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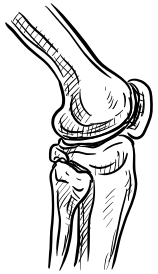

PATHOLOGY

Final | Lecture 3 (A&B)

MSS & skin tumors pt.8

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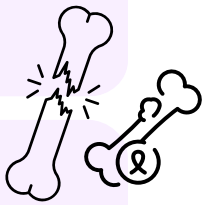

﴿ وَإِن تَتَوَلَّوْا يَسْتَبْدِلْ قَوْمًا غَيْرَكُمْ ثُمَّ لَا يَكُونُوا أَمْثَالَكُم ﴾

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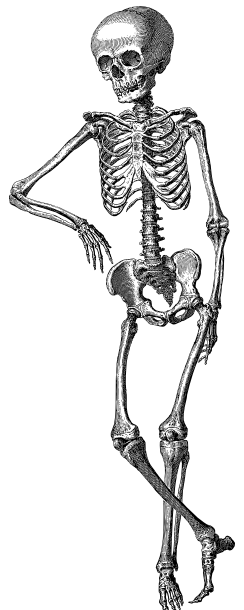


SUPPURATIVE ARTHRITIS

- Bacterial infection
- Hematogenous spread
- < 2 years: H. influenza; older children s 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 s Rx: aspiration of joint; antibiotics

SUPPURATIVE ARTHRITIS

Suppurative arthritis or septic arthritis is an acute joint infection characterized by pus formation and inflammation within the joint space. It often occurs in conjunction with acute osteomyelitis. For example, if osteomyelitis affects the distal femur, the adjacent knee joint is commonly involved due to the proximity and shared blood supply. However, septic arthritis can also occur independently without any bone involvement.

Clinical Presentation

The condition presents acutely with systemic manifestations. Prompt diagnosis is essential, as delayed treatment can lead to joint destruction.

Diagnosis

Joint aspiration is a key diagnostic step. The synovial fluid will typically show:
(High white blood cell (WBC) count, Presence of bacteria on Gram stain or culture, Cultures help identify the causative organism and determine antibiotic sensitivity)

Etiology

The infection is usually hematogenous in origin (spread through the bloodstream).
The causative organisms vary with age:
In children under 2 years, Haemophilus influenzae is a common pathogen. Empirical antibiotic coverage should include H. influenzae until culture and sensitivity results are available.

Imaging

Radiographic findings may initially be normal, especially early in the disease.
More sensitive imaging, such as ultrasound or MRI, may be needed to detect joint effusion or early osteomyelitis.

LYME ARTHRITIS

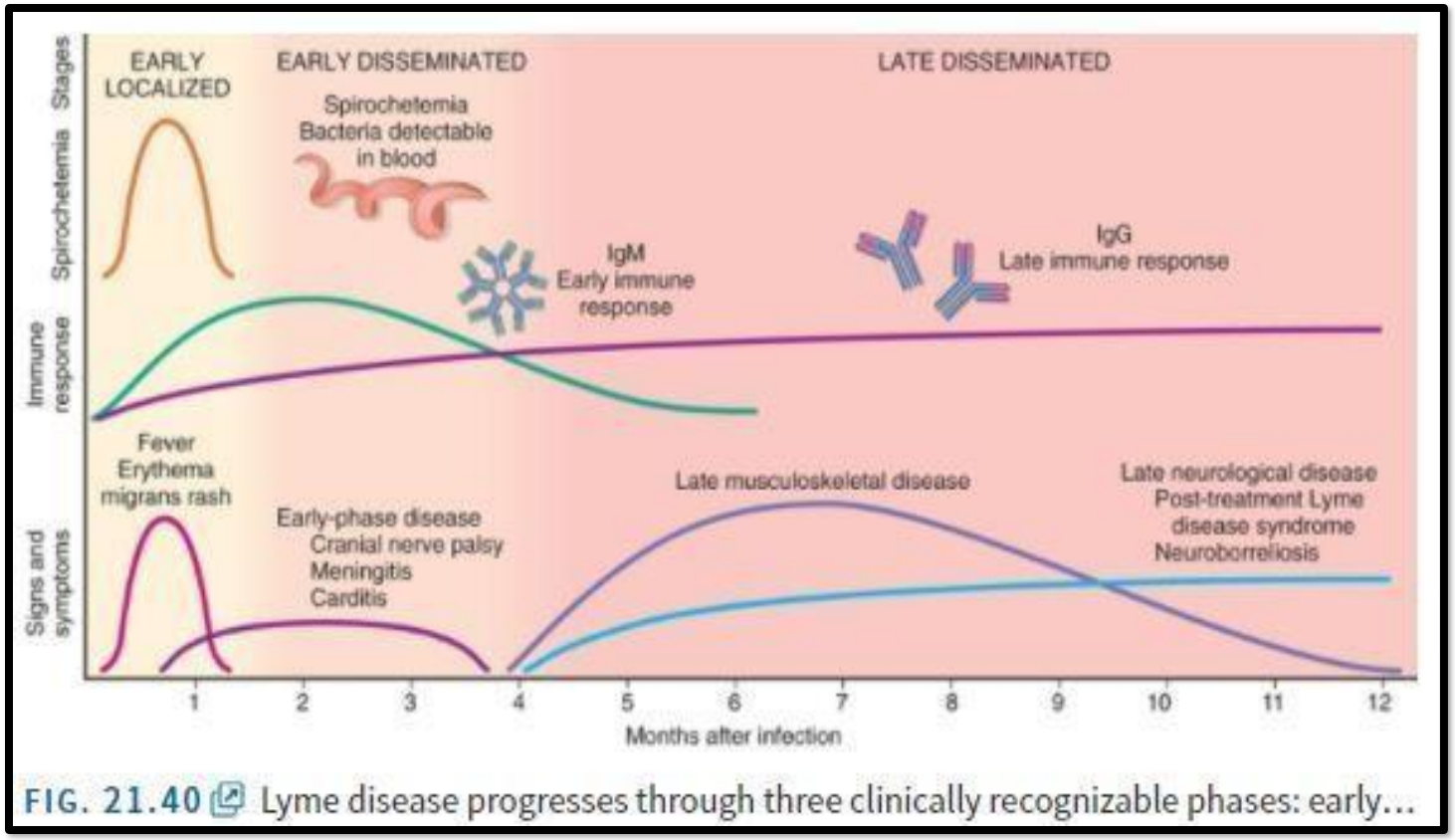


FIG. 21.40 Lyme disease progresses through three clinically recognizable phases: early…

Lyme disease is caused by the bacterium Borrelia burgdorferi, which has an interesting story§ behind its name (click HERE). This disease is a bacterial-induced arthritis that is rare in our country but is more commonly observed in the northeastern United States. The higher prevalence in that region is due to the presence of ticks, which act as vectors transmitting the organism through their bites

LYME ARTHRITIS

Lyme disease is a systemic infectious disease that can present with a specific type of arthritis as part of its broader clinical picture. It is caused by spirochetes, specifically the bacterium Borrelia.

Initial Phase
The disease begins with generalized systemic symptoms, such as fever. A characteristic skin rash may appear, known as erythema migrans. In some cases, the infection can spread to the cranial nerves, causing neuritis and cranial nerve palsy. The organism may also invade the meninges, resulting in meningitis, or reach the heart, leading to carditis.

Immune Response
The initial infection triggers a primary immune response, mainly involving IgM antibodies. As the infection spreads (disseminates), a secondary immune response occurs with the production of IgG antibodies.

Musculoskeletal Involvement
During the period when both IgM and IgG responses are active, musculoskeletal symptoms, including infectious arthritis, can begin to appear. This arthritis may sometimes be self-limiting, while in other cases, it requires treatment.

Late Manifestations
After treatment, some patients may experience late neurological deficits, known as post-treatment Lyme disease syndrome or neuroborreliosis.

Lyme disease progresses in multiple phases and is driven by both the infection itself and the immune response. It is a systemic condition.

CRYSTAL-INDUCED ARTHRITIS

- Crystals deposited in joints causing disease
- Crystals triggers inflammatory reaction that destroys cartilage
- It can present as an acute condition, chronic condition, or begin acutely and then progress into a chronic phase over time
- Endogenous (Produced inside your body) crystals:
  - ✓ Monosodium urate, MSU (GOUT)
  - ✓ Calcium pyrophosphate dihydrate, CPPD (PSEUDOGOUT)

- ✓ Diagnosis is confirmed by aspiration of joint fluid, followed by microscopic examination to identify the crystals
- ✓ Crystals can be found in urine or joint fluid, and their identification is essential for diagnosis
- ✓ One of the key diagnostic tools is the polarizing microscope, which helps differentiate between types of crystals based on their birefringence properties

- Gout is caused by monosodium urate (MSU) crystals, which show negative birefringence under polarized light.
- CPPD disease is caused by calcium pyrophosphate dihydrate (CPPD) crystals, which show positive birefringence under polarized light.

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, risk increases with: 20-30 years of age, obesity, alcohol, genetic predisposition, drugs (thiazides)

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**

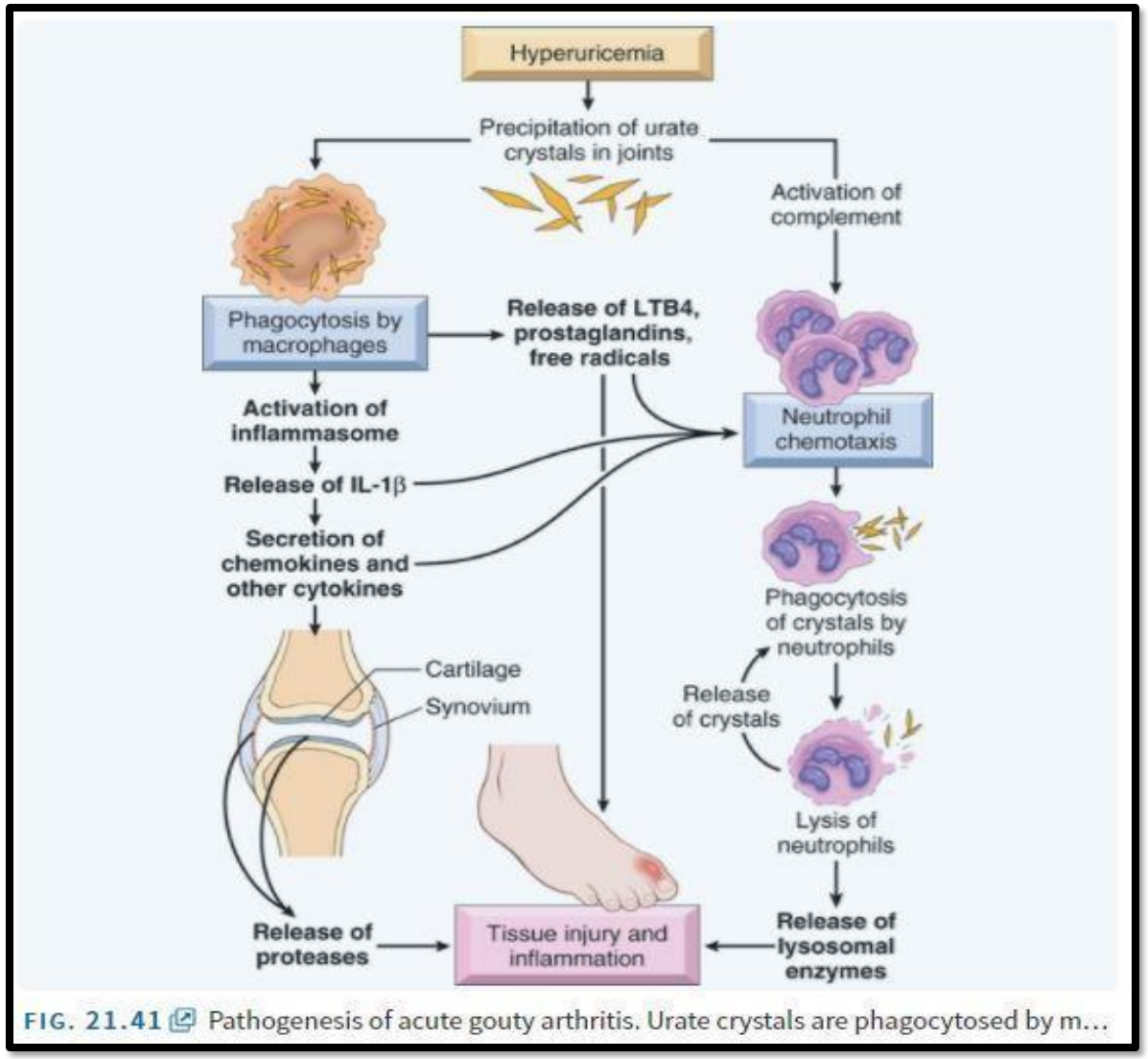


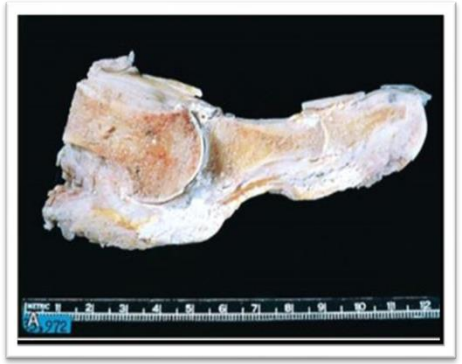
FIG. 21.41 Pathogenesis of acute gouty arthritis. Urate crystals are phagocytosed by m…

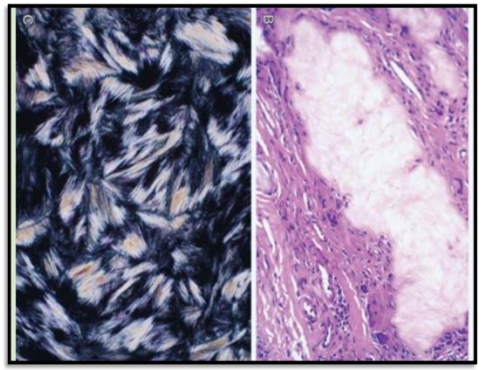
Gout is a form of hyperuricemia, where excess uric acid leads to the formation of monosodium urate (MSU) crystals in the joints

MORPHOLOGIC CHANGES OF GOUT

Acute arthritis	Dense inflammation of synovium, MSU crystals in neutrophils, -ve birefringent
Chronic tophaceous arthritis	Repetitive attacks s 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 s pyelonephritis

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





PSEUDOGOUT

- > 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, hemochromatosis
- Acute, subacute and chronic forms
- Trx: supportive, no preventive measures so far

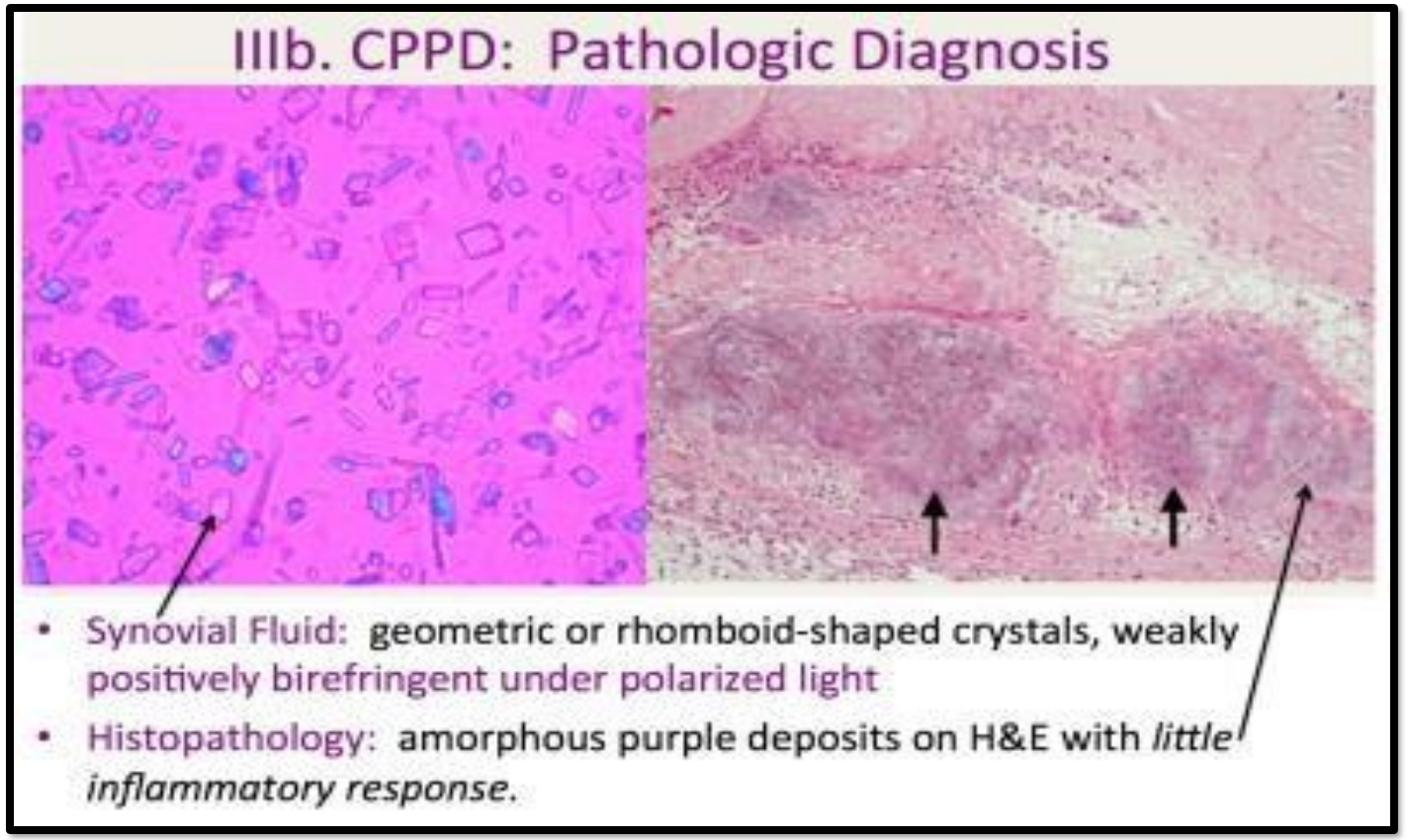
Diagnosis & Treatment

Diagnosis is more challenging than gout and requires joint aspiration with polarizing microscopy.

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

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

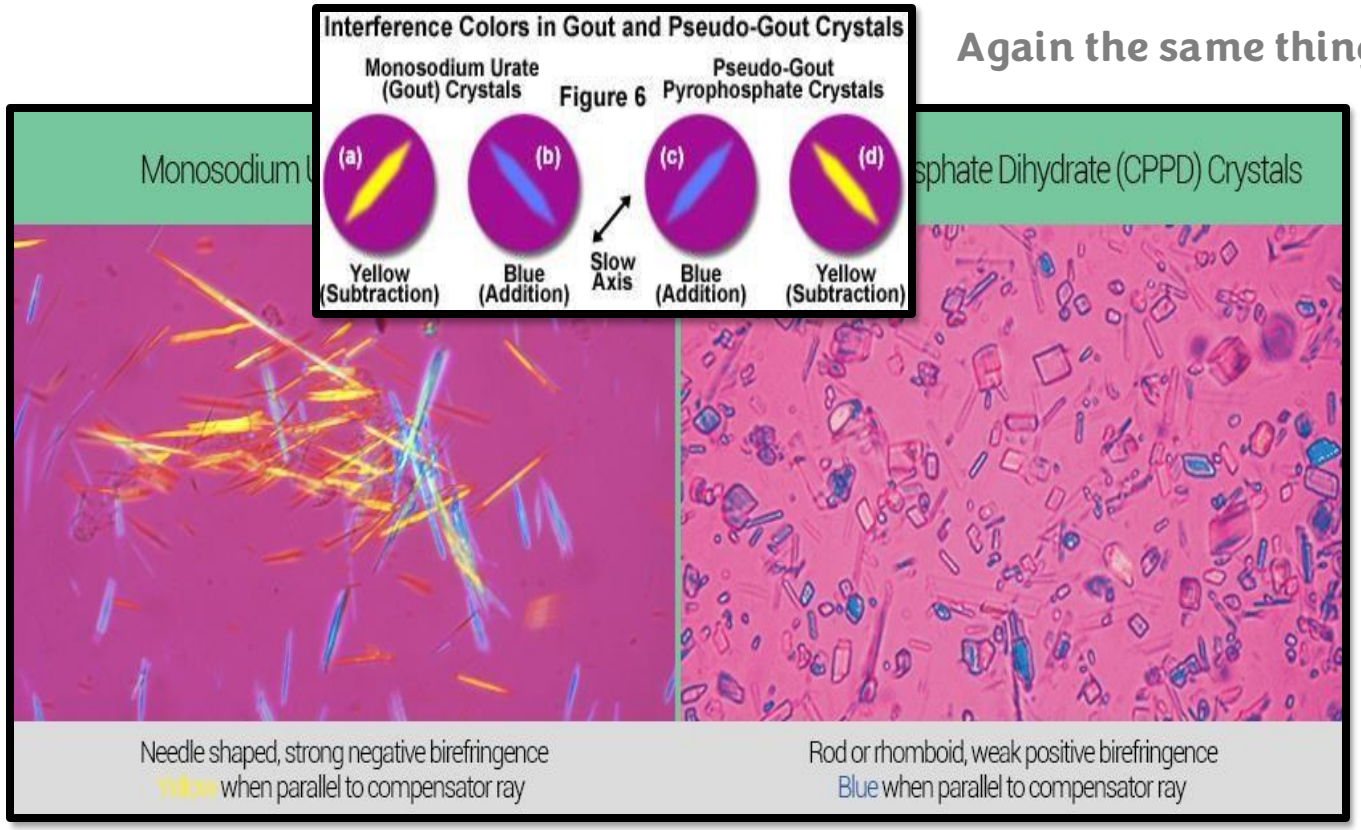
PSEUDOGOUT



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)
- True synovial cyst (Baker cyst around the knee): herniation process

✓ When a swelling with fluid appears behind the knee, the primary diagnosis is often a Baker's cyst (true synovial cyst)
✓ However, to confirm it's a Baker's cyst and not another type of tumor, surgical removal may be necessary. Baker's cysts are usually benign but need to be differentiated from other conditions

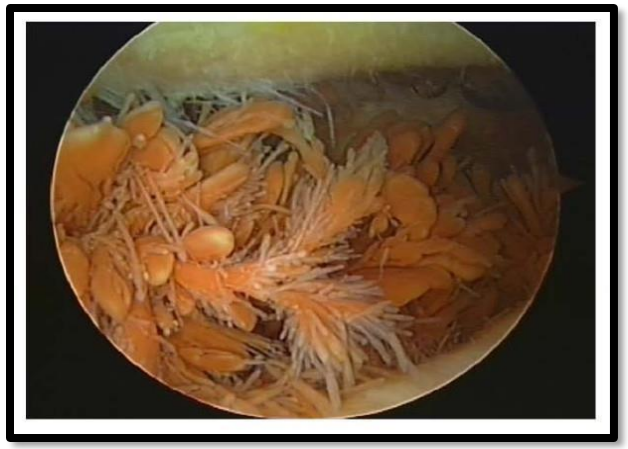
True vs. False Cysts in Surgery
True cysts have a lining, while false cysts lack one
If the cyst has an epithelial lining, it is called an epithelial cyst (like in the pancreas or skin)
If the cyst has a synovial lining, it is called a synovial cyst

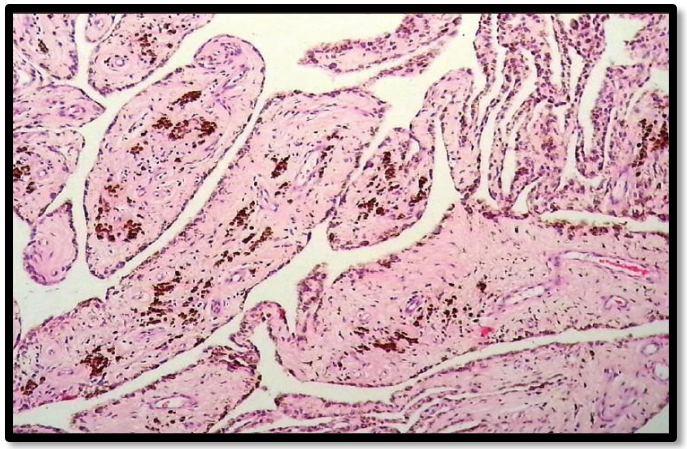
TENOSYNOVIAL GIANT CELL TUMOR

- Benign neoplasm of synovium (multinucleated giant cells)
- Diffuse (pigmented villonodular synovitis, PVNS, large joints) or localized small hands tendons (treated by removing the tumor and damaged joint tissue).
- T(1;2)(p13q;37); affecting type VI (6) collagen α-3

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.





SOFT TISSUE TUMORS

- Benign >>>>>>malignant
- Incidence: 1% and cause 2% cancer death
- Sarcomas are aggressive and metastasize mainly to lungs, hematogenous 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)

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

- Most are sporadic; very few arise from tumor suppressor gene mutations (NF1, Gardner syndrome, Li-Fraumeni syndrome, Osler- Webber-Rendu Syndrome)

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 (risk factors), burns s toxins. (Secondary sarcomas)

SOFT TISSUE TUMORS

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

Unlike epithelial tumors, which can have a progression from normal epithelium to metaplasia (abnormal tissue growth), then dysplasia, carcinoma in situ (localized cancer) and finally superficial then deep invasion, sarcomas like liposarcomas do not follow such a precursor lesion pattern. Liposarcomas typically arise directly as malignant tumors withOUT any benign precursor lesion like a lipoma transforming into a liposarcoma

- 15-20% simple karyotype, single signature mutation (Ewing and synovial sarcoma)

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.

- 80-85% complex karyotype (genomic instability), LMS and pleomor. Sarcoma

SOFT TISSUE TUMORS

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

✓ Grading of Sarcomas

Grading of sarcomas is done based on how closely the tumor cells resemble the normal cells from which they originated (differentiation).

- Low-grade sarcomas: These tumors resemble normal tissue more closely and grow more slowly.

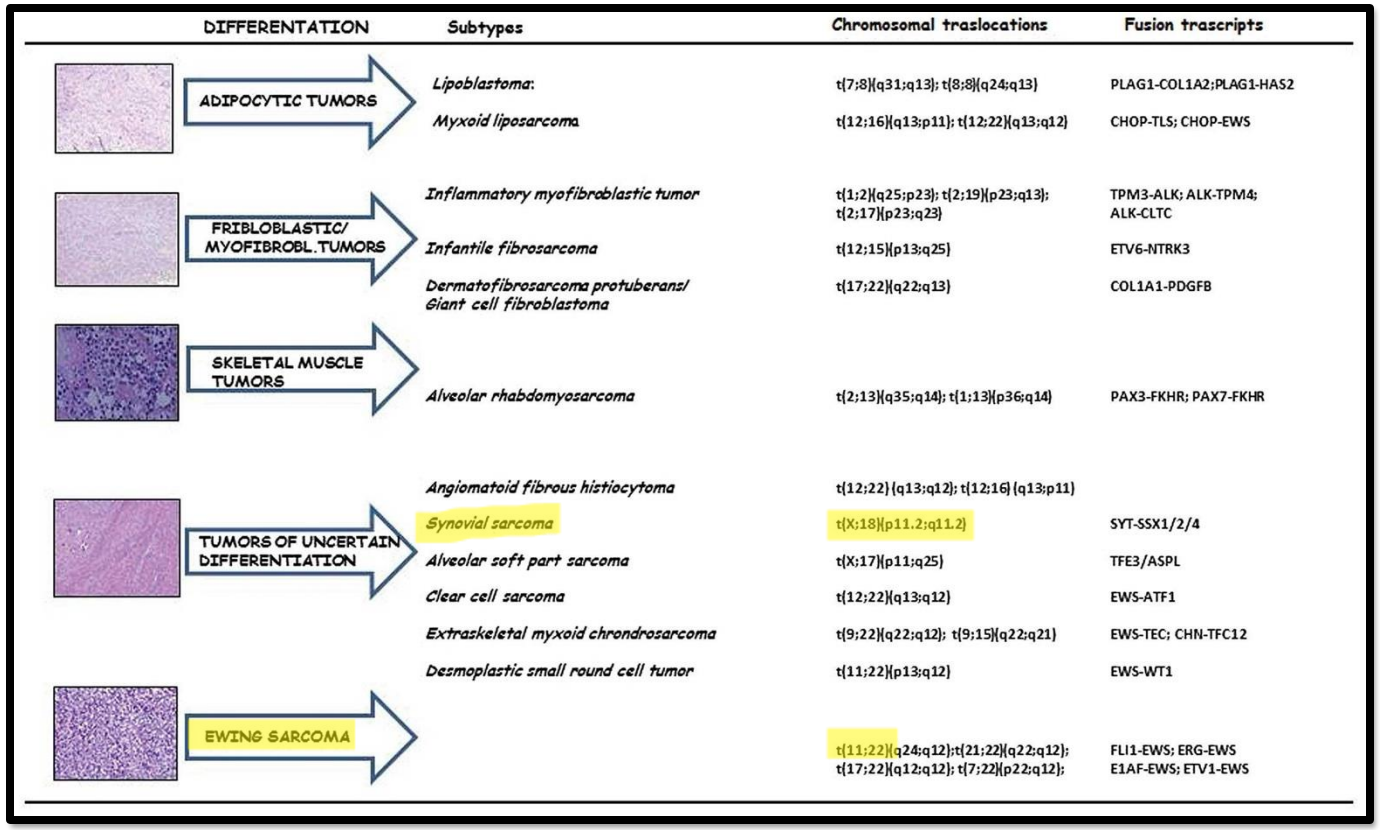
Examples: Well-differentiated liposarcoma and myxoid liposarcoma (to be discussed)

- High-grade sarcomas: These tumors have more abnormal cell structures and are more aggressive, growing and spreading more rapidly.

Examples: Pleomorphic liposarcoma (to be discussed) , (Osteosarcoma and Ewing sarcoma → high grade by definition)

✓ Staging and Prognosis

- Staging refers to the extent of the tumor and its spread to other parts of the body. The stage is the most important factor in determining prognosis.
- Stage 4 is the most advanced stage and generally correlates with the worst prognosis, as it indicates that the cancer has metastasized to distant organs.
- Early diagnosis is crucial because it allows for more effective treatment before the tumor spreads, improving the overall chances for a positive outcome.



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

Only memorize synovial & Ewing sarcoma

ADIPOSE TISSUE TUMORS:

LIPOMA

Benign

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

Occurs under the skin(subcutaneous) and is removed either for cosmetic purposes (due to disfigurement) or to ensure it is not malignant or painful (pressing on nerves)

LIPOSARCOMA

Malignant

- Most common sarcomas in adults. >50 years
- Extremities and retroperitoneum

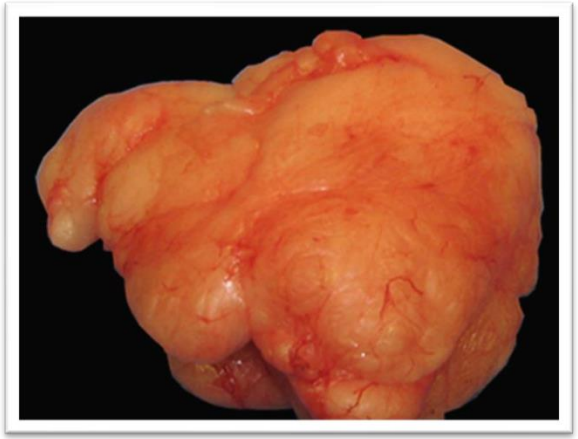
  Usually thigh or retroperitoneal
- 3 types:
  - WD (MDM2 gene chr 12) — Well differentiated
  - Myxoid, t(12,16)
  - Pleomorphic (Very aggressive)

Low grade

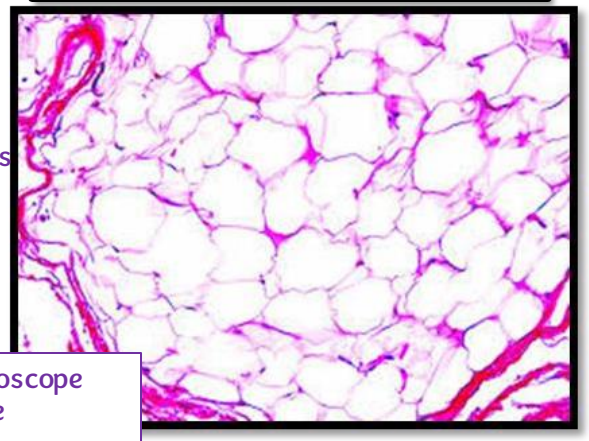
A 65-year-old patient presents with a large retroperitoneal mass measuring 20×20×15 cm
→ it's liposarcoma until proven otherwise

LIPOMA PATHOLOGIC FEATURES:

Pump shows under the skin :
-well circumscribed making it easy to remove
-no change in size with time (stays the same size five years later)

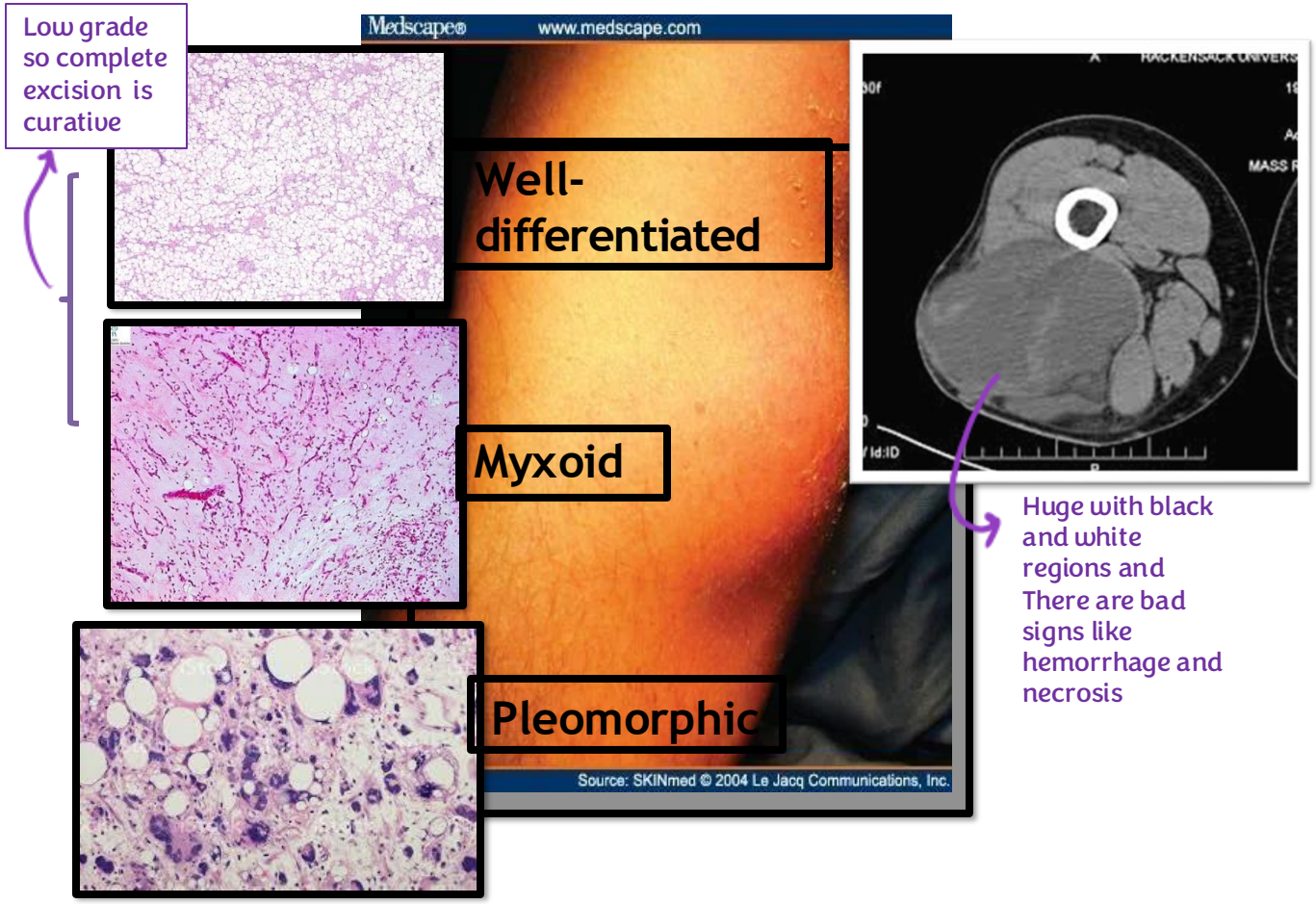


Benign
Look like normal adipocytes

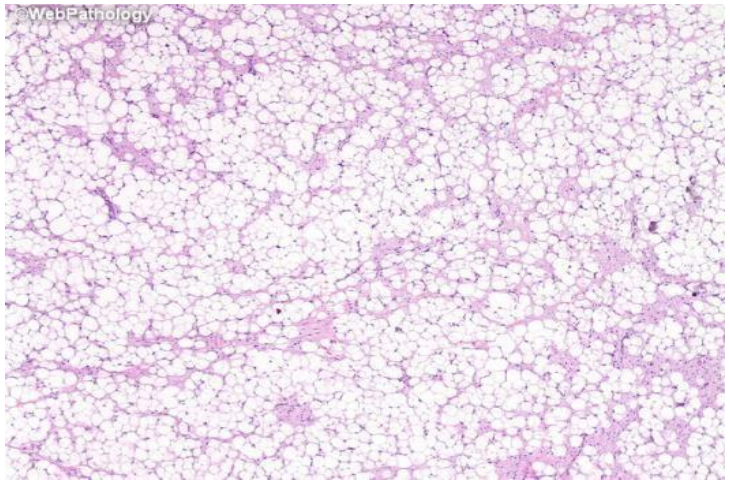


We use a microscope for a definitive diagnosis

LIPOSARCOMA FEATURES:



Well- differentiated



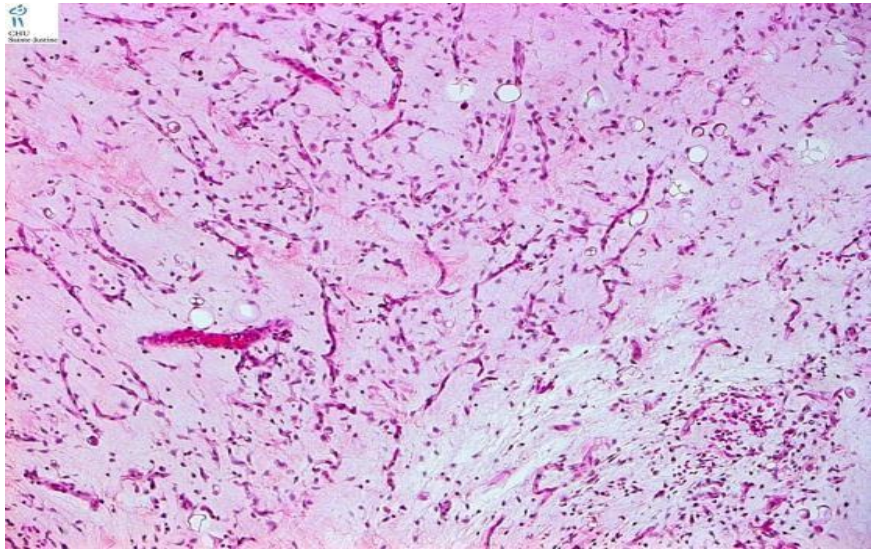
Look like benign adipocytes

Very difficult to differentiate large lipoma from liposarcoma
Also called atypical lipomatous tumor (LDLM2 to confirm)

In the past when a "lipoma" was found in deep soft tissue (like retroperitoneum or thigh) and seems atypical in behavior or appearance , they would look for lipoblasts to confirm liposarcoma.

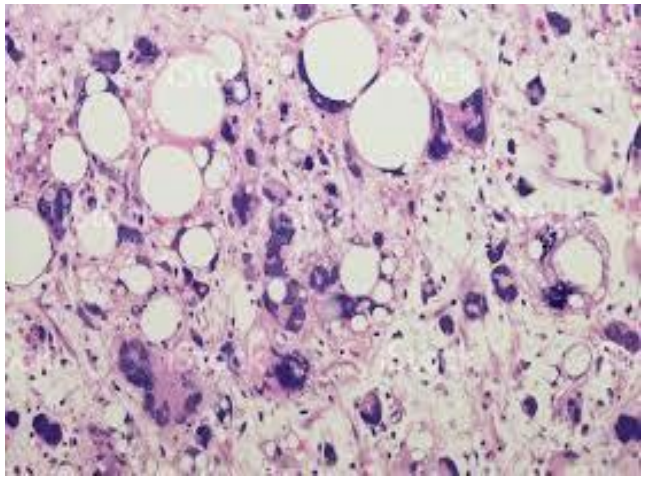
Myxoid

Also a low grade tumor



Greyish background
'more cellular' → not adipocytes
A different marker is used

Pleomorphic



No significant translocations

features :
- Older patients
- Larger
- Retroperitoneum & Thigh (can happen anywhere but these two are the most common ones)
- Less common than the previous two
- Lung nodules appear indicating lung metastasis

a lot of ugly cells
with Karyotyping / chromosomal analysis
→ multiple abnormal karyotypes → 6-7 abnormalities

SOME NOTES

As we know, cancers are typically named based on the organ they originate from. However, this is not the case for synovial sarcoma, as it does not arise from the synovial lining of the joints. Instead, it is named so because, under the microscope, the tumor cells resemble synovial tissue.

features of benignancy :
-well circumscribed
- formation of a fibrous capsule or a pseudocapsule
-easily removed without damaging surrounding structures
Features of malignancy :
-larger
-harder to remove
-infilterative(invade and destroy surrounding tissue)

Generally, sarcoma is a malignant tumor of mesenchymal origin and tends to arise de novo (from the beginning without precursor lesions)
while a carcinoma (which originates from epithelial cells often derived from ectoderm or endoderm) often arises from precursor lesions
and that is why screening tests are useful for early detection.
Lipomas (benign) and liposarcomas (malignant) both usually arise de novo meaning there are no precursor lesions

A liposarcoma is not a progression from a lipoma; each arises independently.

Soft tissue tumors can occur anywhere in the body where adipocytes are present but the most common location is the subcutaneous tissue (under the skin)

Pigmented Villonodular Synovitis (PVNS) also called tenosynovial giant cell tumor s a true neoplastic lesion of synoviocytes (cells lining the synovium).
It leads to joint pain ,locking, and swelling.
Arthroscopy may reveal brownish (pigmented) tissue due to hemosiderin deposition.

CLINICAL QUESTIONS FROM DOCTOR'S NOTES

A 50-year-old woman presents with multiple new lung nodules on chest imaging. Ten years ago, she underwent surgery to remove what was pathologically diagnosed as a "benign fibroid" (leiomyoma) from her uterus. A biopsy of one of the new lung nodules now confirms metastatic leiomyosarcoma.
Which of the following best explains the current findings?

a) A previously benign uterine leiomyoma has undergone malignant transformation over time.
b) The benign uterine fibroid regrew locally and spread to the lungs.
c) The original uterine lesion was likely malignant (leiomyosarcoma) but was misdiagnosed.
d) Metastatic disease is unrelated to the prior uterine tumor.

c

CLINICAL QUESTIONS FROM DOCTOR'S NOTES

A 45-year-old patient presents with a painless mass in the posterior aspect of the knee. Imaging reveals a well-circumscribed myxoid tumor located near the popliteal vein and adjacent nerves. Due to its close proximity to neurovascular structures, the mass was surgically shaved rather than fully excised. The patient is currently undergoing conservative follow-up with serial MRI scans.
Which of the following best explains the management decision in this case?

a) The tumor was likely to regress on its own
b) Complete excision could injure nearby nerves or vessels
c) MRI cannot be used if the tumor is fully excised
d) The tumor had already metastasized

b

FIBROUS TUMORS

- Nodular fasciitis
- Fibromas (benign) and Fibrosarcoma (malignant)
- Fibromatoses:
  - ✓ Superficial
  - ✓ Deep (Desmoid tumor)

NODULAR FASCIITIS

- Nodular fasciitis: thought to be reactive process
- Now, clonal, t(17;22) producing MYH9- USP6 fusion gene.

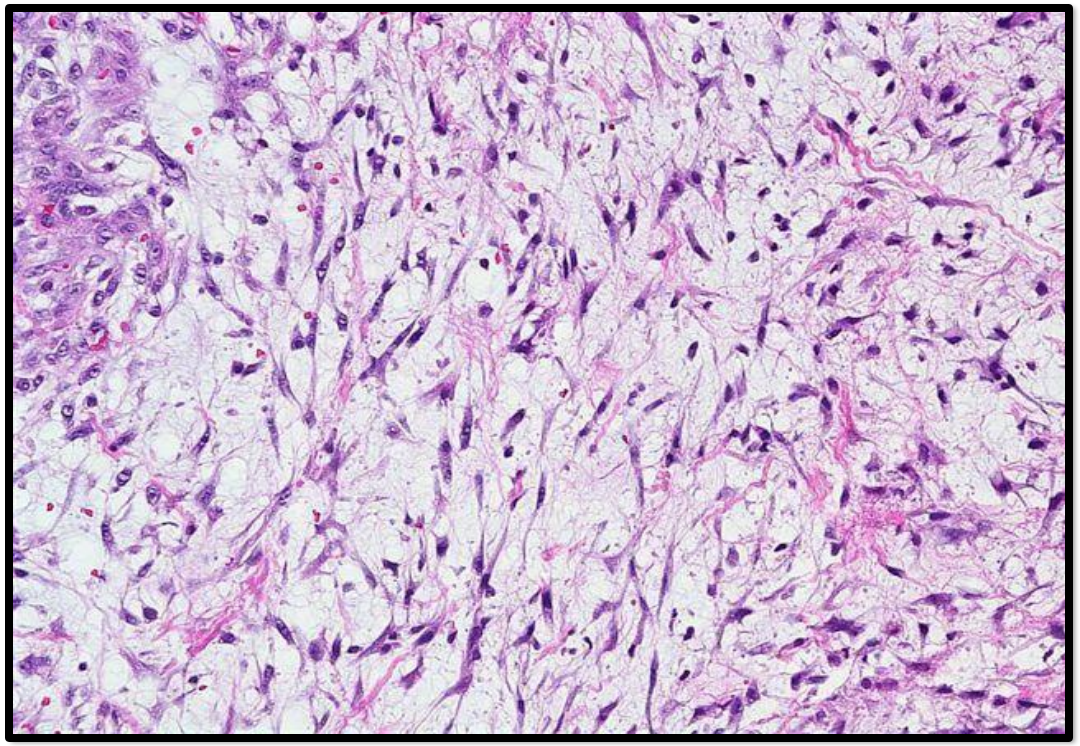
There is a characteristic clonal molecular alteration identified in these tumors, and researchers who have discovered this change interpret it as evidence that the lesion is a true neoplasm, rather than merely an inflammatory or reactive proliferative process

- Classic clinical scenario: Trauma history, recent rapid size increase of the soft tissue mass at the side of tumor (cheat wall, hand, leg, etc)
- Maybe self-limiting.

It is considered self-limited if confidently diagnosed as a reactive process, and this forms the basis for the argument made by those who believe it is not a true tumor—even when a clonal genetic alteration is present

- IMPORTANT: not to diagnose it malignant to avoid subjecting patients to unnecessary and potentially harmful treatments, such as radiation or surgery
- Culture-like histology

NODULAR FASCIITIS



This is the classic cultured-like appearance of nodular fasciitis. It is composed of bland spindle cells, which may occasionally show frequent mitotic activity. These spindle cells are arranged in broad areas resembling tissue culture. In some cases, inflammatory cells—such as plasma cells, neutrophils, and lymphocytes—are also present. Their presence can serve as a clue to the diagnosis. The term 'nodular fasciitis' reflects these features: it presents as a nodule and contains scattered inflammatory cells within a background that mimics cultured tissue under the microscope

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1	2-6		Added information
V1 → V2			

Additional Resources:

رسالة من الفريق العلمي:

سبحان الله و بحمده عدد خلقه و رضا نفسه و زنة عرشه و مداد كلماته
ما تنسوا أهلنا في غزة من دعائكم