10

MSS

Musculoskeletal System

Pathology

Doctor 2018 | Medicine | JU

Done by

Lana Mango

Contributed In The Scientific Correction

Dena Kofahi

Contributed In The Grammatical Correction

Batool Bdour

Doctor

Mousa Al Abbady

Please note that this is the last Pathology sheet for the MSS.

Soft Tissue Tumors

- Can be **Benign** or **Malignant**

- **Incidence**: **1%** and cause **2%** cancer death
- 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.
- **BENIGN** soft tissue tumors are far more common than **MALIGNANT** soft tissue tumors
- **Most** soft tissue tumors are **Sporadic**

Sarcoma

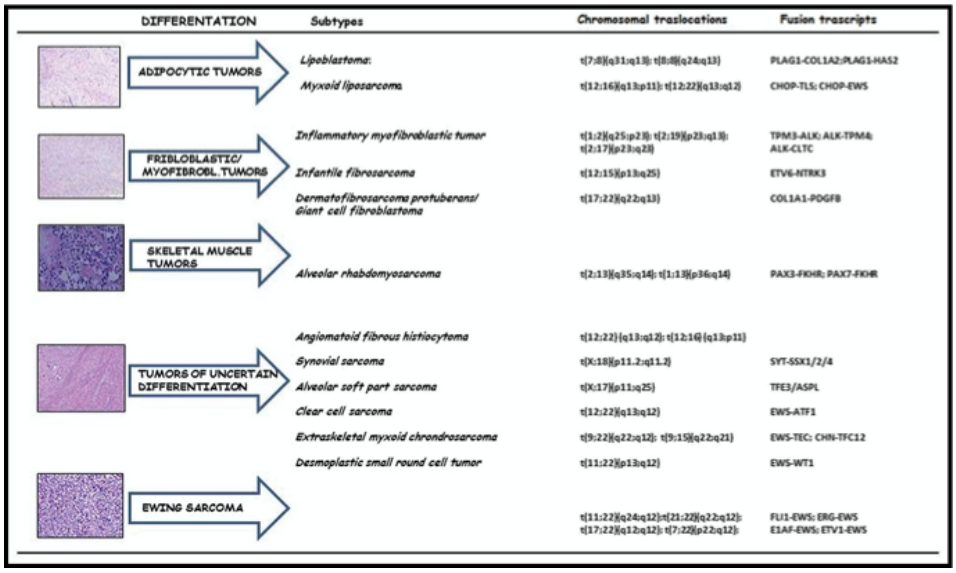
- Aggressive
- Are capable of metastasizing by hematogenous spread, and they spread to the lungs.
- Upon **Dx**, you must perform a full scan of the lungs in order not to miss any lung metastases. Additionally, this needs to be done for staging purposes.
    - Note: **Lung metastasis** is a **bad prognostic sign**. The more extensive the metastasis, the worse the prognosis.
- Not all types of sarcoma have a simple karyotype.
    - **Almost 1/5 (15-20%)** of them have **significant** mutations and translocations: **Ewing Sarcoma and Synovial Sarcoma.** (They have signature translocations)
    - The **majority (80-85%)** of sarcomas have **complex and multiple karyotypes** (genomic instability), like leiomyosarcoma and undifferentiated pleomorphic sarcoma
    - This means the karyotypes for most sarcomas can't be used for proper or definite diagnosis. (NOT A SIGNIFICANT CHARACTERISTIC)
    - **Genetic analysis** is not used to diagnose high grade sarcoma unless the suspected type of sarcoma is **Ewing Sarcoma, Synovial Sarcoma or sometimes liposarcoma.**

- Associated with genetic diseases
- **Most common location** of Sarcomas: large extremities (Thighs and retroperitoneal space)
- **Secondary sarcoma (Radiation Induced)**: Occurs as a complication of radiotherapy (A patient who has performed radiotherapy in the past in order to treat a primary disease) as the patient develops sarcoma years later.
- **There are no sarcoma precursors**. So, a sarcoma is a sarcoma from the start, it is not derived from a benign form.
- One theory states that sarcomas develop as a result of: Pluripotent mesenchymal cell mutations → Insufficient tumor suppressive function of the immune system → SARCOMA
- **Tx:** Management depends on the grade and stage of the sarcoma
- Clinically, soft tissue tumors have a wide range from benign, to intermediate, to highly malignant tumors.
- **Dx**:
  - Clinical
  - Radiology
  - Pathological features (Histology)
  - Grading (higher grade → Worse prognosis)
  - Staging (lung metastasis → stage 4)

– ***NOTE***: to determine the stage, the grade is important –

All of the following are combined to give proper diagnosis.

Regarding the following table which clearly shows the chromosomal translocations of different tumors, the professor told us to focus on the translocations for Synovial and 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 lipozarcoma	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

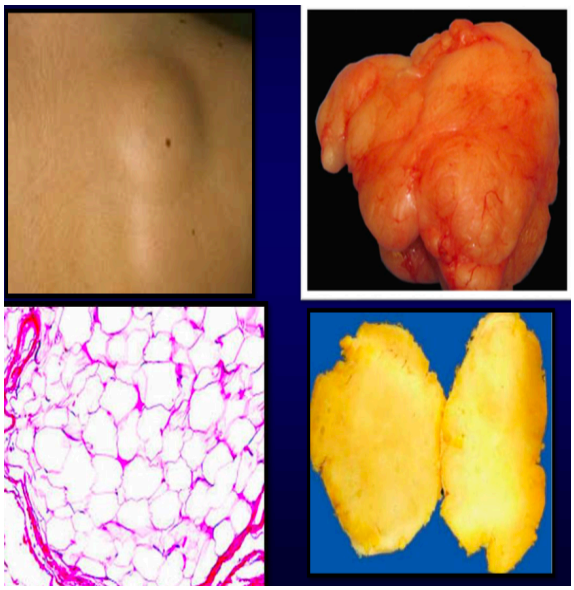
TYPES OF SOFT TISSUE TUMORS:

❖ **ADIPOSE TISSUE TUMROS (LIPOMA AND LIPOSARCOMA)**

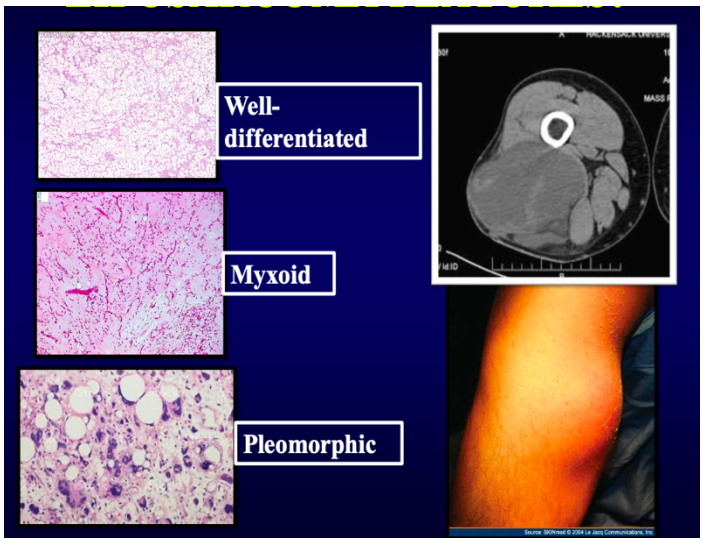
- Adipose cells are important as they are found all over the body, such as in subcutaneous tissue, between tissues, and around organs.

	Lipoma	**Liposarcoma**
Prevalence	**MOST COMMON SOFT TISSUE TUMOR**	**MOST COMMON SARCOMA IN ADULTS (>50 yrs)** (Much less common than lipoma)
Pathogenicity	A clone that forms a benign tumor	A clone that forms a malignant tumor.
Site	**Most common in subcutaneous tissue**	**Can occur anywhere but is most common in extremities and retroperitoneum**
Size	**smaller**	**larger**
Gross appearance	- Lobulated - Smooth - Glistening yellow - No necrosis - encapsulated and well circumscribed - not infiltrative (surgeon can easily remove it with his finger)	- bulky lipomatous tumor - necrosis present - Infiltrative
Histological appearance	- **Benign adipocytes**	**Types:** 1. **Grade 1**: Well differentiated **similar to lipoma in appearance (simplest)** 2. **Myxoid** 3. **Grade 3:** Pleomorphic **(aggressive)**
Treatment	**Excision mostly for** - cosmetic reasons - When it applies pressure/compresses a nerve. - **DIAGNOSIS:** To make sure it isn't liposarcoma.	With complete excision of a grade 1 liposarcoma it is probably curable.

Possible liposarcoma case: A 70 years old man comes with a thigh mass that is around 15-20 cm, it is a **sarcoma** until proven otherwise.



LIPOMA



LIPOSARCOMA

How to differentiate between a low grade liposarcoma (well differentiated) and benign lipoma? (you would need to take many sections to fully confirm, but a genetic test is easier)

1. **IF IT TESTS POSITIVE for the MDM2 gene translocation → Liposarcoma**
2. **If the tumor is not completely/fully excised easily → Liposarcoma**

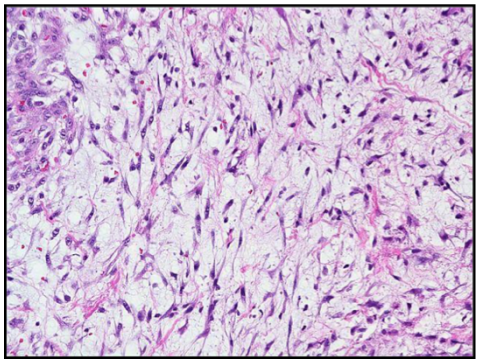
❖ **FIBROUS TUMORS (Fibroma and Fibrosarcoma)**

- Cell of origin: fibroblasts

Three major groups of fibroblast tumors:

1) **Nodular fasciitis**
   - Culture-like histology **(inflammatory cells).**
   - Debated on whether it's a reactive process or a tumor.
   - Clonal, t(17;22)
   - Considered a TUMOR **BUT IT IS NOT CANCEROUS**
   - ***BENIGN***
   - **Recent history of trauma** and **rapid increase in the size**. ← characteristic of Nodular Fasciitis. (Patient may tell you it grew 5 cm in one or two weeks. Patient may also not remember trauma)

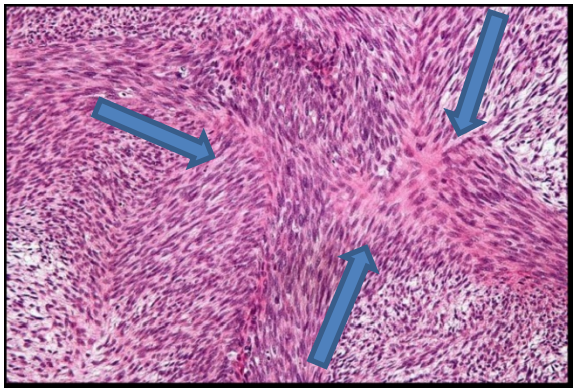
- It is very important not to be misdiagnosed as a sarcoma ***<u>as it is not malignant.</u>*** You would end up subjecting the patient to unnecessary chemotherapy and radiotherapy (and as stated earlier one complication of radiotherapy is development of a sarcoma).



- **Histology**:
  - Atypia
  - Fibroblastic proliferation
  - Frequent mitosis
  - Tissue culture-like appearance (many fibroblasts, some inflammatory cells)

2) Fibroma and Fibrosarcoma

Fibroma	**fibrosarcoma**
Very common	Less common than fibromas
Skin and subcutaneous tissue (can occur in tongue)	Can occur anywhere (usually superficial cutaneous)
Benign	Malignant
Less cellular than fibrosarcoma	More cellular, storiform pattern (cells arranged in many different directions) and increased mitosis
	Good prognosis (usually not high grade). Rarely metastasizes to the lung and are removable
	Seen in children



In this image you can see the storiform pattern of fibrosarcomas. The arrows indicate the different directions in which the cells are arranged.

3) Fibromatoses

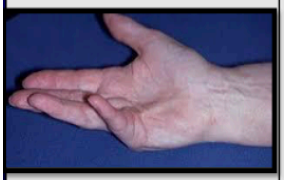
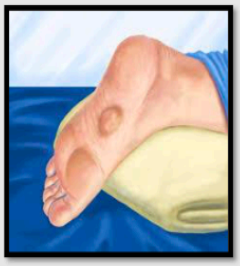
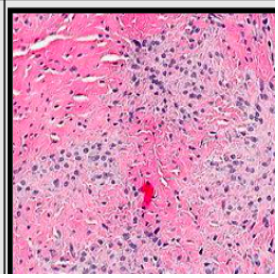
- Benign tumors from proliferating fibroblasts
- Do not metastasize
- Infiltrative

NOTE: INFILTRATION is considered a feature of malignancy, but in this case it is NOT malignant. It's considered as infiltrative and BENIGN fibroblastic proliferation

- Does not spread to the lungs, but it has local destructive abilities
- Two types: Superficial and Deep (both look the same)
- They infiltrate around but do not spread to the lungs
- Hereditary

1. Superficial fibromatoses:

- Infiltrative benign fibroblastic proliferation
- As they are superficial you can see them.
- Hereditary (may run in the family)
- Not lethal (we die with them not from them)
- Has a negative impact on local function

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

A. Palmar

B. Plantar – May cause issues when wearing shoes

C. Penile: (Peyronie Disease)

- In the penis
- Painful erection
- Difficult to treat

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2. Deep Fibromatoses (Desmoid tumor)

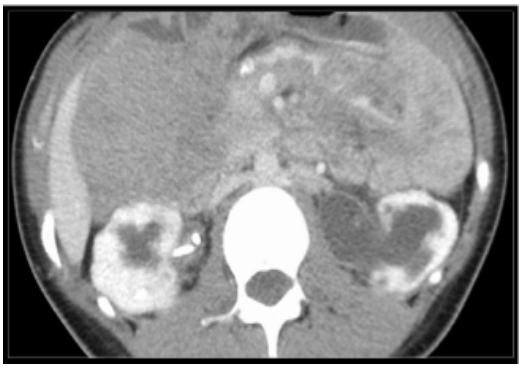
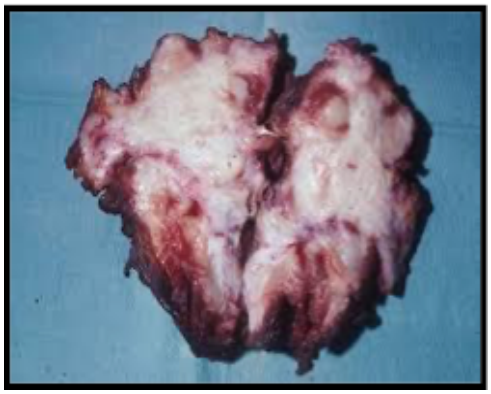
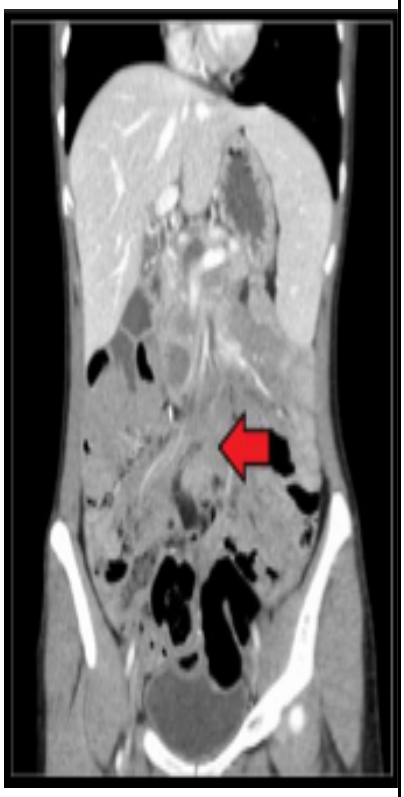
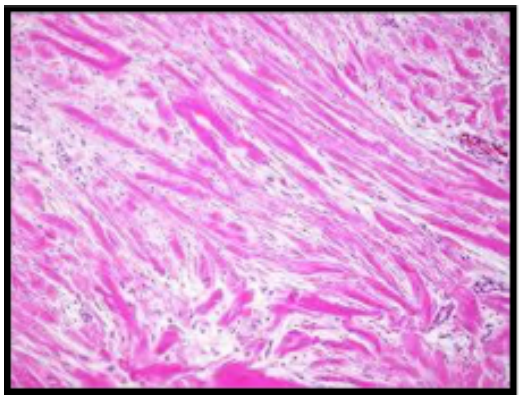
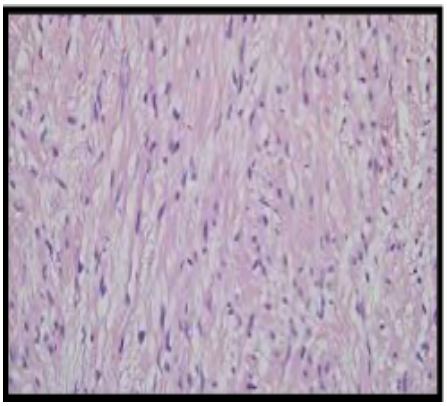
- Deep infiltrative but bland fibroblastic proliferation.
- Recurrence is very common
- Lethal: not due to metastasis

(REMEMBER IT DOES NOT METASTASIZE)

Why are they lethal then? Because they cause local destruction of vital organs ***(They are infiltrative)***

- More aggressive, but still benign.
- Occur most frequently in the 20s-30s, more common in **females**
- Location: More common in the **abdominal wall, mesentery and limbs**
- Diagnosis is not easy

- Specific mutations: Mutations in **CTNNB1 (β-catenin)** or APC genes leading to increased Wnt signaling. We can even stain β-catenin to confirm it's a desmoid tumor.
- Mostly sporadic; but patients with Gardner (FAP - Familial Adenomatous Polyposis) syndrome are susceptible
- When associated with Gardener's syndrome, the surgeon is advised to perform a colonoscopy – High risk for colon carcinoma (complete colectomy is performed for prophylaxis)
- Complete excision is not easy since it is difficult to identify the borders of the tumor (where it starts or originates and where it ends).

- An Intraabdominal desmoid is very destructive. Patient dies due to nonfunctional intraabdominal organs.

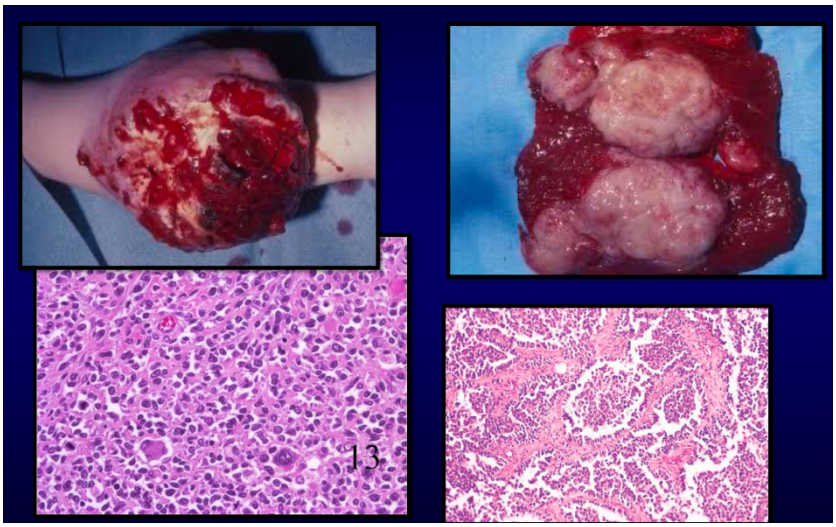
- Histology: bland (no mitosis, no neoplasia but it is INFILTRATIVE)

❖ SKELETAL MUSCLE TUMORS

- **NOT AS COMMON AS FIBROCYTE and LIPOCYTE tumors**
- Almost all are malignant; except rhabdomyoma which is benign.

Rhabdomyoma	Rhabdomyosarcoma
Rare Benign Occurs with tuberous sclerosis Seen on heart and tongue	More common* Malignant prototype **Most common child sarcoma** Aggressive Bulky, lobulated and fleshy 3 types (embryonal 60%; alveolar 20%; pleomorphic 20%) – not imp - Treatment: surgery and chemotherapy, may include radiotherapy. Can metastasize to the lung

***Note:** **Usually the benign form is more common, but skeletal muscle tumors are an exception as the malignant form is more common than the benign form.**



- **LOBULATED**, **FLESHY** AND **BULKY** TUMOR.
- If the tumor looks like this grossly, it is considered a malignant tumor until proven otherwise.
- Part of the differential diagnosis with small blue cell tumor. You have to investigate and use special stains, especially with a child, to see if it's rhabdomyosarcoma or not.

❖ SMOOTH MUSCLE TUMORS:

<table>
<tr><th><u>Leiomyoma</u></th><th>Leiomyosarcoma</th></tr>
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- Cannot transform into leiomyosarcoma
- Benign
- **Most common soft tissue tumor in the uterus**: Could lead to infertility and menstrual cycle problems, including menorrhagia. Commonly known as a fibroid
- Vary in size
- Dx: morphology and histology alone
- Few can have specific mutations (fumarate hydratase on chromosome 1q42.3

Histology:

- Smooth muscle Cell proliferation
- No necrosis
- Little mitosis

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- Malignant
- 10-20% of soft tissue sarcomas
- Seen in adults, more common in females
- Deep soft tissue, extremities and retroperitoneum or from great vessels. Also seen in uterus.
- Complex genotypes

Characteristics:

- Hemorrhagic **– difficult to remove –**
- Necrosis
- increased mitosis
- Infiltration of surrounding tissues.

Treatment: Depends on location, size and grade – surgery and chemotherapy

</td></tr>
<tr><td><u>NOTE</u>: Most imp feature distinguishing leiomyoma from leiomyosarcoma: <u>mitotic count</u> (less than 3- in leiomyoma)</td></tr>
<tr><td>

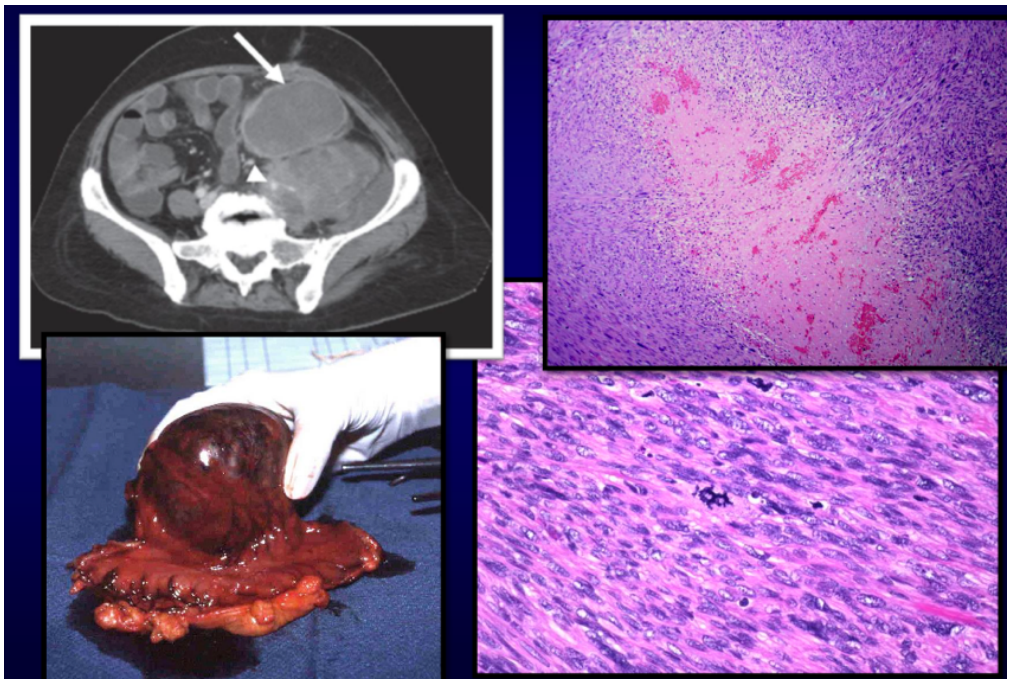
- Well circumscribed
- Not infiltrative

</td></tr>
</table>

Case: A 45 years old woman comes with lung metastases. When tested, they are found to be smooth muscle leiomyosarcomas. The doctor tries to look for the primary site- where they metastasized from-but nothing is present. Then the patient says that she had her uterus removed 5 years ago, and the doctors had told her it was benign. In this case: Either the pathologist then had not properly taken sections or did not notice the leiomyosarcoma.

Leiomyosarcoma:

Radiologically: Infiltrative tumor obstructing the wall of the jejunum, part of the intestinal wall must be removed with the tumor.



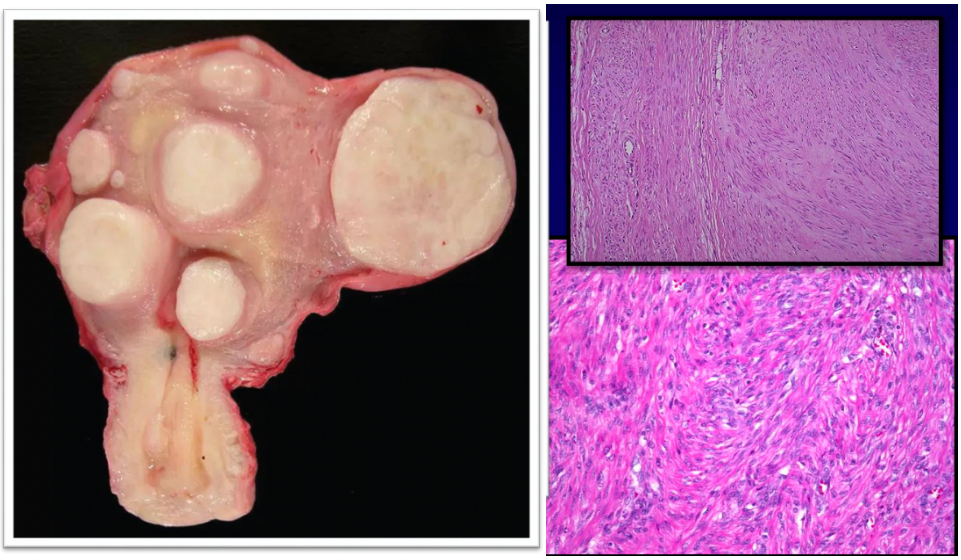
- Red, hemorrhagic
- Necrosis is a radiological sign of malignancy
- Histological: Abnormal mitosis, necrosis, ugly cells. (unlike leiomyoma)

Leiomyoma:

A female (35-40 years of age) with multiple leiomyomas (9 in number)

- She must have a uterectomy

Histology is bland with smooth muscle proliferation, no necrosis with little mitosis



Classic gross and histological appearane

<u>Tumors of uncertain origin (unclear histogenesis)</u>

Uncertain mesenchymal lineage, cell of origin is unknown.

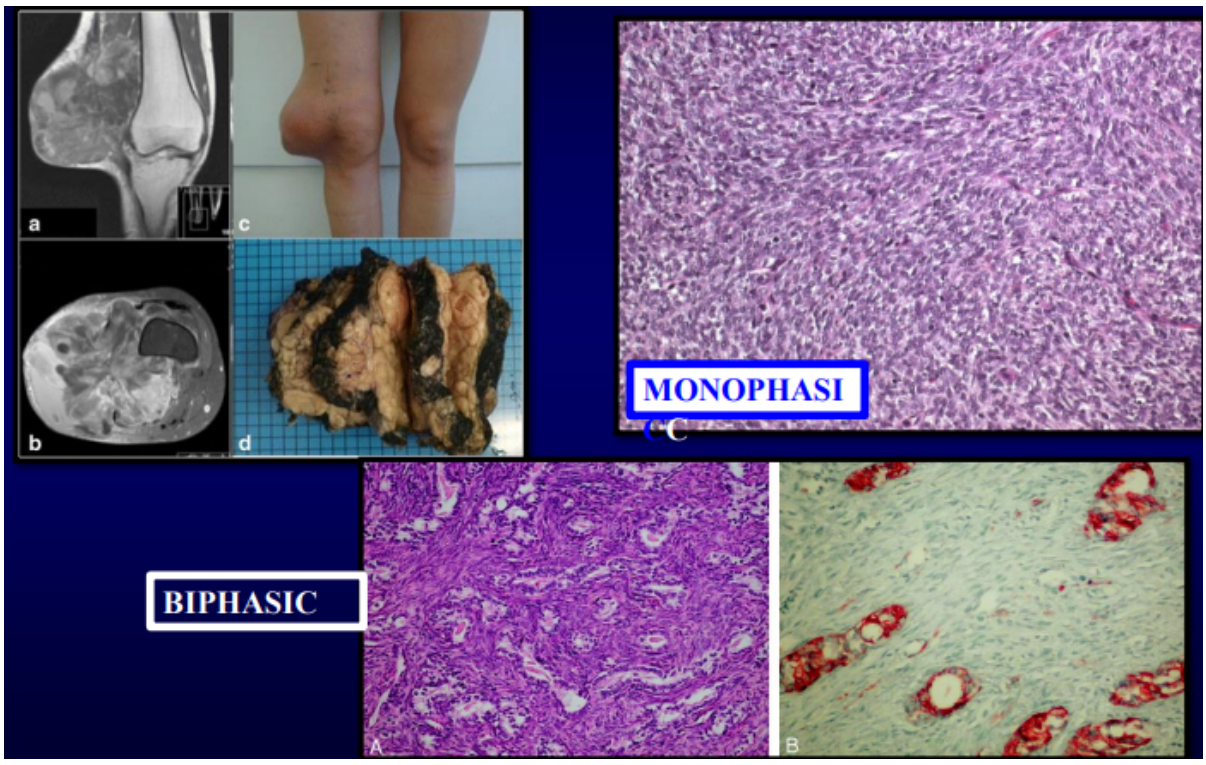
1. **<u>Synovial sarcoma:</u>**

- Name is misnomer (It was thought to occur in the synoviocyte- but it doesn't)
- Usually occurs near a joint
- More common in 20-40-year old's.

- Translocation T(X;18) (p11;q11) → Makes fusion genes SS18 (signature characteristic)
- Histologically:

1. Monophasic: spindle cells
2. Biphasic: spindle cells and epithelial (glands)
3. STAIN: keratin stain – to emphasize biphasic nature, however spindle cells may also be positive for the keratin stain.

- **Trx**: aggressive with limb sparing excision, chemotherapy and radiation
- Prognosis: 25-65% - depending on the stage
- Metastasis: Lung and lymph nodes (one of the few sarcomas that reaches the lymph nodes). Therefore, staging includes excision and lymphadenopathy.
- Bulky, large around the knee (that's why it was thought to have synovial origin)

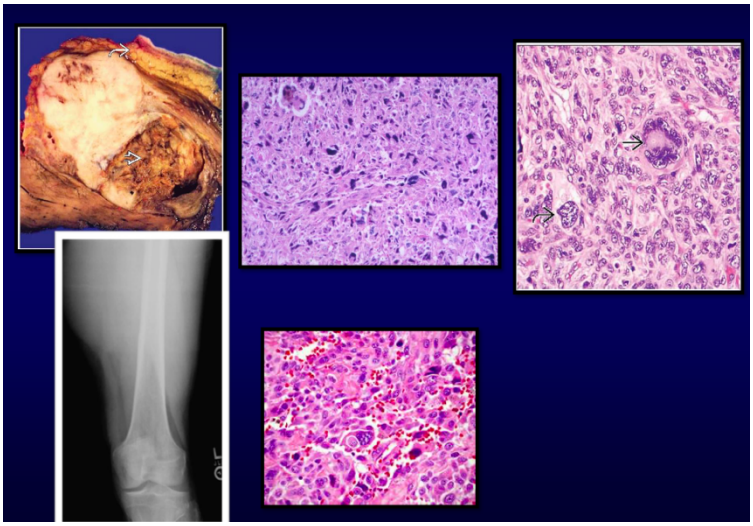


2. Undifferentiated pleomorphic sarcoma

- Old terminology: **MFH Malignant Fibrous Histiocytoma**
- Ugly, aggressive sarcoma with difficult treatment.
- Aneuploid and complex genetic abnormalities
- Large tumors; anaplastic and pleomorphic cells, abnormal mitoses, and necrosis
- Bulky and infiltrative
- Hemorrhage
- Occurs in older patients and in the retroperitoneum and thighs
- Stains for soft tissues such as smooth muscle and fat cells are negative.

- Treatment: Aggressive with surgery and adjuvant chemotherapy. May also use radiotherapy.
- Prognosis is poor.
- If you do all the tests, it's a high grade tumor, there is no differentiation, and it can't be diagnosed, it's classified as an undifferentiated pleomorphic sarcoma.
- Genetically very complex, there is no signature translocation.
- Difficult to remove surgically

Histologically:



- Anaplastic
- Large, pleomorphic cells
- Mitosis
- Poorly differentiated (undifferentiated)
- Necrosis

Grossly

- Bulky
- Hemorrhagic
- Infiltrative

(Another type of tumor with uncertain origin is Ewing's sarcoma)