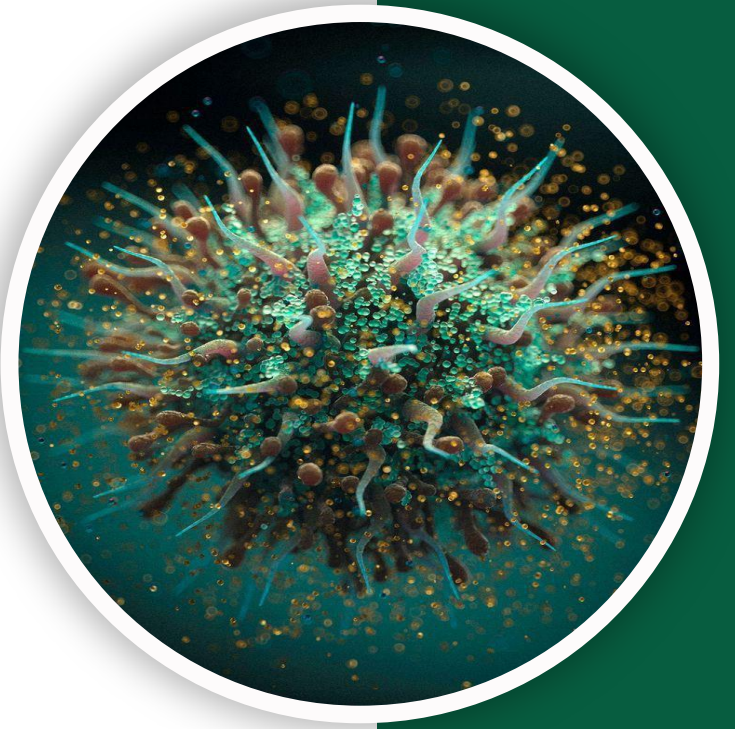
بسم الله الرحمـٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

MSS Pathology | FINAL 3+4

MSS & Skin Tumors Pt.9+Pt.10



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Mohammad Al-Amawi

REMEMBER FROM GENERAL PATHOLOGY

- Benign tumors are usually less cellular with lower mitotic activity and lower tissue infiltration than their malignant counterparts.

- APC (adenomatous polyposis coli) is a tumor suppressor gene that is associated with colonic polyps. These polyps are benign adenomas but can be premalignant, especially in individuals with mutations in the APC gene. Over time, they can transform into colorectal cancer, particularly in conditions like familial adenomatous polyposis (FAP).

- Signature mutations are specific mutations that distinguish a neoplastic transformation. They can be used for karyotyping and diagnosis of certain tumors.

FIBROUS TUMORS

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

NODULAR FASCIITIS

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

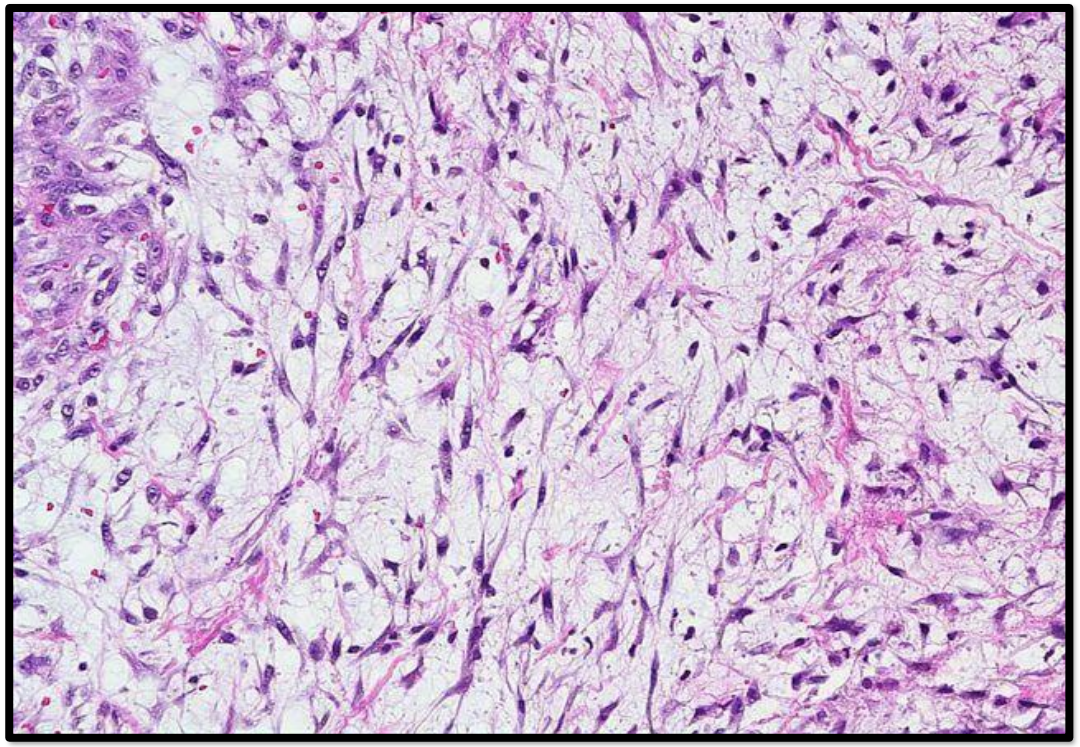
There is a characteristic clonal molecular alteration identified in these tumors, and researchers who have discovered this change interpret it as evidence that the lesion is a true neoplasm, rather than merely an inflammatory or reactive proliferative process

- The classic clinical scenario: **Trauma history, recent rapid size increase** of the soft tissue mass at the side of tumor (chest 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.
- **The appearance under the microscope is called: Culture-like histology**

NODULARFASCIITIS



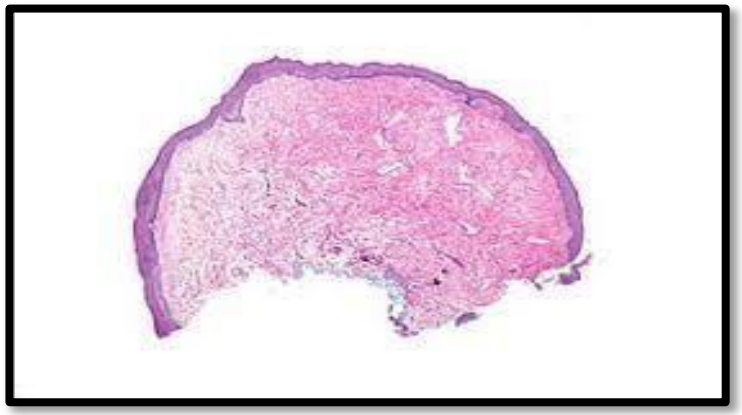
شكلها زي كإنّك
زارع خلايا
بالمختبر
Cultur like

This is the classic culture type 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

Fibroblastic tumors: FIBROMAS & FIBROSARCOMAS:

1) Fibromas:

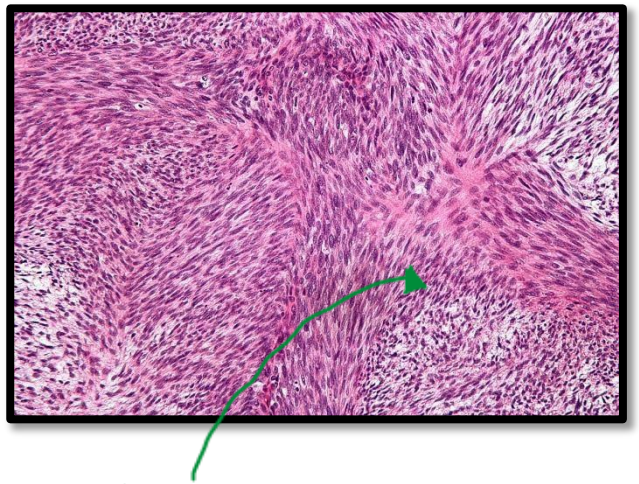
- benign proliferation of fibroblasts,
- very common,
- Involves skin and subcutaneous tissue
- Less cellular than fibrosarcomas.



Bland, spindle–shaped, benign fibroblasts.
Bland: no necrosis, no atypia, no abnormal mitosis?

2) Fibrosarcomas:

- malignant counterpart;
- usually superficial cutaneous tumors of fibroblasts, cellular, storiform pattern with increased mitosis;
- less common than fibromas.



Sometimes *necrosis* is present.

Storiform pattern:
Right and acute angles created by this unique appearance of malignant cells (fibroblasts in this case).

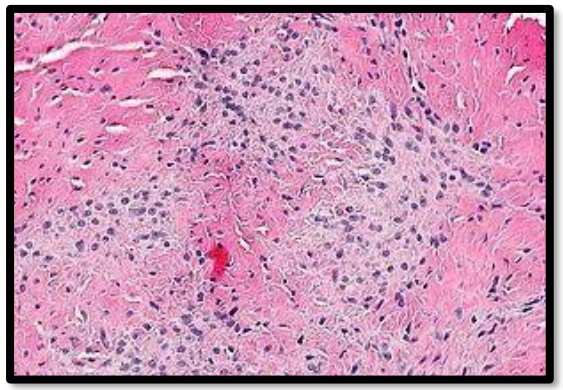
Fibromatoses: **benign** syndromes involving fibroblast proliferation.
They have 2 types – **Superficial (This Slide), and Deep (Next Slide).**

1) SUPERFICIAL FIBROMATOSES:

- **Infiltrative benign fibroblastic proliferation**
- Occur in **cutaneous and subcutaneous** tissue close to the skin
- **May run in families;**

No metastasis, but affects the local environment and function of related organs.

PALMAR (DUPUYTREN CONTRACTURE)	PLANTAR FIBROMATOSES	PENILE (PEYRONIE DISEASE)
Palmar fascia is involved. Can affect any finger. Can cause loss of function.	Sole of foot is involved. Affects walking. Patient is prone on their abdomen for diagnosis.	Dorsolateral aspect of the penis Can cause pain during erection or sexual intercourse.

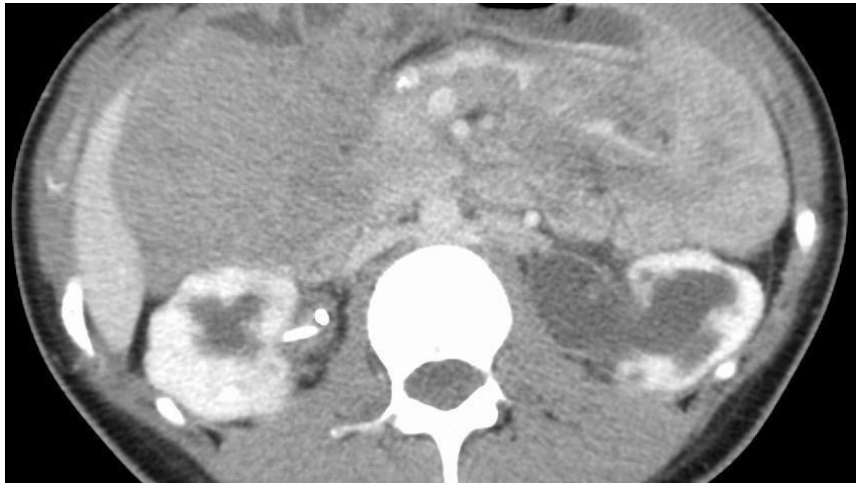


2) DEEP FIBROMATOSES (DESMOID TUMORS):

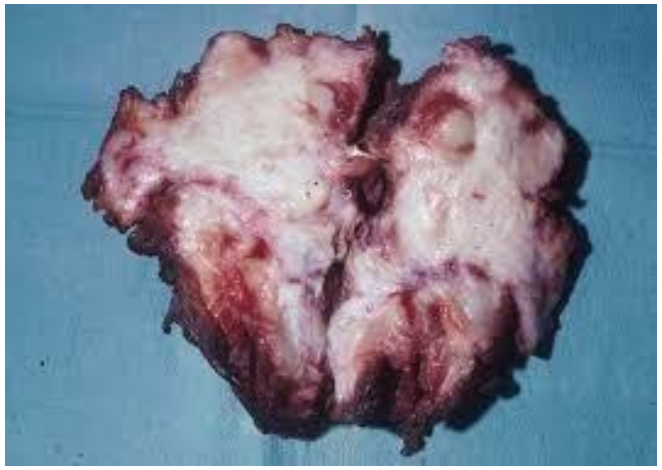
- Deep infiltrative but bland (no atypia, no necrosis, no abnormal mitosis) fibroblastic proliferation; doesn't metastasize, but Recurs.
- Similar to superficial fibromatoses, but deeper and usually cannot be seen by the eye since it is inside the body.
- 20-30 years, females more common.
- Abdominal wall, mesentery (intra-abdominal) and limbs.
- Mutations in *CTNNB1* (ß-catenin) or *APC* (Adenomatous Polyposis Coli) genes leading to increased Wnt signaling, which is a **biological pathway** that tells cells to **grow and multiply**.
  Deep fibromatoses are positive for specific immunohistochemical ß-catenin stains, which target the signature mutation in the process.
- Mostly are sporadic; but patients with Gardner (FAP) syndrome are susceptible (can be familial).
- Complete excision (which is not easy due to infiltration, so wider margins must be removed) is needed to prevent recurrence, which is very common
- These tumors kill patients by local infiltration (by affecting vital organs such as the liver, kidneys, pancreas, etc...) NOT metastasis.

Frozen abdomen: Large adhesive masses in the abdomen; can be caused by desmoid tumors.

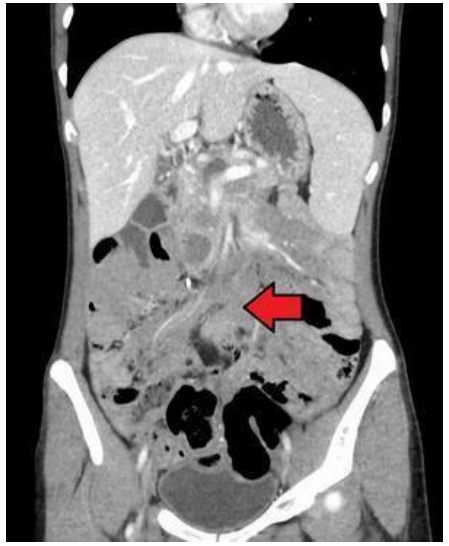
2) DEEP FIBROMATOSES (DESMOID TUMOR):



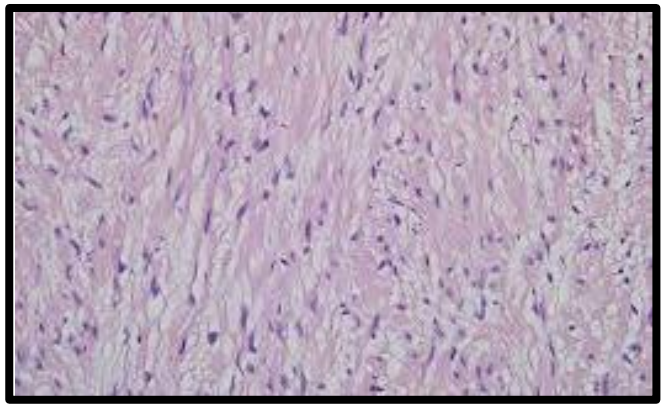
CT scan showing bland tissue surrounding internal vital organs.

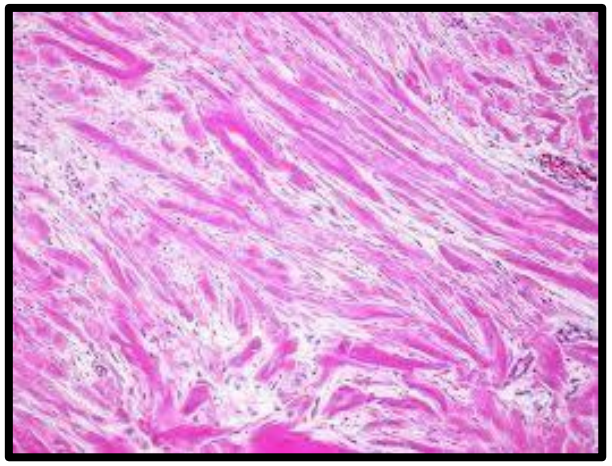


Tumor mass extracted by surgery; it appears **whitish** because of the **dense infiltrative fibroblastic bland proliferation.**



Longitudinal view also showing bland tissue infiltration surrounding internal vital organs.





Although the tumor is benign, the affected patients usually do not survive for long as their **vital internal organs are destroyed.**

SKELETAL MUSCLE TUMORS:

- Almost all malignant; except rhabdomyoma which is benign, rare, occurs with tuberous sclerosis.
- The most common site of rhabdomyoma is the in heart & tongue.
- Rhabdomyosarcoma (RMS) is the malignant prototype of skeletal muscles sarcoma; most common child sarcoma.
- 3 types (embryonal 60%; alveolar 20%; pleomorphic 20%)
- Specific mutations are common, especially in alveolar types
- Aggressive tumors (high-grade);
- treated by Surgery, Chemotherapy +/- Radiotherapy, Multimodality approach for treatment.

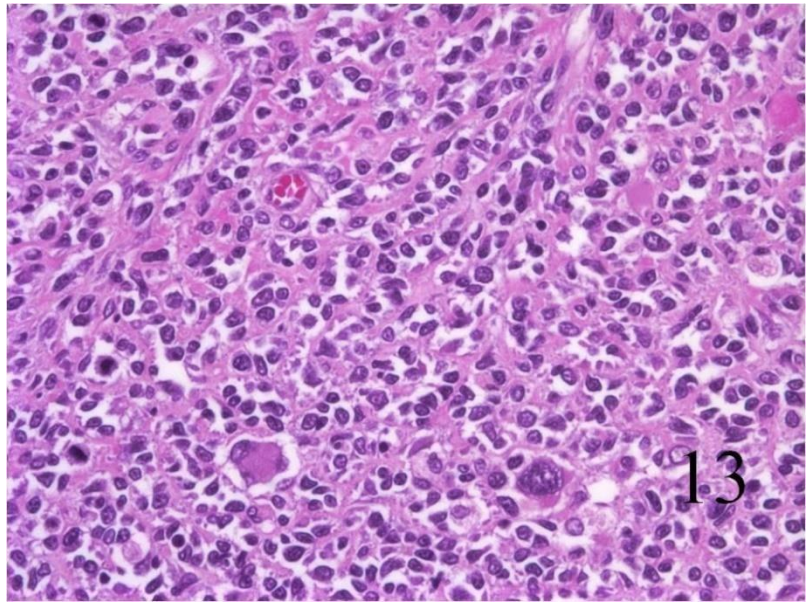
RHABDOMYOSARCOMA

Gross appearance:

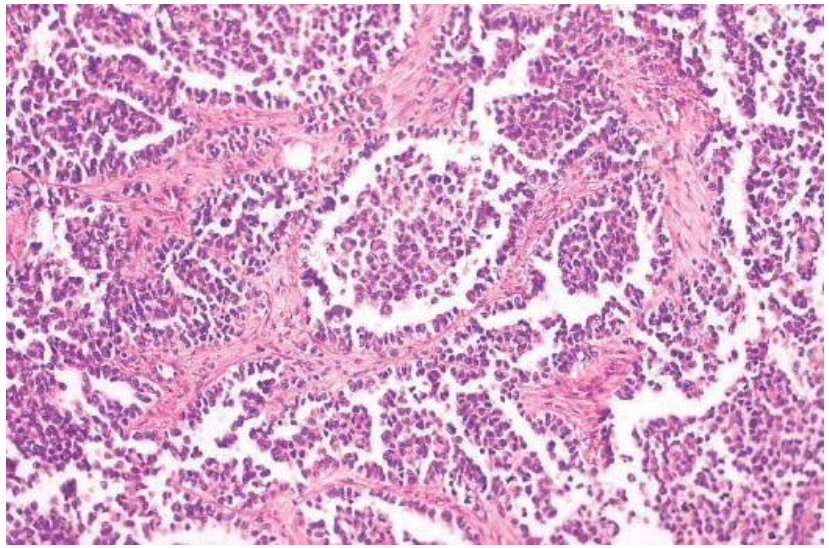
Large, fleshy, hemorrhagic tumors
Nodules and infiltration **(malignant)**

Microscopic appearance:

Pleomorphic rhabdomyosarcoma



Alveolar rhabdomyosarcoma



It resembles the **lung alveolae.**

In Low-power (as the figure above):
Small blue cell tumor (similar to Ewing sarcoma; specific markers are needed to know the cell of origin).

In high-power:
Cross-striations, which are specific to skeletal muscle fibers, can be seen.

Usually, specific markers are used to confirm the diagnosis (in both cases).

SMOOTH MUSCLE TUMORS:

- Leiomyoma (benign) and leiomyosarcoma (malignant)
- Leiomyoma (LYM): very common; can occur in any site but mostly in the uterus (fibroid) → Smooth muscles are everywhere!
- Menorrhagia and infertility
- LYM vary in size and location; most of them are:
  - well-circumscribed
  - not infiltrative, not hemorrhagic, not necrotic
  - White, with whorly* cross-sections
- Few can have specific mutations (Fumarate hydratase on chromosome 1q42.3); mutations are of low diagnostic value because gross inspection and histology is usually the way to go

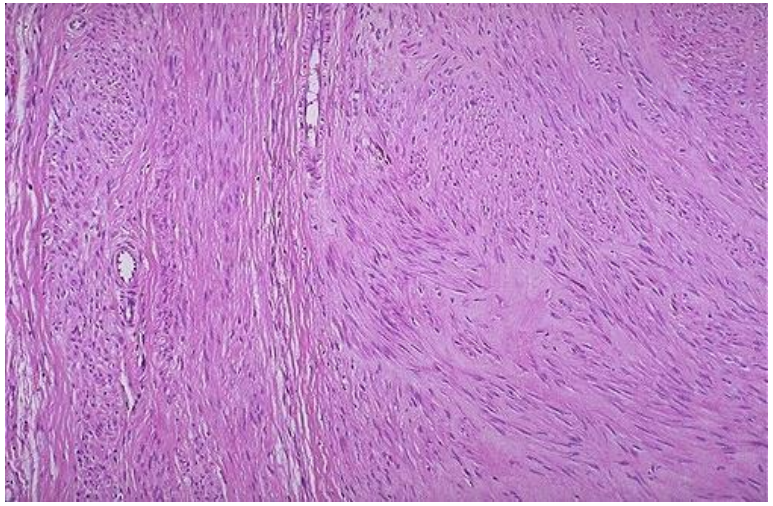
***Whorly:** whirly, wheely (see next slide's image)

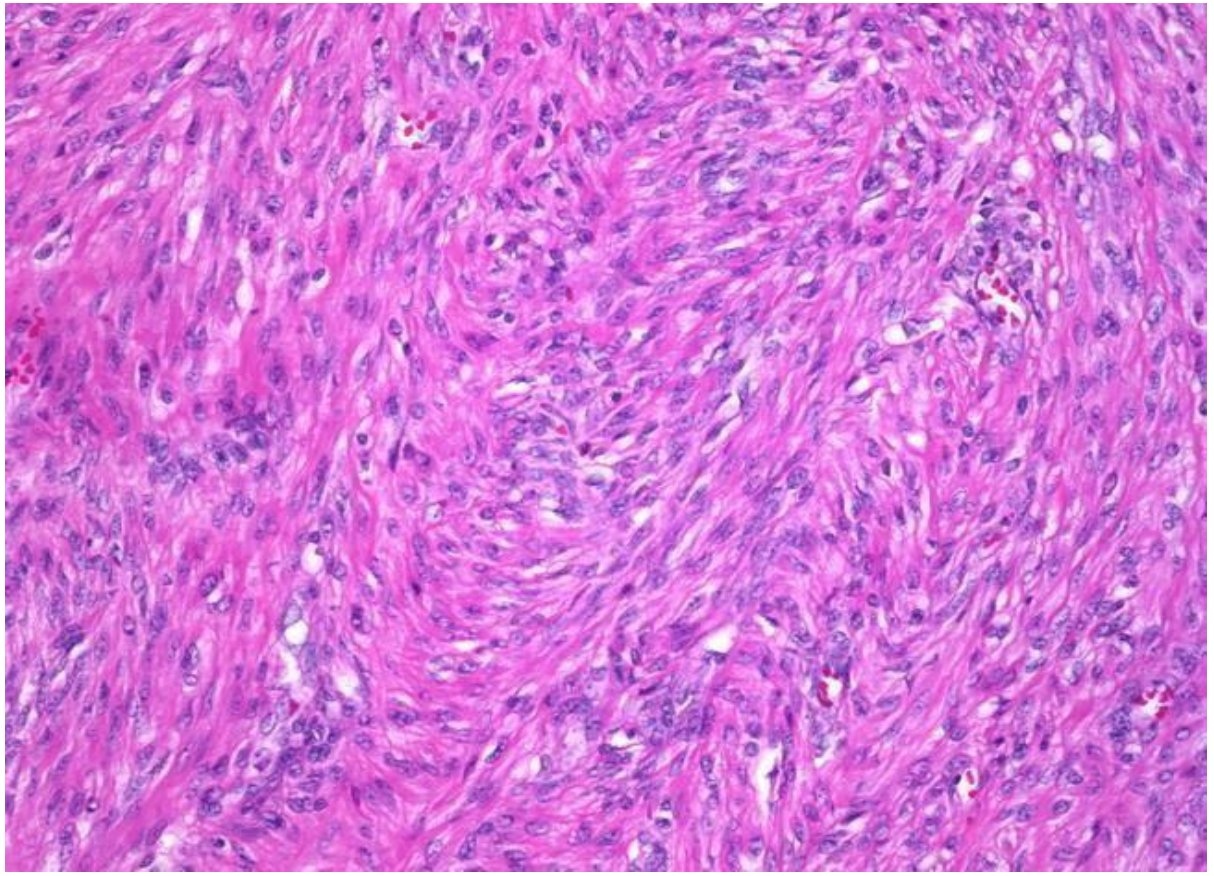
LEIOMYOMA FEATURES:

1: Submucosal 2: Intramural 3: Subserosal

- This is a **uterus** that has been removed and opened for inspection after the detection of multiple fibroids by imaging; the patient had also probably suffered from **menorrhagia** prior to the intervention.
- These firm, **white, whorly**, well-circumscribed masses are leiomyomas (or **fibroids**).
- They are distributed all over the uterine tissues.
- Grossly inspected, these masses clearly suggest the **benignity** of the neoplasia occurring here; notice the clear demarcation with **no necrosis or hemorrhage.**
- Anatomical distribution of the fibroids is shown by the numbers on the figure; the professor mentioned them in the lecture, but I think they are out of scope; you can memorize the image with the #'s just in case.

LEIOMYOMA FEATURES:





Histologically:

- Benign smooth muscle cells
- No increased mitosis or atypia
- No hemorrhage
- No necrosis

Mitosis count is done by counting the number of dividing cells per high-power field at time of inspection. The number should not exceed a certain limit.

LEIOMYOSARCOMA:

- 10-20% of soft tissue sarcomas
- Adults; more in females
- Deep soft tissue, extremities and retroperitoneum or from great vessels
- Can also occur in the uterus, but rarely (only 1-2%; leiomyomas 98-99%)
- Complex genotypes without specific signature mutations.

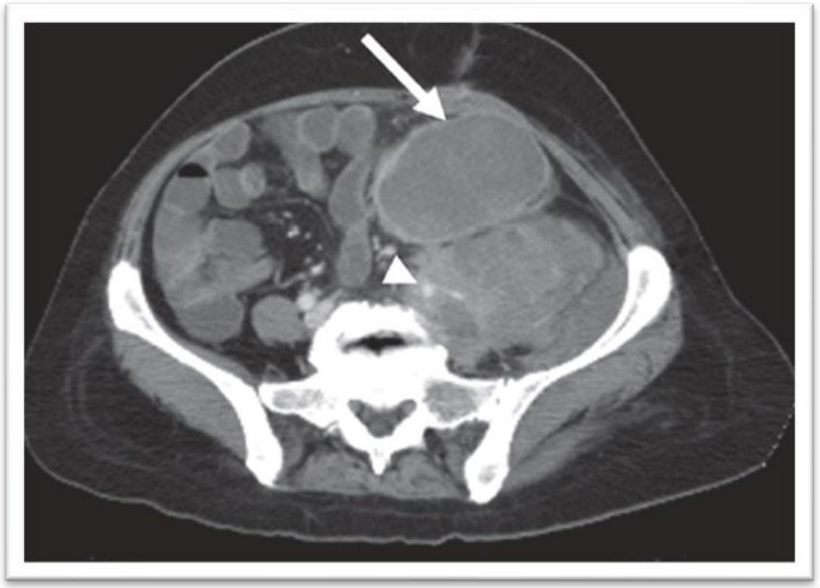
Unlike leiomyomas

- Hemorrhage
- Necrosis
- Increased mitosis
- Infiltration of surrounding tissue

- Treatment: depends on location, size and grade

A combination of techniques may be used in severe cases.

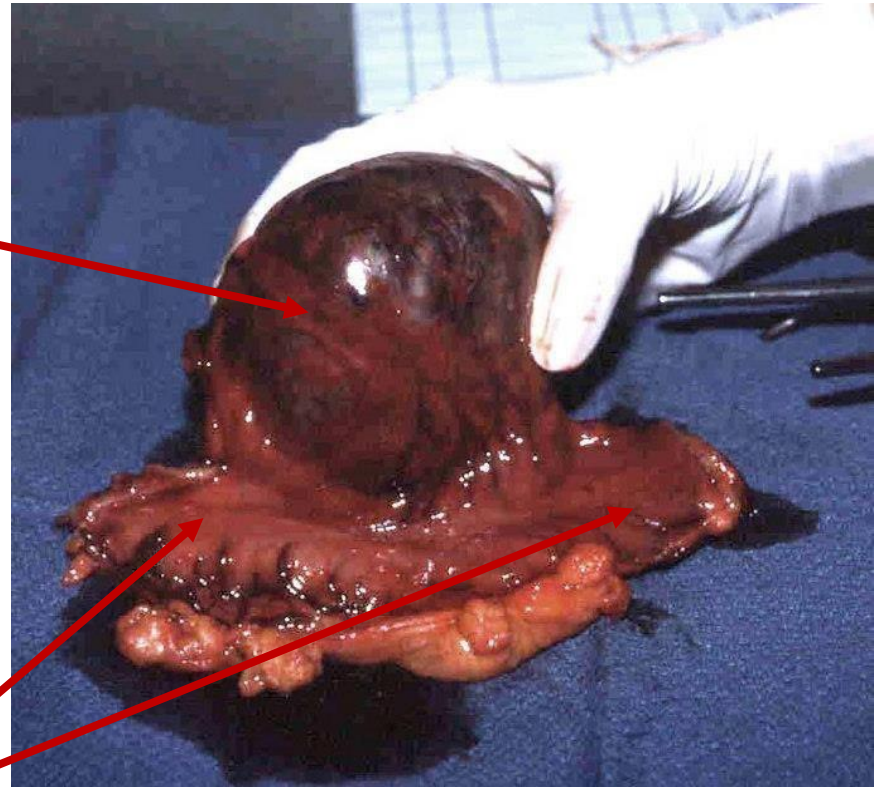
LEIOMYOSARCOMA FEATURES:



CT scan of large intra-abdominal leiomyosarcoma.

Radiologically, hemorrhage and necrosis suggests malignancy and abdominal infiltration.

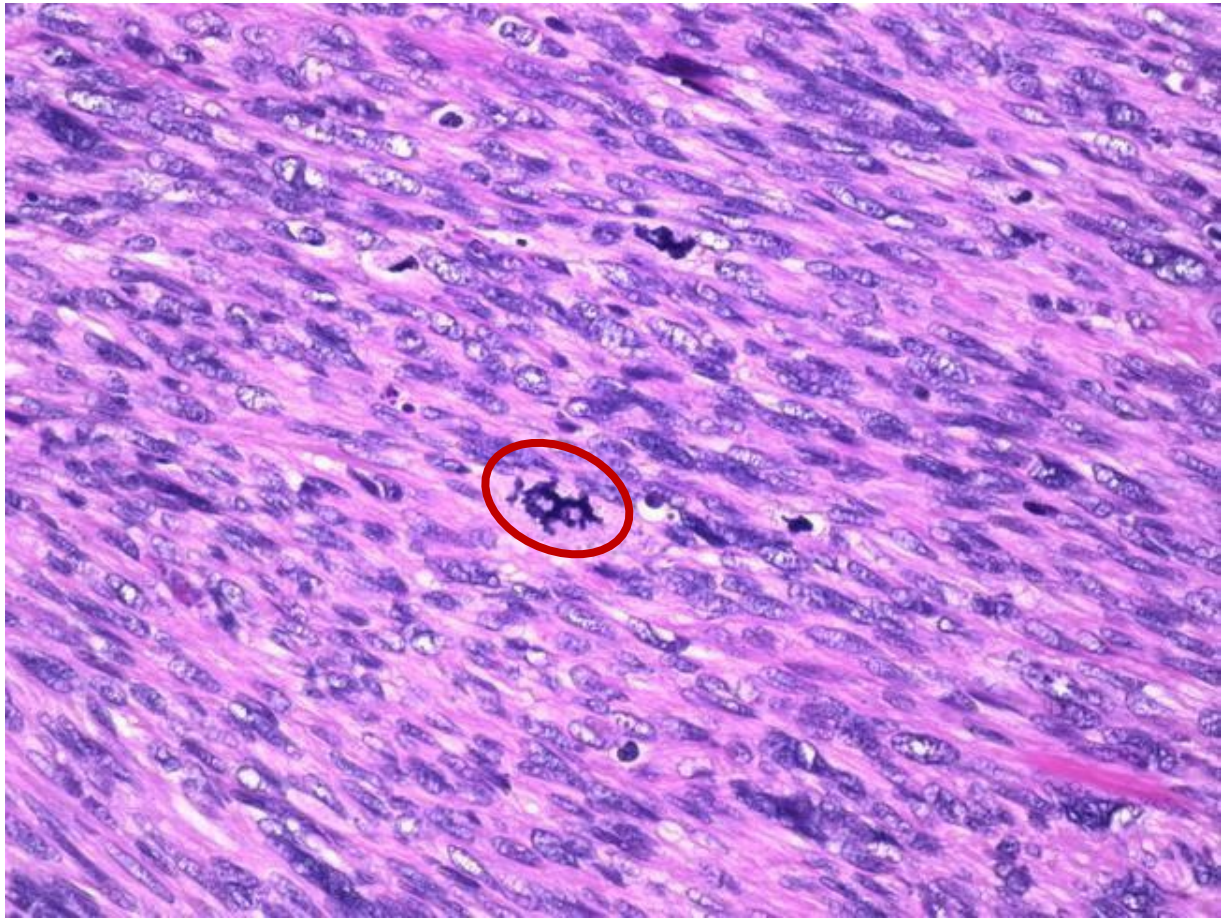
Tumor arising from small bowel



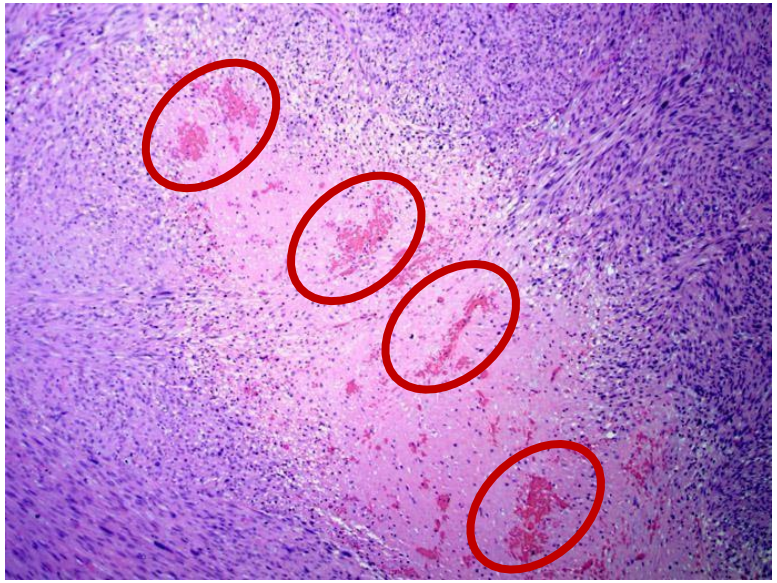
Part of the small bowel wall removed due to infiltration of the tumor; wider margins must be removed to make sure the whole malignancy is removed.

After surgical excision. **Hemorrhage** is evident.

LEIOMYOSARCOMA FEATURES:



- High-grade, pleomorphic, abnormal mitosis (encircled)
- Very high cellularity



- Hemorrhage (encircled)
- Necrosis (anucleic center)
- Very high cellularity (on the margins)

TUMORS OF UNCERTAIN ORIGIN:

Uncertain mesenchymal lineage:

- Synovial sarcoma
- Undifferentiated pleomorphic sarcoma

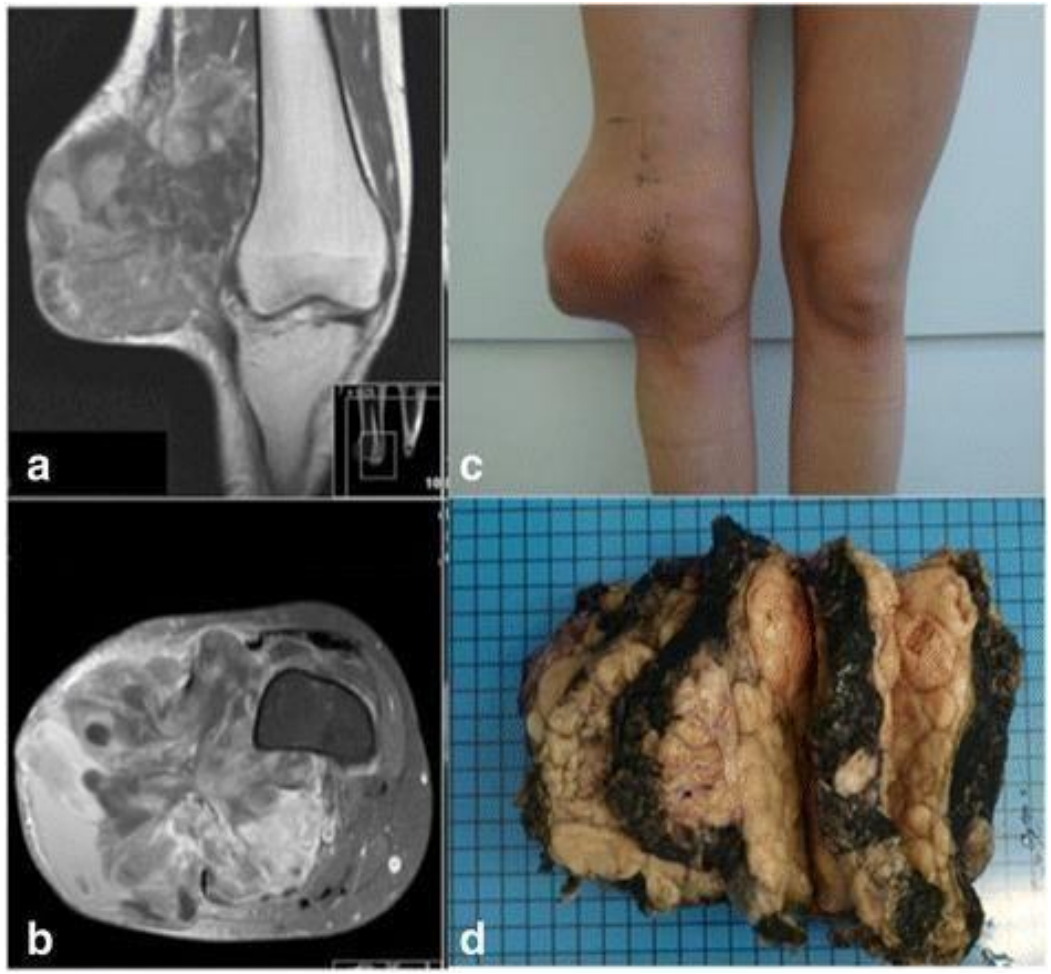
Ewing sarcoma (if you remember the MID material!!)
is also of **uncertain origin**.

SYNOVIAL SARCOMA:

- Name is misnomer; classically it was though to originate from joints, thus the name, but it can occur anywhere
- 10% of all soft tissue sarcomas; young adults 20-40s age
- Deep seated mass of long history
- T(X;18)(p11;q11) → fusion genes → fusion protein SS18
- The translocation is detected by FISH analysis
- The fusion protein SS18 can be detected as well
- Monophasic (only spindle cells) or biphasic (spindle cells and glands)
- Both types have same prognosis; prognosis depends on the typical prognostic factors such as stage and grade of the tumor.
- Trx: aggressive with limb sparing excision + Chemotherapy
- 5-year survival is 25-65% depending on stage
- Metastasis: lung and lymph nodes

Sarcomas usually hematogenously metastasize to the lung, however synovial sarcoma is an exception since spreads to the lymph nodes as well.

SYNOVIAL SARCOMA FEATURES:



Figures [a → d]
Show different gross aspects of synovial sarcoma around the knee joint.

Radiology shows

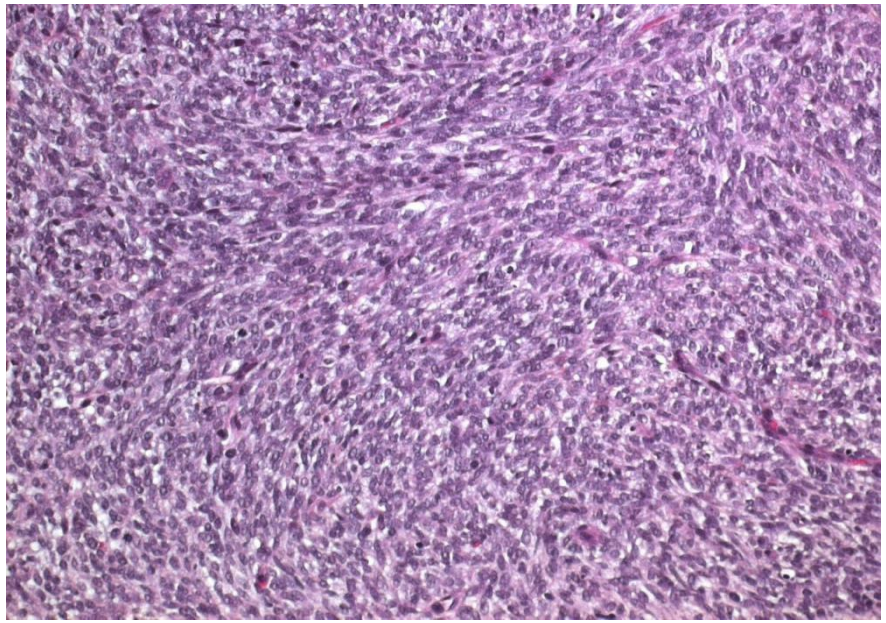
- **heterogeneity**
- **hemorrhage**
- **necrosis**

The black color in figure ‘d’ is ink, which is used to check if the tumor has reached the margins or not.

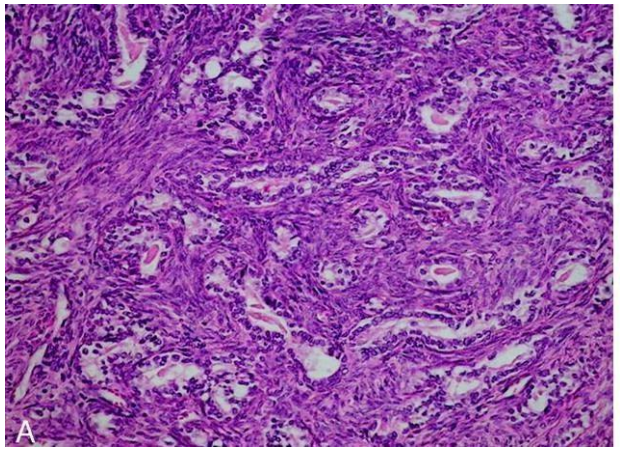
SYNOVIAL SARCOMA FEATURES:

Histologically divided into monophasic and biphasic:

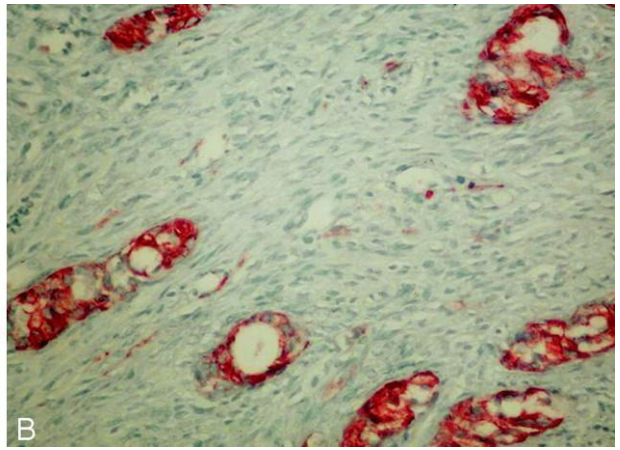
MONOPHASIC



BIPHASIC



BIPHASIC



Only spindle-shaped cells with frequent mitosis, so other types – leiomyosarcoma, fibrosarcoma, etc… are probable.

To decide what type of malignancy this is, specific immunohistochemical stains are needed.

In addition to **spindle-shaped cells**, epithelium can show up as **glandular tissue.**

"This is synovial sarcoma until proven otherwise"
~ Dr. Mousa Alabbadi

Keratin stain can be used to detect glandular tissue as it is keratin-positive.

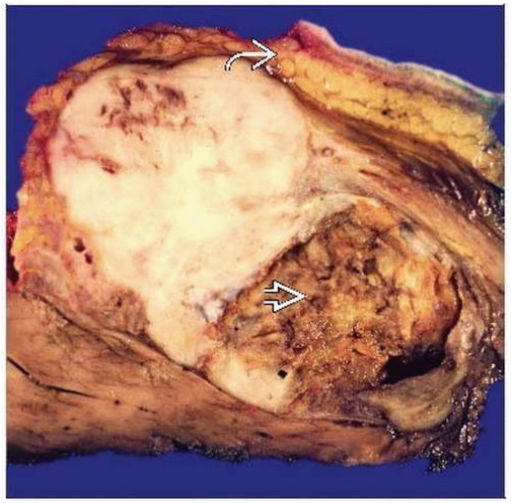
High–grade

Malignant

UNDIFFERENTIATED PLEOMORPHIC SARCOMA (UPS):

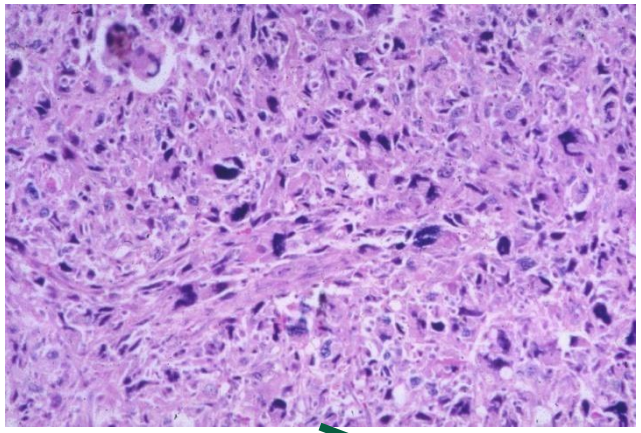
- High grade mesenchymal sarcomas of pleomorphic cells that lack cell lineage, so there is no exact cell type, and stains will not show any exact result for the cell of origin
- Deep soft tissue and extremities and retroperitoneum
- Old terminology: malignant fibrous histiocytoma (MFH), but this name is not used anymore because current methods to identify the cell of origin are available.
- Aneuploid (chromosomes are not 46) and complex genetic abnormalities with multiple possible abnormalities
- Large tumors; anaplastic (ugly, strange-looking) and pleomorphic cells, abnormal mitoses, necrosis, and hemorrhage
- Treatment: aggressive with surgery and adjuvant Chemotherapy +/- Radiotherapy; poor prognosis

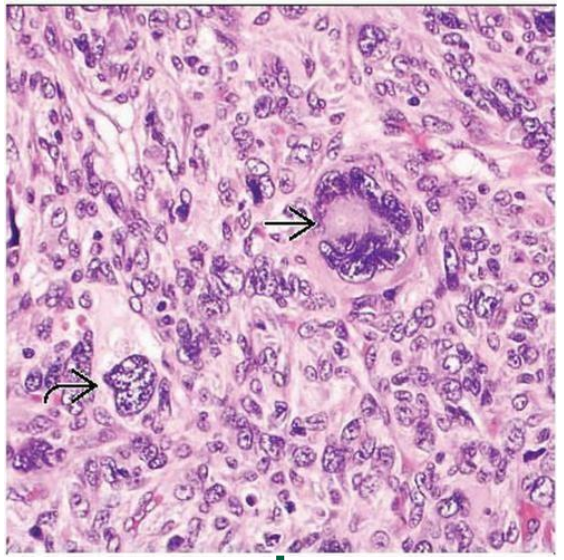
UPS FEATURES:

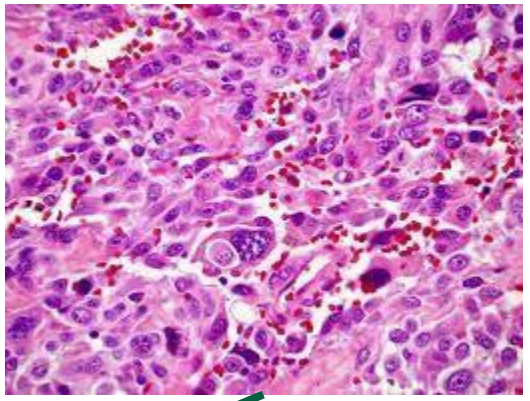


Large, infiltrative masses.
Deep in the soft tissue.

Radiology of **UPS** of the thigh.







Ugly, bizarre cells of unknown origin.

The diagnostic step in this case may include checking some stains specific for tissue types.

If no decision is made and the cells lack lineage (have no specific type), just call it undifferentiated pleomorphic sarcoma (UPS).

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.

رسالة من الفريق العلمي:

- التَمِسُوها في العَشْرِ الأَوَاخِرِ : في تسعٍ تَبَقَّيْنَ ، أَوْ سبعٍ تَبَقَّيْنَ ، أَوْ خمسٍ تَبَقَّيْنَ ، أَوْ ثلاثٍ تَبَقَّيْنَ ، أَوْ آخرِ ليلةٍ

خلاصة حكم المحدث : صحيح

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اللهمّ إنك عفو
تُحبُّ العَفوَ
فَاعفُ عنّا♡

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			
V1 → V2			