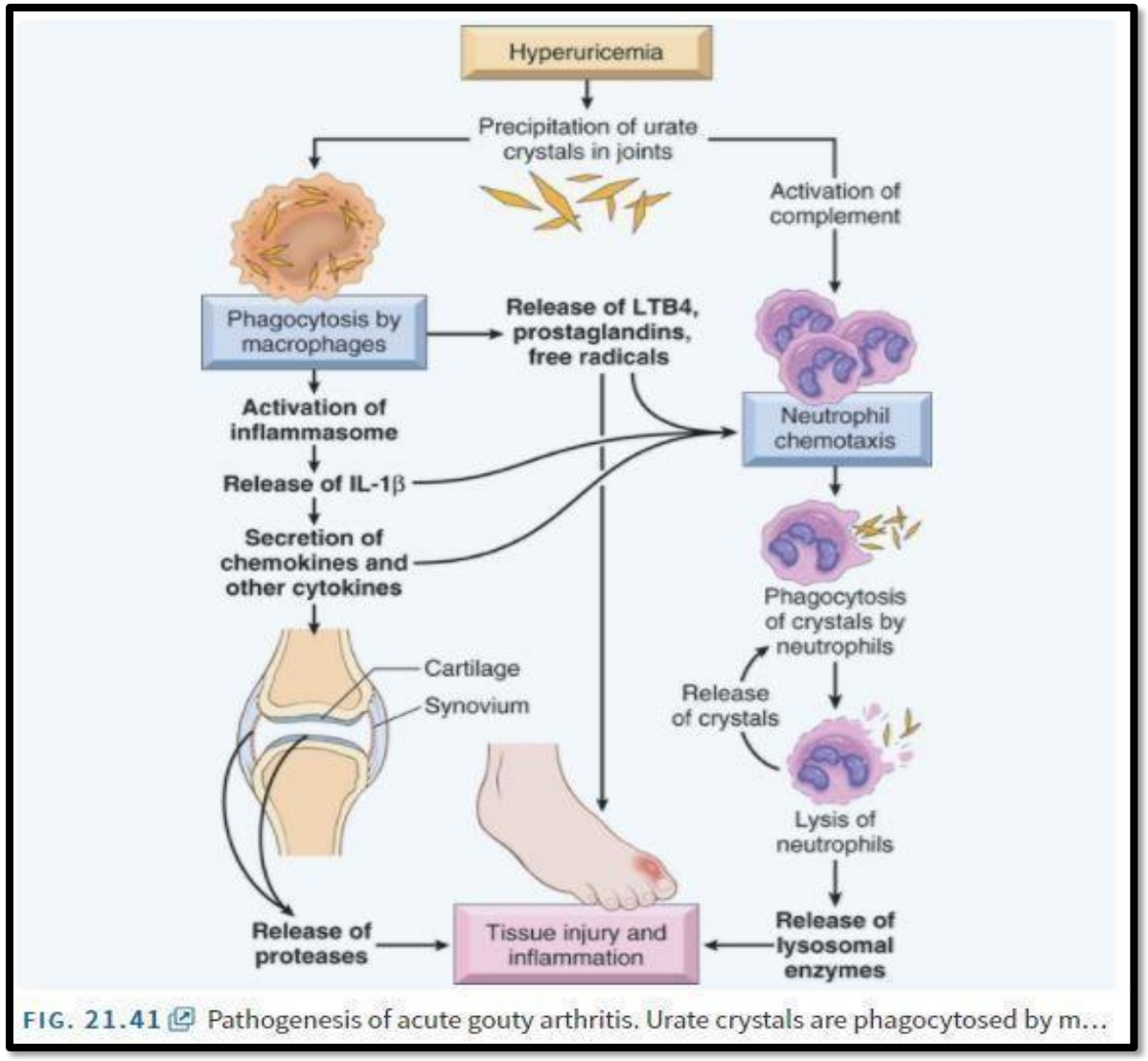


FIG. 21.41 Pathogenesis of acute gouty arthritis. Urate crystals are phagocytosed by m…

Gout is a form of hyperuricemia, where excess uric acid leads to the formation of monosodium urate (MSU) crystals in the joints

MORPHOLOGIC CHANGES OF GOUT

Clinically, gout may present with a **sudden acute attack**, often representing the **first episode experienced by the patient**. This acute attack typically involves severe pain, swelling, redness, and warmth in the affected joint. To confirm the diagnosis, **joint aspiration (arthrocentesis)** is performed, especially during the first presentation. **Synovial fluid** is obtained from the affected joint and examined **under a polarized light microscope**.

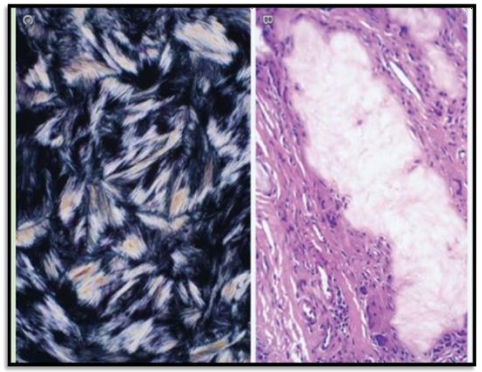
Microscopic examination allows visualization of **monosodium urate crystals**, which are characteristic of gout. These crystals must be differentiated from those seen in **pseudogout** because the two conditions may present with similar clinical symptoms.The distinction is made based on the shape and birefringence of the crystals under polarized light microscopy. (next slides)

MORPHOLOGIC CHANGES OF GOUT

Acute arthritis	Dense inflammation of synovium, MSU crystals in neutrophils, -ve birefringent
Chronic tophaceous arthritis **After years with gout**	Repetitive attacks s crystals deposition in the joint; thick synovium, pannus
Tophi in various sites **The tophus can precipitate anywhere**	Cartilage, ligaments, bursae and tendons
Gouty nephropathy **When causing a disease in the kidney**	MSU crystals deposition in kidney; nephrolithiaisis s pyelonephritis

- **Trx: life style modifications, NSAIDs** (Indomethacine)
- **Colchicine in acute gout & Familial Mediterranean Fever (FMF)**
- **Xanthine oxidase** (the enzyme that convert purine to uric acid) **inhibitors (Allupurinol** (brand name: Zyloric) **)in chronic and prevention**

This is the big toe they amputated it because it became bothersome to the patient, when they cut it from the middle it shows the chalky material that precipitated from crystals



Not only the joints are the targets but also the kidneys !

PSEUDOGOUT

ستبقى تائها حتى تصلي .!

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

In a patient with an underlying hematologic disorder who has required repeated blood transfusions every two months for 5-10 years, the development of joint inflammation should raise suspicion for pseudogout rather than gout

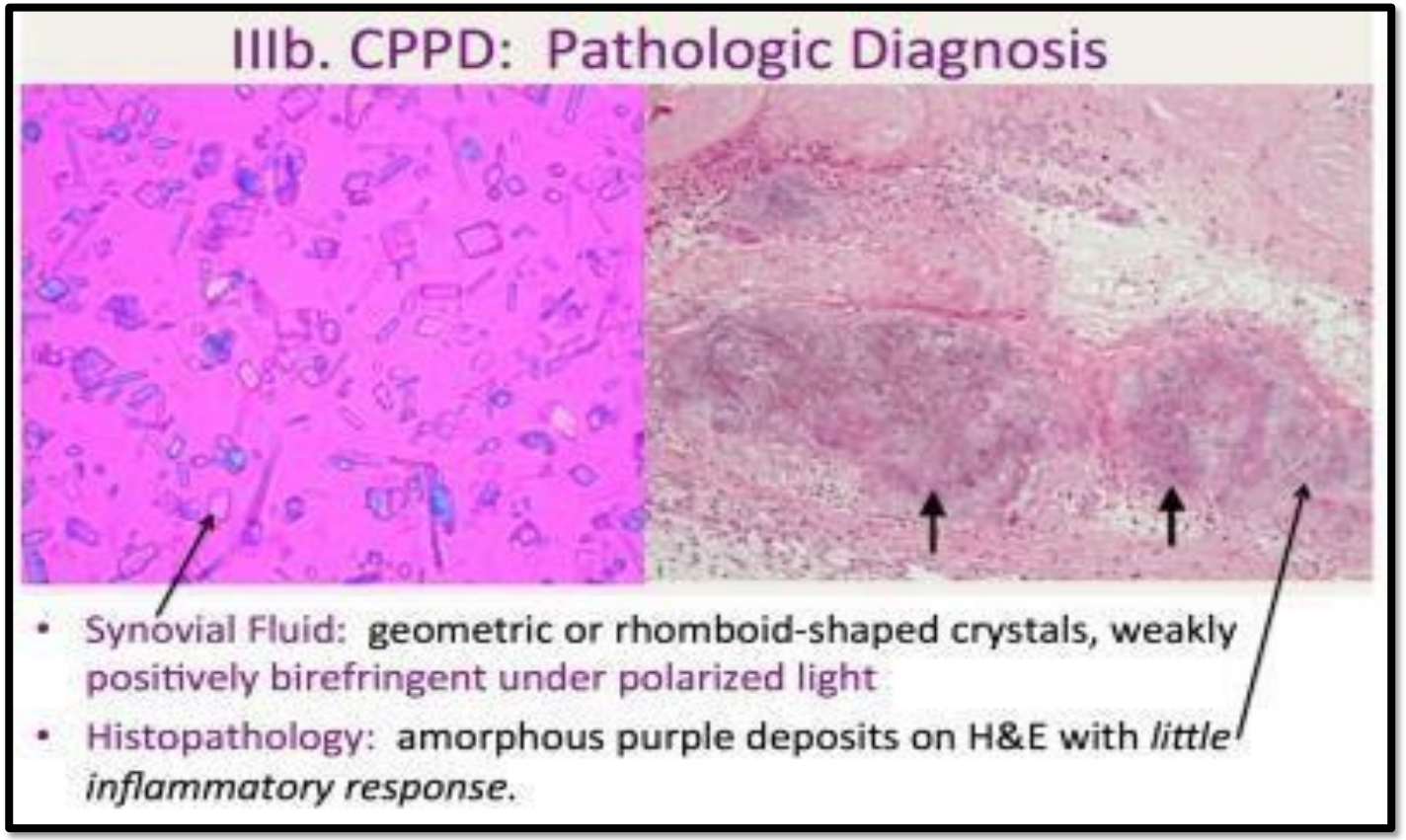
Diagnosis & Treatment

Diagnosis is more challenging than gout and requires joint aspiration with polarizing Microscopy but in gout it's obvious; big toe swollen and very painful in acute attack.

Under the microscope, CPPD crystals appear rhomboid-shaped and exhibit positive birefringence.

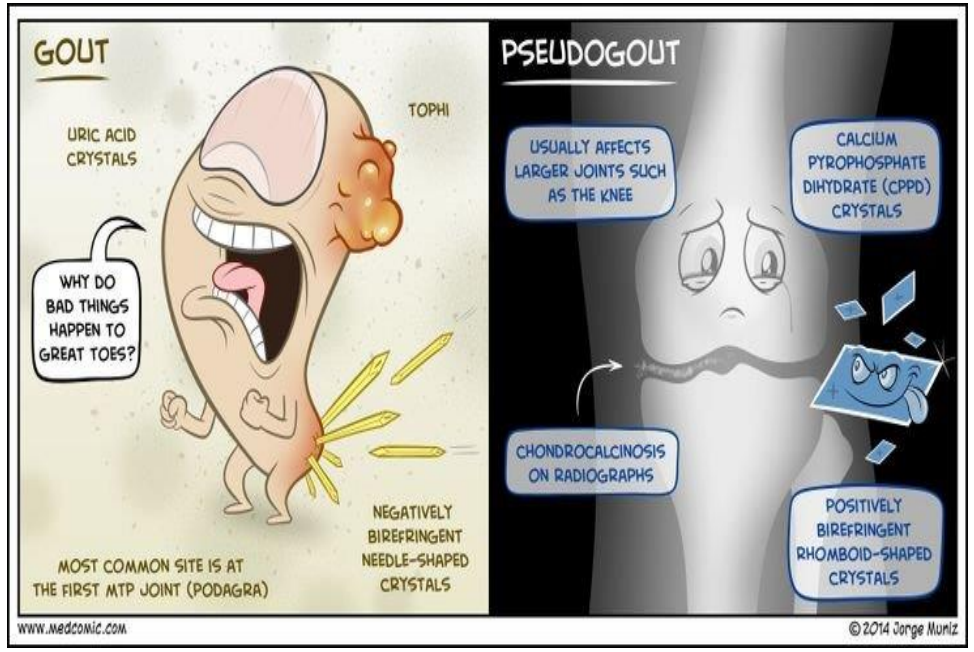
NSAIDs are the first-line treatment for acute attacks (supportive)

PSEUDOGOUT

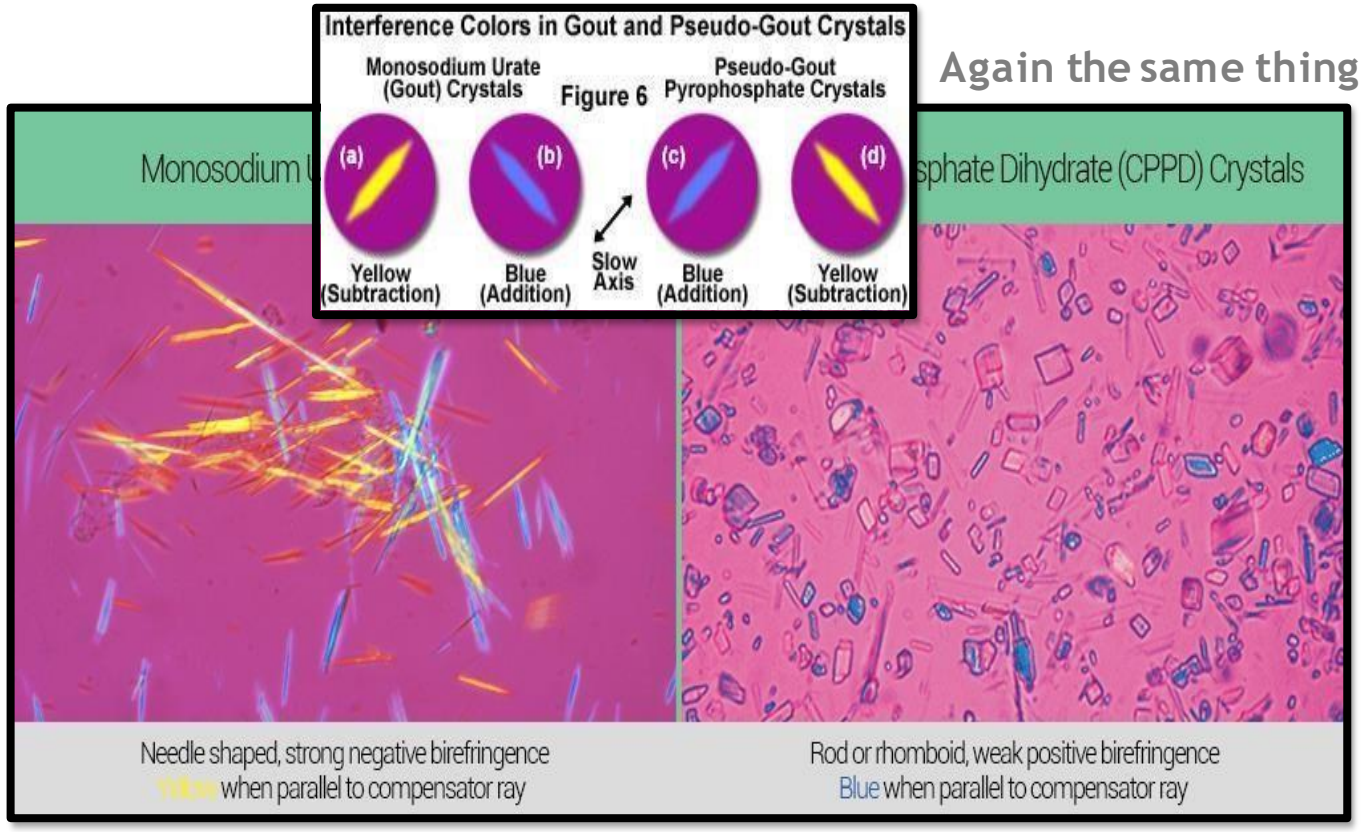


Shape: Rhomboid (square/diamond-shaped)
Unlike gout, where needle-shaped crystals with negative birefringence are seen, CPPD crystals appear rhomboid and show positive birefringence.

NEGATIVE VS POSITIVE BIERFRINGENCE



Again the same thing ☺



Using a polarizing microscope is a precise but somewhat challenging procedure for diagnosing crystal-induced arthritis.

Crystal Identification:

- Gout (MSU Crystals): **Needle-shaped (yellow). Negative birefringence**
- CPPD (Calcium Pyrophosphate Crystals): **Rhomboid-shaped. Positive birefringence**

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 (misnomer) and tenosynovial giant cell tumor are the most frequent
- Ganglion cyst: common condition; close to a joint, dorsum of wrist (hand) and dorsum of the foot ; not true cyst, no communication with synovial joint; may cause pressure pain (on nerves) ; treated by surgical removal (these are typically soft tissue and are benign). In the past, this condition was thought to represent a **herniation of the synovium**, but histological examination usually shows **negative synovial markers**, indicating that it is not a true synovial cyst.
- True synovial cyst (Baker cyst around the knee (popliteal fossa)): herniation process

✓ When a swelling with fluid appears behind the knee, the primary diagnosis is often a Baker's cyst (true synovial cyst)
✓ However, when it becomes symptomatic and painful it's removed sometimes it puts pressure on the veins and cause DVT (deep vein thrombosis)

True vs. pseudo Cysts in Surgery
True cysts have a lining, while pseudo cysts lack one
If the cyst has an epithelial lining, it is called an epithelial cyst (like in the pancreas or skin)
If the cyst has a synovial lining, it is called a synovial cyst

TENOSYNOVIAL GIANT CELL TUMOR

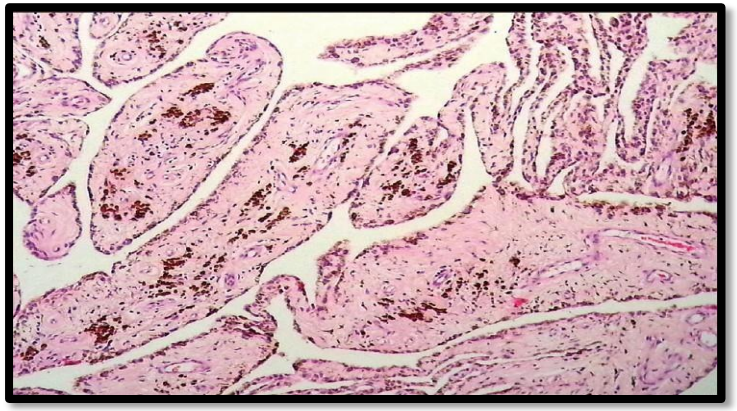
- **Benign neoplasm of synovium (multinucleated giant cells)**
- **Diffuse (pigmented villonodular (fingers and nodules) synovitis** misnomer not an -itis**, PVNS, large joints,** the most common is the knee joint**) or localized small hands tendons (treated by removing the tumor and damaged joint tissue).**
- **t(1;2)(p13;q37) → affecting COL6A3, which affects Macrophage-Colony Stimulating Factor 1 (M-CSF1) fusion, leading to CSF1 overexpression and macrophage recruitment.**

Diagnosis and Procedure

Arthroscopy is commonly used by orthopedic surgeons to enter the joint and observe the synovium directly. The affected synovium often appears dark brown or reddish in color, resembling coral (referred to as the coral-like appearance), which is characteristic of PVNS.

Why brown?

appears pigmented due to hemosiderin deposition. Macrophages ingest red blood cells, break them down, and store iron as hemosiderin, which causes the brownish color. Under the microscope, this brown pigmentation is typically visible. While iron stains, such as Prussian blue (Perls stain), can confirm iron, in this case, the brown pigmentation alone is typically diagnostic no need for special stain



SOFT TISSUE TUMORS

لَا إِلَٰهَ إِلَّا أَنتَ سُبْحَانَكَ إِنِّي كُنتُ مِنَ الظَّالِمِينَ

- Benign >>>>>>malignant
- Incidence in America: 1% and cause 2% cancer death
- Sarcomas are aggressive and metastasize mainly to lungs, hematogenou spread

Soft Tissue Tumors and Sarcomas

Sarcomas are malignant neoplasms that arise from mesenchymal tissue such as bone, cartilage, or fibroblasts, but not from epithelial cells. These tumors are typically aggressive and can metastasize to other parts of the body

For osteosarcoma, the lungs are the most common site for metastasis, so a CT scan or PET/CT scans of the chest is essential to rule out lung metastases

Metastasis and Lymphatic Involvement

Sarcomas typically do not spread to lymph nodes, but some rare types may do so (like synovial and epithelioid sarcoma)

When a patient presents with a large soft-tissue mass in the thigh measuring more than 20 cm, particularly in an elderly patient such as a 70-year-old, it is considered a sarcoma until proven otherwise, you do chest x-ray and find nodules, bad news this sarcoma stage 4 very poor survival

SOFT TISSUE TUMORS

- **Most are in extremities (thigh)**

Sarcomas can originate from any soft tissue. For example Uterus: Leiomyosarcoma, Heart: Rhabdomyosarcoma (cardiac RMS), Thigh soft tissue (most common): Pleomorphic sarcoma and liposarcoma

No genetic predisposition or inheritance

- **Most are sporadic ; very few arise from tumor suppressor gene mutations (NF1 (neurofibromatosis type 1), Gardner syndrome, Li-Fraumeni syndrome, Osler- Webber-Rendu Syndrome)** have higher risk of sarcomas of soft tissues higher than the general population

Sporadic sarcomas appear without a clear marker. However, some sarcomas are associated with genetic predispositions, including mutations in tumor suppressor genes, particularly p53, which is one of the most common genetic abnormalities in cancer

- **Few occur after exposure to radiation the most common (risk factors), burns &toxins. (Secondary sarcomas)**

Radiotherapy is commonly used in the treatment of several cancers, including prostate cancer, lung cancer, breast cancer, and sarcomas. However, the tissues exposed to radiation therapy may have an increased risk of developing secondary sarcomas. Therefore, a history of prior radiation exposure is an important risk factor to consider when evaluating a patient who presents with sarcoma

SOFT TISSUE TUMORS:

- **No precursor lesions; theory that they arise from pluripotent mesenchymal stem cell which acquire somatic mutation:**

1. Carcinomas (e.g., colon, cervical, and endometrial):

These cancers typically follow a specific, **step-by-step sequence of progression:**

- Normal epithelium
- Atypia (abnormal tissue growth)
- Dysplasia
- Carcinoma in situ (localized cancer)
- Invasion (breaking through the basement membrane)

2. Sarcomas (e.g., liposarcomas) and Benign Tumors (e.g., lipomas):

Unlike carcinomas, these tumors (which come from mesenchymal cells) do not follow a step-by-step precursor pattern.

- **Liposarcomas** arise directly as malignant (cancerous) tumors right from the start, and doesn't begin as a benign tumor.
- A **lipoma** simply stays benign, and **doesn't transform into liposarcoma.**

SOFT TISSUE TUMORS:

- **15-20% simple karyotype, single signature mutation (Ewing and synovial sarcoma) (You must know both of their translocations mentioned on slide 18):**
- **80-85% complex karyotype (genomic instability), LMS and Pleomorphic Sarcoma**

Soft tissue tumors are genetically divided into a smaller group (15-20%) with simple karyotypes driven by **single signature mutations (such as Ewing and synovial sarcomas)**, and a vast majority (80-85%) with complex karyotypes characterized by **widespread genomic instability (such as LMS [leiomyosarcoma] and pleomorphic sarcoma)**, where you can find 10 abnormal chromosomes for example.

Molecular testing here is essential for confirming the diagnosis of certain cancers, as it can identify specific genetic translocations. **Ewing's sarcoma and synovial sarcoma** are examples where molecular testing is critical for identifying targeted therapies based on specific genetic mutations or translocations. These targeted therapies can greatly improve treatment outcomes by focusing on specific genetic aberrations in the tumor.

SOFT TISSUE TUMORS:

- **Wide range (benign-highly malignant).**
- **Diagnosis, grade and stage are all important.**

Importance of Grade and Stage in Sarcomas and Carcinomas:

• **Sarcomas:** Both **Grade** and **Stage** are **highly important** for determining the prognosis and treatment.
• **Carcinomas (for comparison): Stage** is generally considered the **more important** factor.

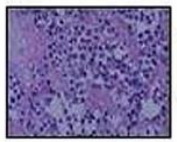
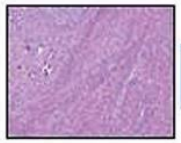
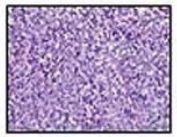
Tumor Grade:

• **Definition:** Grade refers to how abnormal the tumor cells look under a microscope compared to normal, healthy cells. It helps predict how fast the tumor will grow and spread.
• **Well-Differentiated (Low Grade):** The cells look closer to **normal**. This generally indicates a **good** prognosis and slower growth.
• **Poorly Differentiated (Grade 3 / High Grade):** The cells look very **abnormal**. This indicates a **bad** prognosis and aggressive growth.

Metastasis (Spreading):

• **High Risk: Advanced** and **high-grade** sarcomas are usually the ones that metastasize (spread to other parts of the body).
• **Low Risk: Low-grade** sarcomas typically do not metastasize.

Only memorize synovial & Ewing sarcoma:

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 Benign

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

Occurs under the skin (subcutaneous) and is easily removed.

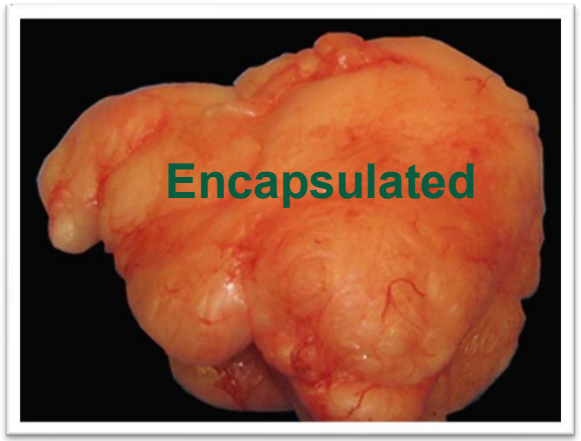
LIPOSARCOMA Malignant

- Most common sarcomas in adults. >50 years.
- Extremities (thigh) and retroperitoneum (large masses; can reach 20cm).
- 3 types: (not important)
  - Well (MDM2 gene chr 12)
  - Myxoid, t(12,16)
  - Pleomorphic (aggressive)

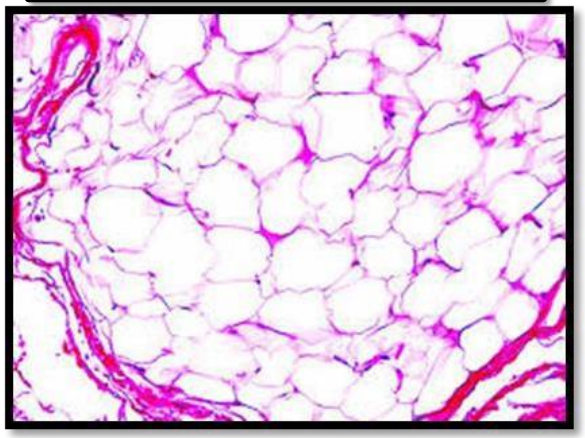
A 65-year-old patient presents with a large thigh mass measuring 20×20×15 cm:
→ it's liposarcoma until proven otherwise

LIPOMA PATHOLOGIC FEATURES:

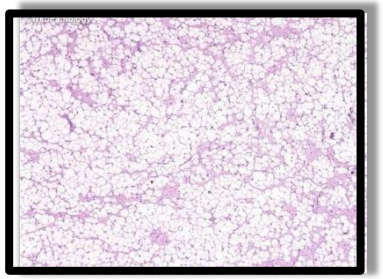
Pump shows under the skin :
-Well circumscribed (not infiltrating the structure around it) making it easy to remove.
-Little or No change in size with time (stays the same size five years later).



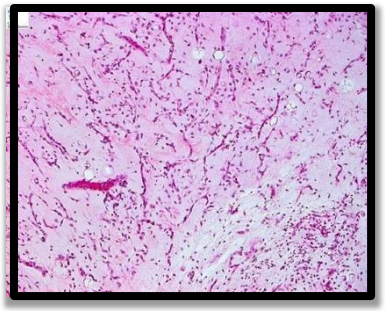
Benign looks like mature adipocytes.



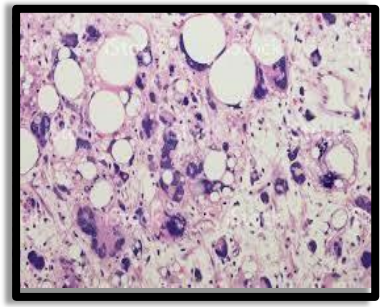
LIPOSARCOMA FEATURES:



Well- differentiated:
Grade 1



Myxoid:
Grade 1/2



Pleomorphic:
High grade+ bad prognosis

Huge with black and white regions (heterogenous). There are bad signs like hemorrhage and necrosis

رسالة من الفريق العلمي:

عن أبي هريرة -رضي الله عنه-، عن النبيّ -صلّى الله عليه وسلّم- أنّه قال:
"مَن رَأَى مُبتَلًى فقال: الحمدُ للهِ الذي عافَانِي مِمَّا ابْتلاكَ به، وفَضَّلَنِي على كَثيرٍ مِمَّنْ خلق تَفضِيلًا، لَمْ يُصِبْهُ ذلكَ البلاءُ".

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Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			